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Bringing together the world's sarcoma specialists®

2018 Annual Meeting

Final Program

November 14 - 17, 2018

Rome Cavalieri Hotel • Rome, Italy

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2018 CTOS President

Paolo Dei Tos, MD and Andrew Wagner, MD, PhD
Program Co-Chairs

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greatly appreciates your support of the 2018 Annual Meeting. Your funding is vital and will advance the medical science and care of patients with bone and soft tissue tumors.

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2018 Annual Meeting

Program At-a-Glance

Wednesday, 14 November, 2018

12:00 pm - 6:00 pm	Registration and Poster Set Up	*Salon de Cavalieri 1 & Gallery*
6:00 pm - 8:00 pm	**Welcome Reception**	*San Pietro Gallery*

Thursday, 15 November, 2018

6:00 am - 7:00 pm	Registration	*Salon de Cavalieri 1 & Gallery*
7:00 am - 8:00 am	Coffee and Posters	*Salon de Cavalieri 1 & Gallery*
7:00 am - 11:00 am	**TARPSWG Semiannual Meeting**	*Ellisse Room*
8:00 am - 5:30 pm	**4th International Sarcoma Nurse and Allied Professionals Meeting (iSNAP) - "Collaboration in Sarcoma Care - Realizing Better Outcomes"**	*Caravaggio Room*
9:00 am - 11:00 am	**SARC PROGRAM**	*Salon del Cavalieri 2,3,4*
10:30 am - 11:00 am	Morning Coffee Break	*Salon de Cavalieri 1 & Gallery*
11:15 am - 11:30 am	**OPENING REMARKS**	*Salon del Cavalieri 2,3,4*
11:30 am - 1:00 pm	**SESSION 1 – Sarcoma of the Year: Intimal Sarcoma**	*Salon del Cavalieri 2,3,4*
1:00 pm - 2:00 pm	Lunch	*Belle Arti & Garden Lobby*
2:00 pm - 3:30 pm	**SESSION 2 – Soft Tissue Sarcoma: Chemotherapy**	*Salon del Cavalieri 2,3,4*
3:30 pm - 4:00 pm	Afternoon Coffee Break	*Salon de Cavalieri 1 & Gallery*
4:00 pm - 6:00 pm	**SESSION 3 – GIST**	*Salon del Cavalieri 2,3,4*
6:00 pm - 7:00 pm	**Poster Viewing Reception**	*Salon de Cavalieri 1 & Gallery*

Friday, 16 November, 2018

6:00 am - 6:00 pm	Registration	*Salon de Cavalieri 1 & Gallery*
7:00 am - 8:00 am	Coffee and Posters	*Salon de Cavalieri 1 & Gallery*
7:00 am - 8:00 am	Executive Committee Meeting	*San Giovanni*
8:00 am - 10:00 am	**SESSION 4 – Soft Tissue Sarcoma: Targeted Therapy**	*Salon del Cavalieri 2,3,4*
10:00 am - 10:30 am	Morning Coffee Break	*Salon de Cavalieri 1 & Gallery*
10:30 am - 11:00 am	**Presentation of Young Investigator Awards**	*Salon del Cavalieri 2,3,4*
11:00 am - 12:00 pm	**HERMAN SUIT LECTURE – Cristina Antonescu**	*Salon del Cavalieri 2,3,4*
12:00 pm - 1:30 pm	Lunch	*Belle Arti & Garden Lobby*
12:00 pm - 1:30 pm	Board of Directors Meeting	*San Giovanni*
1:30 pm - 3:30 pm	**SESSION 5 – Benign and Intermediate Grade Bone/ Soft Tissue Lesions**	*Salon del Cavalieri 2,3,4*
3:30 pm - 4:00 pm	Afternoon Coffee Break	*Salon de Cavalieri 1 & Gallery*
4:00 pm - 6:00 pm	**SESSION 6 – Ewing Sarcoma**	*Salon del Cavalieri 2,3,4*
7:00 pm - 10:00 pm	**Gala – Reception and Dinner at the beautiful Villa Miani next door to the Cavalieri Hotel. Cocktail Attire**	*Villa Miani*

Saturday, 17 November, 2018

6:30 am - 5:30 pm	Registration	*Salon de Cavalieri 1 & Gallery*
7:00 am - 8:00 am	Coffee and Posters	*Salon de Cavalieri 1 & Gallery*
8:00 am - 9:00 am	**Poster Discussion**	*Salon del Cavalieri 2,3,4*
9:00 am - 10:30 am	**SESSION 7 – Osteosarcoma/Chondrosarcoma/Chordoma**	*Salon del Cavalieri 2,3,4*
10:30 am - 11:00 am	Morning Coffee Break	*Salon de Cavalieri 1 & Gallery*
11:00 am - 12:00 pm	**NINA AXELRAD LECTURE – Jean-Yves Blay**	*Salon del Cavalieri 2,3,4*
12:00 pm - 1:00 pm	Lunch	*Belle Arti & Garden Lobby*
1:00 pm - 1:30 pm	**Liddy Shriver Early Career Research Award**	*Salon del Cavalieri 2,3,4*
1:30 pm - 3:30 pm	**SESSION 8 – Soft Tissue Sarcoma: Biology**	*Salon del Cavalieri 2,3,4*
3:30 pm - 4:00 pm	Afternoon Coffee Break	*Salon de Cavalieri 1 & Gallery*
4:00 pm - 5:30 pm	**SESSION 9 – Soft Tissue Sarcoma: Local Therapy**	*Salon del Cavalieri 2,3,4*
5:30 pm - 6:00 pm	CTOS Business Meeting	*Salon del Cavalieri 2,3,4*
6:00 pm	ADJOURN	

TARPSWG Semiannual Meeting

Thursday, November 15th
07.00 to 11.00 am

Cavalieri Hotel, Rome
Ellisse Room

Agenda

07.00-07.15	Welcome introduction (A. Gronchi)
07.15-08.00	RESAR project – an update on site activation, recruitment status and plans (M. Fiore M. Fairweather and D. Strauss)
08.00-08.20	Report from the REC committee on 2017-2018 activities and status of ongoing projects (C. Nessim)
08.20-08.45	The STREXIT project (C. Swallow)
08.45-09.30	STRASS 2 study (W. Van Houdt)
09.30-09.45	Recurrent RPS series: secondary manuscripts after the nomogram (CP Raut)
09.45-10.00	RT in primary retroperitoneal Liposarcoma: a propensity matched substudy from the original 1007 series (R. Haas)
10.00-10.15	Chemotherapy in primary RPS; a propensity matched substudy from the original 1007 series (C. Honoré)
10.15-11.00	TARPSWG governance and formalization: present perspective and future directions (all)
11.00	Start of CTOS official program
8.30	TARPSWG dinner

Symposium within the frame of CTOS 2018

ADDRESSING 3 HOT TOPICS IN THE MANAGEMENT OF SOFT TISSUE SARCOMA

Thursday, 15th November, 2018
19:00 - 20:30hrs
Rome Cavalieri Hotel
PLENARY ROOM
Salon de Cavalieri

PROGRAMME

19.00 - 19.05 **Welcome and Introduction**
Chair: Peter Reichardt, Germany

19.05 - 19.30 **Topic 1. Which goals should we pursue in each line of treatment?**
Javier Martin-Broto, Spain

19.30 - 19.55 **Topic 2. Treatment by subtypes: Wish, prediction or reality?**
Jean-Yves Blay, France

19.55 - 20.20 **Topic 3. Old age and sarcoma, few options for such a big population of patients**
Robin Jones, UK

20.20 - 20.30 **Questions and closing**
Peter Reichardt, Germany

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9:00 am - 11:00 am – SARC PROGRAM – *Salon del Cavalieri 2,3,4*

Chawla/Rosenfeld Developmental Therapeutics Symposium

Emerging and Novel Biologically Targeted Approaches for Sarcoma Patients

SARC collaborating to cure sarcoma

Introduction
Elizabeth Lawlor, MD, PhD
Robert Maki, MD, PhD

Enhancing Activity of B7-H3 CAR T Cells for Pediatric Sarcomas
Robbie Majzner, MD

Discussion / Q & A

Translating PARP Inhibition as a Therapeutic Target into Benefit for Patients with Sarcoma
Sandra Strauss, MD, PhD

Discussion / Q & A

Epigenetic Changes following the Loss of PRC2 in MPNST: Emerging Therapeutic Opportunities
Keila Torres, MD, PhD

Discussion / Q & A

2019 Career Development Update
Elizabeth Lawlor, MD, PhD

10:30 am - 11:00 am	**Morning Coffee Break**	*Salon de Cavalieri 1 & Gallery*

11:15 am - 11:30 am **OPENING REMARKS** *Salon del Cavalieri 2,3,4*

11:30 am - 1:00 pm – SESSION 1 – *Salon del Cavalieri 2,3,4*

Sarcoma of the Year: Intimal Sarcoma

Moderators: **Olivier Mir** and **Elizabeth Baldini**

Biology and Pathology of Intimal Sarcoma – *A. Paolo dei Tos*

Paper 001 3042623

SYSTEMIC TREATMENTS IN MDM2 + INTIMAL SARCOMA: A MULTICENTRE EXPERIENCE WITH ANTHRACYCLINE, GEMCITABINE AND PAZOPANIB WITHIN THE WORLD SARCOMA NETWORK (WSN)

Anna Maria Frezza[1]*; Tarek Assi*[2]*; Luigi Mariani*[3]*; Armelle Dufresne*[4]*; Siontis Brittany*[5]*; Kan Yonemori*[6]*; Emi Noguchi*[6]*; Eytan Ben-Amy*[7]*; Mrinal Gounder*[8]*; Robin Jones*[9]*; Pawel Teterycz*[10]*; Florence Duffaud*[12]*; Maria Abbondanza Pantaleo*[11]*; Vinod Ravi*[13]*; Bruno Vincenzi*[14]*; Giacomo Giulio Baldi*[15]*; Alexander Fedenko*[16]*; Hans Gelderblom*[17]*; Robert Maki*[18]*; Jean-Yves Blay*[4]*; Axel Le Cesne*[2]*; Scott Schuetze*[5]*; Paolo Casali*[1]*; Katherine Thornton*[7]*; Silvia Stacchiotti*[1]

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Paper 002 3026957

PRIMARY MALIGNANT SARCOMAS OF THE HEART AND GREAT VESSELS: A RETROSPECTIVE ANALYSIS OF PRESENTATION, MANAGEMENT AND OUTCOMES

Luke Smith[1]*; Han Hsi Wong*[2]*; Marius Berman*[3]*; Dochka Davidson*[2]*; Gail Horan*[2]*; David Jenkins*[3]*; Helen Hatcher*[2]

[1]*School of Clinical Medicine, University of Cambridge, Cambridge, United Kingdom;* [2]*Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom;* [3]*Royal Papworth Hospital NHS Foundation Trust, Cambridge, United Kingdom*

Paper 003 3042337

CLINICAL "REAL WORLD" NEXT GENERATION SEQUENCING REVEALS UNIQUE ABERRATIONS IN INTIMAL SARCOMA

Jason Roszik*; Anthony P. Conley; Roman Groisberg; Vinod Ravi; Roberto Carmagnani Pestana; Shiraj Sen; Vivek Subbiah*

The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Paper 004 3042847

OUTCOMES OF MULTIMODALITY TREATMENT WITH INDUCTION CHEMOTHERAPY, MAXIMAL RESECTION, AND PROTON BASED RADIATION THERAPY FOR CARDIAC AND PULMONARY VESSEL SARCOMAS

Yen-Lin E. Chen[1]*; Rouyu Miao*[1]*; Edwin Choy*[2]*; Gregory M. Cote*[2]*; Thomas F. DeLaney*[1]
[1]*Radiation Oncology, Massachusetts General Hospital, Boston, MA, USA;* [2]*Hematology Oncology, Massachusetts General Hospital, Boston, MA, USA*

Discussion – *Robert Maki*

1:00 pm - 2:00 pm **Lunch** *Belle Arti & Garden Lobby*

2:00 pm - 3:30 pm – SESSION 2 – *Salon del Cavalieri 2,3,4*

Soft Tissue Sarcoma: Chemotherapy

Moderators: **Wei-Wu (Tom) Chen** and **Claudia Valverde**

Paper 005 3042630

THE IMPACT OF CHEMOTHERAPY ON SURVIVAL OF PATIENTS WITH EXTREMITY AND TRUNK WALL SOFT TISSUE SARCOMA: REVISITING THE RESULTS OF THE EORTC-STBSG 62931 RANDOMISED TRIAL USING SARCULATOR, A VALIDATED NOMOGRAM-BASED RISK ASSESSMENT TOOL

Sandro Pasquali[1]*; Sara Pizzamiglio*[2]*; Nathan Touati*[2]*; Saskia Litiere*[2]*; Sandrine Marreaud*[2]*; Bernd Kasper*[3]*; Hans Gelderblom*[4]*; Silvia Stacchiotti*[1]*; Ian Judson*[5]*; Angelo P. Dei Tos*[6]*; Paolo Verderio*[1]*; Paolo Casali*[1]*; Penella J. Woll*[7]*; Alessandro Gronchi*[1]
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Paper 006 3042737

PROPENSITY SCORE MATCHING ANALYSIS OF DOXORUBICIN PLUS DACARBAZINE, DOXORUBICIN PLUS IFOSFAMIDE OR DOXORUBICIN ALONE AS FIRST-LINE TREATMENT FOR ADVANCED, METASTATIC OR UNRESECTABLE LEIOMYOSARCOMA: A RETROSPECTIVE STUDY FROM THE EORTC SOFT TISSUE AND BONE SARCOMA GROUP

Lorenzo D'Ambrosio[1]*; Nathan Touati*[2]*; Jean-Yves Blay*[3]*; Tiziana Venesio*[4]*; Ronan Flippot*[17]*; Anna M. Czarnecka*[5]*; Sophie Piperno-Neumann*[6]*; Javier Martín-Broto*[7]*; Roberta Sanfilippo*[8]*; Daniela Katz*[9]*; Florence Duffaud*[10]*; Bruno Vincenzi*[11]*; Bernd Kasper*[12]*; Daniel P. Stark*[13]*; Filomena Mazzeo*[14]*; Armin Tuchscherer*[15]*; Saskia Litiere*[2]*; Ward Sents*[2]*; Silvia Stacchiotti*[8]*; Hans Gelderblom*[16]*; Alessandro Gronchi*[8]
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Paper 007 3042520

PHASE 1B STUDY OF OLARATUMAB PLUS DOXORUBICIN AND IFOSFAMIDE IN PATIENTS WITH ADVANCED OR METASTATIC SOFT TISSUE SARCOMA: INITIAL RESULTS

Sebastian Bauer[1]; *Neeta Somaiah*[2]; *Silvia Stacchiotti*[3]; *Peter Reichardt*[4]; *Hector Soto Parra*[5]; *Rainer Hamacher*[1]; *Andrew Lithio*[6]; *Gary Mo*[6]; *Samuel Ramage*[6]; *Jonathan Trent*[7]
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Paper 008 3042717

ANTHRACYCLINE-BASED VERSUS GEMCITABINE-BASED ADJUVANT CHEMOTHERAPY IN FIGO STAGE 1 UTERINE LEIOMYOSARCOMA

Roberta Sanfilippo[1]; *Rosanna Mancari*[2]; *Sara Manglaviti*[1]; *Giorgio Bogani*[1]; *Domenica Lorusso*[1]; *Elena Fumagalli*[1]; *Rossella Bertulli*[1]; *Angelo Paolo Dei Tos*[3]; *Paola Collini*[1]; *Francesco Raspagliesi*[1]; *Nicoletta Colombo*[2]; *Paolo Casali*[1]
[1]*Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy;* [2]*Gynaecology department, IEO, Milan, Italy;* [3]*General Hospital Treviso, Trevisto, Italy*

Paper 009 3042702

EUROPEAN PHASE I/II TRASTS TRIAL OF TRABECTEDIN PLUS RADIOTHERAPY IN PATIENTS WITH METASTATIC SOFT TISSUE SARCOMA (STS): A COLLABORATIVE SPANISH (GEIS), ITALIAN (ISG) AND FRENCH (FSG) SARCOMA GROUPS STUDY

Javier Martín-Broto[1]; *Antonio Lopez-Pousa*[2]; *Nadia Hindi*[1]; *Josefina Cruz*[3]; *Javier Peinado*[1]; *Carlo Morosi*[4]; *Josep Isern Verdun*[2]; *Maria Carmen Dolado*[5]; *Rosa Maria Alvarez Alvarez*[5]; *Ana Alvarez González*[5]; *Tiziana Venesio*[6]; *Marco Gatti*[6]; *Pablo Luna Fra*[7]; *Ignacio Alastuey*[7]; *Jean-Yves Blay*[8]; *Marie-Pierre Sunyach*[8]; *Inmaculada Rincon*[10]; *Alessandro Gronchi*[4]; *Jesus Romero*[9]
[1]*Institute of Biomedicine Research (IBIS)- University Hospital Virgen del Rocio/CSIC/University of Seville, Seville, Spain;* [2]*Hospital Sant Pau, Barcelona, Spain;* [3]*University Hospital of Canary Islands , Santa Cruz De Tenerife, Spain;* [4]*Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy;* [5]*University Hospital Gregorio Marañon, Madrid, Spain;* [6]*Candiolo Cancer Institute - FPO, IRCCS, Candiolo, Italy;* [7]*University Hospital Son Espases, Palma de Mallorca, Spain;* [8]*Centre Léon Bérard, Lyon, France;* [9]*Hospital Puerta de Hierro, Madrid, Spain;* [10]*University Hospital Virgen del Rocio, Seville, Spain*

Discussion – *Florence Duffaud*

3:30 pm - 4:00 pm **Afternoon Coffee Break** *Salon de Cavalieri 1 & Gallery*

4:00 pm - 6:00 pm – SESSION 3 – *Salon del Cavalieri 2,3,4*

GIST

Moderators: **Richard Riedel** and **Sebastian Bauer**

Paper 010 3042567

MULTICENTRIC RETROSPECTIVE ANALYSIS OF PATIENTS WITH *KIT* EXON 9 MUTATED GIST

Almudena Callejo Goena[1]; *Sara Faouzi*[2]; *Olivier Bouche*[3]; *Thomas Chevalier*[4]; *Nicolas Isambert*[5]; *Florence Duffaud*[4]; *Olivier Collard*[6]; *Nicolas Penel*[7]; *Olivier Mir*[2]; *Philippe Terrier*[8]; *Jean-Yves Blay*[9]; *Axel Le Cesne*[2]
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Paper 011 3041313

A WEB-BASED SURVEY OF PERCEIVED COGNITIVE IMPAIRMENTS AND OTHER PATIENT-REPORTED OUTCOMES IN GIST PATIENTS

Robert Ferguson[1]; Jessica Manculich[2]; Hsuan Chang[2]; Beth Snitz[3]; Dana Bovbjerg[4]; ***Anette Duensing***[5]
[1]Biobehavioral Oncology Program, UPMC Hillman Cancer Center, Dept. of Medicine, University of PIttsburgh School of Medicine, Pittsburgh, PA, USA; [2]Biobehavioral Oncology Program, UPMC Hillman Cancer Center, Pittsburgh, PA, USA; [3]Dept. of Neurology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA; [4]Biobehavioral Oncology Program, UPMC Hillman Cancer Center, Dept. of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA; [5]Cancer Therapeutics Program, UPMC Hillman Cancer Center, Dept. of Pathology, University of PIttsburgh School of Medicine, Pittsburgh, PA, USA

Paper 012 3027631

AVAPRITINIB IS HIGHLY ACTIVE AND WELL-TOLERATED IN PATIENTS (PTS) WITH ADVANCED GIST DRIVEN BY DIVERSE VARIETY OF ONCOGENIC MUTATIONS IN KIT AND PDGFRA

Michael Heinrich[1]*; Margaret von Mehren[2]; Robin L. Jones[3]; Sebastian Bauer[4]; Yoon-Koo Kang[5]; Patrick Schöffski[6]; Ferry Eskens[7]; Cesar Serrano[8]; Philippe Cassier[9]; Olivier Mir[10]; William D. Tap[11]; Piotr Rutkowski[12]; Jonathan Trent[13]; Shreyaskumar Patel[14]; Sant P. Chawla[15]; Teresa Zhou[16]; Tamieka Lauz[16]; Oleg Schmidt-Kittler[16]; Khalid K. Mamlouk[16]; Beni B. Wolf[16]; Suzanne George[17]*
[1]OHSU Knight Cancer Institute, Portland, OR, USA; [2]Fox Chase Cancer Centre, Philadelphia, PA, USA; [3]Royal Marsden Hospital and Institute of Cancer Research, London, United Kingdom; [4]University of Duisburg-Essen, Essen, Germany; [5]Asan Medical Centre, Seoul, Korea (the Republic of); [6]University Hospitals Leuven, Leuven Cancer Institute, Leuven, Belgium; [7]Erasmus MC Cancer Institute, Rotterdam, Netherlands; [8]Vall d' Hebron Institute of Oncology , Barcelona, Spain; [9]Centre Léon Bérard, Lyon, France; [10]Institut Gustave Roussy; Edouard Vaillant Villejuif, Villejuif, France; [11]Memorial Sloan Kettering Cancer Centre, New York, NY, USA; [12]Maria Sklodowska-Curie Institute - Oncology Center, Warszawa, Poland; [13]Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL, USA; [14]MD Anderson Cancer Center, Houston, TX, USA; [15]Sarcoma Oncology Centre , Santa Monica, CA, USA; [16]Blueprint Medicines Corporation, Cambridge , MA, USA; [17]Dana Farber Cancer Institute, Boston, MA, USA

Paper 013 3033840

INITIAL RESULTS OF PHASE 1 STUDY OF DCC-2618, A BROAD-SPECTRUM KIT AND PDGFRAINHIBITOR, IN PATIENTS (PTS) WITH GASTROINTESTINAL STROMAL TUMOR (GIST) BY NUMBER OF PRIOR REGIMENS

Suzanne George[3]*; Michael Heinrich[10]; Ping Chi[4]; Albiruni Razak[5]; Margaret von Mehren[6]; Michael Gordon[7]; Kristen Ganjoo[2]; Neeta Somaiah[8]; Jonathan Trent[11]; Julie Wolf[9]; Rodrigo Ruiz-Soto[1]; Oliver Rosen[1]; Filip Janku[8]*
[1]Deciphera, Waltham, MA, USA; [2]Stanford University, Palo Alto, CA, USA; [3]Dana-Farber Cancer Institute, Boston, MA, USA; [4]MSKCC, New York, NY, USA; [5]Princess Margaret Cancer Centre, Toronto, ON, Canada; [6]Fox Chase Cancer Center, Philadelphia, PA, USA; [7]Pinnacle Oncology Hematology, Scottsdale, AZ, USA; [8]MDACC, Houston, TX, USA; [9]Biostats Consultants, Denver, CO, USA; [10]OHSU, Portland, OR, USA; [11]University Miami, Miami, FL, USA

Discussion – *Victor Villalobos*

Paper 014 3041747

NON-INVASIVE DETECTION OF CTDNA REVEALS INTRATUMOR HETEROGENEITY AND IS ASSOCIATED WITH TUMOR BURDEN IN GASTROINTESTINAL STROMAL TUMOR

Boye Kjetil[1]*; Heidi Namløs[2]; Skyler J. Mishkin[3]; Tale Barøy[2]; Susanne Lorenz[4]; Bodil Bjerkehagen[5]; Eva Stratford[2]; Else Munthe[2]; Brian A. Kudlow[3]; Ola Myklebost[2]; Leonardo A. Meza-Zepeda[2]*
[1]Department of Oncology, Oslo University Hospital, Oslo, Norway; [2]Department of Tumor Biology, Oslo University Hospital, Oslo, Norway; [3]Archer DX, Inc., Boulder, CO, USA; [4]Genomics Core Facility, Oslo University Hospital, Oslo, Norway; [5]Department of Pathology, Oslo University Hospital, Oslo, Norway

Paper 015 3042824

UTILITY OF CIRCULATING TUMOR DNA (CTDNA) IN THE MANAGEMENT OF PATIENTS WITH GASTROINTESTINAL STROMAL TUMOR (GIST): ANALYSIS OF 184 PATIENTS

Junaid Arshad[1]; Breelyn A. Wilky[1]; Ali Roberts[2]; Becky Nagy[2]; ***Jonathan Trent***[1]
[1]Sarcoma Medical Oncology, Sylvester Comprehensive Cancer Center, Miami, FL, USA; [2]Guardant Health, Redwood City, CA, USA

Paper 016 3030004

CLINICAL VALUE OF CT-DNA IN LOCALIZED AND ADVANCED GIST: CROSS-VALIDATION OF AMPLICON-BASED NGS WITH DD-PCR IN MATCHED TISSUE AND PLASMA SAMPLES

Cesar Serrano[1]*; Ana Vivancos[5]; Antonio Lopez-Pousa[12]; Judit Matito[5]; Francesco M. Mancuso[5]; Claudia Valverde[11]; Sergi Quiroga[6]; Stefania Landolfi[2]; Sandra Castro[7]; Cristina Dopazo[7]; Ana Sebio[12]; Anna C. Virgili Manrique[12]; Maria M Menso[8]; Javier Martín-Broto[9]; Alfonso Garcia-Valverde[10]; Jordi Rosell[10]; Jonathan A. Fletcher[3]; Suzanne George[4]; Joan Carles[11]; Joaquín Arribas[10]*
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Discussion – *Bartosz Chmielowski*

6:00 pm - 7:00 pm **Poster Viewing Reception** *Salon de Cavalieri 1 & Gallery*

Friday, 16 November, 2018

6:00 am - 6:00 pm	Registration	*Salon de Cavalieri 1 & Gallery*
7:00 am - 8:00 am	**Coffee and Posters**	*Salon de Cavalieri 1 & Gallery*
7:00 am - 8:00 am	Executive Committee Meeting	*San Giovanni*

8:00 am - 10:00 am — – SESSION 4 – — *Salon del Cavalieri 2,3,4*

Soft Tissue Sarcoma: Targeted Therapy

Moderators: **Thierry Alcindor** and **Robin Jones**

Paper 017 — 3016595

PROSPECTIVE TRIAL OF CRIZOTINIB (C) IN PATIENTS (PTS) WITH ADVANCED, INOPERABLE INFLAMMATORY MYOFIBROBLASTIC TUMOR (IMFT) WITH AND WITHOUT ALK ALTERATIONS: EORTC PHASE II STUDY 90101 "CREATE"

Patrick Schöffski[1]*; Jozef Sufliarsky*[2]*; Hans Gelderblom*[3]*; Jean-Yves Blay*[7]*; Sandra Strauss*[8]*; Silvia Stacchiotti*[9]*; Piotr Rutkowski*[10]*; Lars Lindner*[11]*; Michael Leahy*[12]*; Antoine Italiano*[13]*; Maria Debiec-Rychter*[14]*; Raf Sciot*[4]*; Sandrine Marreaud*[5]*; Axelle Nzokirantevye*[5]*; Agnieszka Wozniak*[6]
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Paper 018 — 3006132

ACTIVITY AND SAFETY OF CRIZOTINIB IN PATIENTS WITH ADVANCED CLEAR CELL SARCOMA (CCSA) WITH *MET* ALTERATIONS. EUROPEAN ORGANIZATION FOR RESEARCH AND TREATMENT OF CANCER PHASE 2 TRIAL 90101 "CREATE"

Patrick Schöffski[1]*; **Agnieszka Wozniak***[2]*; Silvia Stacchiotti*[3]*; Piotr Rutkowski*[4]*; Jean-Yves Blay*[5]*; Lars Lindner*[8]*; Sandra Strauss*[9]*; Alan Anthoney*[12]*; Florence Duffaud*[14]*; Stephan Richter*[13]*; Raf Sciot*[6]*; Debiec-Rychter Maria*[10]*; Sandrine Marreaud*[7]*; Laurence Collette*[7]*; Sebastian Bauer*[11]
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Paper 019 3025592

MILADEMETAN, AN ORAL MDM2 INHIBITOR, IN WELL-DIFFERENTIATED/DE-DIFFERENTIATED LIPOSARCOMA: RESULTS FROM A PHASE 1 STUDY IN PATIENTS WITH SOLID TUMORS AND LYMPHOMAS

Mrinal Gounder[1]; *Todd M. Bauer*[2]; *Gary K. Schwartz*[3]; *Amy M. Weise*[4]; *Patricia LoRusso*[5]; *Prasanna Kumar*[6]; *Shuquan Chen*[6]; *Jeanne Mendell*[6]; *Jarema Kochan*[6]; *Oleg Zernovak*[6]; *David S. Hong*[7]
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Paper 020 3042882

PHASE 2 STUDY OF THE CDK4 INHIBITOR ABEMACICLIB IN DEDIFFERENTIATED LIPOSARCOMA

Mark A. Dickson[1]; *Sandra D'Angelo*[1]; *Mrinal Gounder*[1]; *Mary L. Keohan*[1]; *Ciara M. Kelly*[1]; *Ping Chi*[1]; *Cristina Antonescu*[4]; *Jonathan Landa*[2]; *Li-Xuan Qin*[5]; *Andrew Koff*[6]; *Aimee M. Crago*[3]; *Sam Singer*[3]; *William D. Tap*[1]
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Discussion – *Javier Martin-Broto*

Paper 021 3042818

PHASE II STUDY OF ATEZOLIZUMAB IN PATIENTS WITH ALVEOLAR SOFT PART SARCOMA

Geraldine O'Sullivan Coyne[1]; *Elad Sharon*[2]; *Nancy Moore*[1]; *Robert Meehan*[3]; *Naoko Takebe*[1]; *Lamin Juwara*[4]; *Laurence Rubinstein*[2]; *William Read*[5]; *Richard F. Riedel*[7]; *Priscilla Merriam*[8]; *James Hu*[6]; *Melissa Burgess*[9]; *James Doroshow*[1]; *Alice Chen*[1]
[1]*Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, MD, USA;* [2]*Cancer Therapy Evaluation Program, National Cancer Institute, Rockville, MD, USA;* [3]*Moderna Therapeutics, Cambridge, MA, USA;* [4]*National Cancer Institute, Bethesda, MD, USA;* [5]*Emory Cancer Center, Atlanta, GA, USA;* [6]*University of Southern California, Los Angeles, CA, USA;* [7]*Duke University School of Medicine, Durham, NC, USA;* [8]*Dana Farber Cancer Institute, Boston, MD, USA;* [9]*UPMC Hillman Cancer Center, Pittsburgh, PA, USA*

Paper 022 3033993

EZH2 INHIBITOR TAZEMETOSTAT (TAZ) INTERIM DATA IN ADULTS AND PEDIATRIC PATIENTS WITH INI1-NEGATIVE SOFT-TISSUE SARCOMAS (STS) INCLUDING EPITHELIOID SARCOMA (ES) (NCT02601950, NCT02601937)

Mrinal Gounder[1]; *Patrick Schöffski*[2]; *Silvia Stacchiotti*[3]; *Victor Villalobos*[4]; *Rashmi Chugh*[5]; *Mark Agulnik*[6]; *Steven Attia*[7]; *Tom Wei-Wu Chen*[8]; *Gupta Abha*[9]; *Thierry Jahan*[10]; *Robin Jones*[22]; *Antoine Italiano*[11]; *Jean-Yves Blay*[12]; *Gregory M. Cote*[13]; *George Demetri*[14]; *Elizabeth Loggers*[15]; *Ravin Ratan*[16]; *Maryam Fouladi*[17]; *Margaret Macy*[18]; *Guy Makin*[19]; *Alicia Clawson*[20]; *Scott Daigle*[20]; *Chelsea Mencio*[20]; *Inbal Sapir*[20]; *Franck Bourdeaut*[21]
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Paper 023 3029169

ACTIVITY OF LAROTRECTINIB IN SARCOMA PATIENTS WITH TRK FUSION CANCER

Noah Federman[1]; *Daniel Orbach*[2]; *Shivaani Kummar*[3]; *Alexander Drilon*[4]; *Ulrik Lassen*[5]; *Birgit Geoerger*[6]; *Cornelis M. van Tillburg*[7]; *Theodore W. Laetsch*[8]; *Steven DuBois*[9]; *Ramamoorthy Nagasubramanian*[10]; *Neerav Shukla*[4]; *Michela Casanova*[11]; *Soledad Gallego*[12]; *Stefan Bielack*[13]; *Atrayee Basu-Mallick*[14]; *Mohamad Farid*[15]; *Jyoti Patel*[16]; *Vicki Keedy*[17]; *Scott Cruickshank*[18]; *Nora C. Ku*[18]; *Michael C. Cox*[18]; *Alberto Pappo*[19]; *George Demetri*[20]; *Douglas Hawkins*[21]

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Discussion – *Neeta Somaiah*

10:00 am - 10:30 am **Morning Coffee Break** *Salon de Cavalieri 1 & Gallery*

10:30 am - 11:00 am **Presentation of Young Investigator Awards** *Salon del Cavalieri 2,3,4*

Paper 036 3035962

SLFN11 IS A SIGNIFICANT DETERMINANT OF PARP INHIBITOR SENSITIVITY IN PEDIATRIC SARCOMAS

Jessica Gartrell; *Marcia M. Mellado-Largarde; Jia Xie; Brandon Bianski; Kaley Blankenship; Michael Clay; Armita Bahrami; Sara Federico; Christopher L. Tinkle; Elizabeth Stewart; Anang Shelat*

St. Jude Children's Research Hospital, Memphis, TN, USA

Paper 021 3042818

PHASE II STUDY OF ATEZOLIZUMAB IN PATIENTS WITH ALVEOLAR SOFT PART SARCOMA

Geraldine O'Sullivan Coyne[1]; *Elad Sharon*[2]; *Nancy Moore*[1]; *Robert Meehan*[3]; *Naoko Takebe*[1]; *Lamin Juwara*[4]; *Laurence Rubinstein*[2]; *William Read*[5]; *Richard F. Riedel*[7]; *Priscilla Merriam*[8]; *James Hu*[6]; *Melissa Burgess*[9]; *James Doroshow*[1]; *Alice Chen*[1]

[1]*Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, MD, USA;* [2]*Cancer Therapy Evaluation Program, National Cancer Institute, Rockville, MD, USA;* [3]*Moderna Therapeutics, Cambridge, MA, USA;* [4]*National Cancer Institute, Bethesda, MD, USA;* [5]*Emory Cancer Center, Atlanta, GA, USA;* [6]*University of Southern California, Los Angeles, CA, USA;* [7]*Duke University School of Medicine, Durham, NC, USA;* [8]*Dana Farber Cancer Institute, Boston, MD, USA;* [9]*UPMC Hillman Cancer Center, Pittsburgh, PA, USA*

11:00 am - 12:00 pm – HERMAN SUIT LECTURE – *Salon del Cavalieri 2,3,4*

How Molecular Discoveries Changed our Morphology-Based Profession

Cristina Antonescu

(Memorial Sloan Kettering Cancer Center, New York, NY)

12:00 pm - 1:30 pm **Lunch** *Belle Arti & Garden Lobby*

12:00 pm - 1:30 pm Board of Directors Meeting *San Giovanni*

1:30 pm - 3:30 pm – SESSION 5 – *Salon del Cavalieri 2,3,4*

Benign and Intermediate Grade Bone/Soft Tissue Lesions

Moderators: **William Tseng** and **Katherine Thornton**

Paper 024 3042858

RISK FACTORS IN TENOSYNOVIAL GIANT CELL TUMOURS OF LARGE JOINTS, EVALUATED IN 30 INTERNATIONAL SARCOMA CENTERS

Monique Mastboom; *Emanuela Palmerini; Floortje Verspoor; Anja Rueten-Budde; Silvia Stacchiotti; Eric Staals; Gerard Schaap; Paul Jutte; Will Aston; Andreas Leithner; Dietmar Dammerer; Akihiko Takeuchi; Quirina Thio; Xiaohui Niu; Jay Wunder; Michiel A. van de Sande*
Orthopaedics oncology, Leiden University Medical Center, Amsterdam, Noord Holland, Netherlands

Paper 025 3038487

POSITIVE ASSOCIATION BETWEEN TUMOR RESPONSE AND PATIENT-REPORTED OUTCOMES IN PHASE 3 ENLIVEN STUDY OF PEXIDARTINIB IN TENOSYNOVIAL GIANT CELL TUMOR (TGCT)

Heather L. Gelhorn[1]; Charles Peterfy[2]; Xin Ye[3]; ***Rebecca M. Speck****[1]; Emanuela Palmerini[4]; Silvia Stacchiotti[5]; Jayesh Desai[6]; Andrew Wagner[7]; Thierry Alcindor[8]; Kristen Ganjoo[9]; Javier Martín-Broto[10]; Christopher Ryan[11]; Qiang Wang[3]; Dale Shuster[3]; William D. Tap[12]; Hans Gelderblom[13]*
[1]Evidera, Bethesda, MD, USA; [2]Spire Sciences, Inc., Boca Raton, FL, USA; [3]Daiichi Sankyo, Inc., Basking Ridge, NJ, USA; [4]Istituto Ortopedico Rizzoli, Bologna, Italy; [5]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [6]Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia; [7]Dana-Farber Cancer Institute, Boston, MA, USA; [8]McGill University, Montreal, QC, Canada; [9]Stanford Cancer Institute, Stanford, CA, USA; [10]Hospital Universitario Virgen del Rocío, Seville, Spain; [11]Oregon Health & Science University, Portland, OR, USA; [12]Memorial Sloan Kettering Cancer Institute, New York, NY, USA; [13]Leiden University Medical Center, Leiden, Netherlands

Paper 026 3042414

PRIMARY VASCULAR TUMORS OF BONE: AN ANALYSIS OF 427 PATIENTS

Marta Sbaraglia*[1]; Alberto Righi[2]; Marco Gambarotti[2]; Dino Gibertoni[3]; Stefania Benini[2]; Piero Picci[2]; Angelo Paolo Dei Tos[1]*
[1]University of Padua , Treviso, Italy; [2]Pathology, IRCCS Rizzoli Orthopaedic Institute, Bologna, Italy; [3]Biomedical and Neuromotor Sciences, Alma Mater Studiorum University of Bologna, Bologna, Italy

Paper 027 3042427

PHASE II TRIAL OF PAZOPANIB IN ADVANCED EXTRASKELETAL MYXOID CHONDROSARCOMA. A COLLABORATIVE SPANISH (GEIS), ITALIAN (ISG) AND FRENCH (FSG) SARCOMA GROUPS STUDY

Silvia Stacchiotti[1]; *Stefano Ferrari*[2]; *Antonio Redondo*[3]; *Emanuela Palmerini*[2]; *Nadia Hindi*[4]; *Maria A. Vaz*[5]; *Anna Maria Frezza*[1]; *Antonio Gutierrez*[6]; *Antonio Lopez-Pousa*[16]; *Tiziana Venesio*[7]; *Antoine Italiano*[8]; *Sarah N. Dumont*[9]; *Jean-Yves Blay*[10]; *Nicolas Penel*[11]; *Daniel Bernabeu*[12]; *Enrique De Alava*[13]; *Dominique Ranchere-Vince*[10]; *Gian Paolo Dagrada*[1]; *Paola Collini*[1]; *Josefina Cruz*[14]; *Javier Martín-Broto*[15]

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Discussion – *Paolo Casali*

Paper 028 3042598

LONGITUDINAL DISTRESS ASSESSMENT AND RESPONSE TOOL (DART) SCREENING IN ADULTS WITH AGGRESSIVE FIBROMATOSIS: HIGH PREVALENCE OF PERSISTENT EMOTIONAL DISTRESS

Abha Gupta[1]; *Nicole Byers*[1]; *Sally Burtenshaw*[2]; *Katrina Ingley*[2]; *Carol Swallow*[2]; *Savtaj Brar*[2]; *Anthony M. Griffin*[2]; *Peter Ferguson*[2]; *Jay Wunder*[2]; *Albiruni Razak*[1]; *Rebecca Gladdy*[2]; *Roberta Klein*[3]; *Madeline Li*[3]

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Paper 029 3042617

CAN WAIT AND SEE BE THE STANDARD OF CARE FOR INITIAL APPROACH TO PRIMARY SPORADIC DESMOID TUMORS? PRELIMINARY DATA FROM AN ITALIAN SARCOMA GROUP PROSPECTIVE STUDY

Chiara Colombo[1]; *Marco Fiore*[1]; *Tiziana Venesio*[2]; *Erica Palesandro*[2]; *Paola Boccone*[2]; *Lorenzo D'Ambrosio*[2]; *Alba Bianco*[1]; *Paola Collini*[1]; *Elena Palassini*[1]; *Silvia Stacchiotti*[1]; *Angelo Paolo Dei Tos*[3]; *Paolo Casali*[1]; *Federica Perrone*[1]; *Alessandro Gronchi*[1]

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Paper 030 3042719

INCORPORATION OF *CTNNB1* MUTATION STATUS INTO A PRE-OPERATIVE DESMOID LOCAL RECURRENCE NOMOGRAM IMPROVES PREDICTIVE VALUE

Iris Wei[1]; *Anthony Villano*[1]; *Andrea Knezevic*[2]; *Bhumika Jadeja*[1]; *Li-Xuan Qin*[2]; *Meera Hameed*[3]; *Sam Singer*[1]; ***Aimee M. Crago***[1]

[1]*Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA;* [2]*Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY, USA;* [3]*Pathology, Memorial Sloan Kettering Cancer Center, New York, NY, USA*

Discussion – *Bernd Kasper*

3:30 pm - 4:00 pm **Afternoon Coffee Break** *Salon de Cavalieri 1 & Gallery*

4:00 pm - 6:00 pm | – SESSION 6 – | *Salon del Cavalieri 2,3,4*

Ewing Sarcoma

Moderators: **Abha Gupta** and **Piero Picci**

Paper 031 3027408

EASY-TO-USE PRACTICAL CLINICAL TOOL FOR SURVIVAL ESTIMATION IN EWING SARCOMA AT DIAGNOSIS AND AFTER SURGERY

Sarah E. Bosma[1]*; Carlo Lancia*[2]*; Anja J. Rüten-Budde*[2]*; Andreas Ranft*[3]*; Hans Gelderblom*[4]*; Marta Fiocco*[2]*; Michiel A. van de Sande*[1]*; Sander Dijkstra*[1]*; Uta Dirksen*[3]
[1]Orthopedics, Leiden University Medical Center, Leiden, Netherlands; [2]Mathematical Institue, Leiden University, Leiden, Netherlands; [3]Pediatrics III, University Hospital Essen, University Duisburg-Essen, Sarcoma Center, West German Cancer Center, Essen, Germany; [4]Medical Oncology, Leiden University Medical Center, Leiden, Netherlands

Paper 032 3042243

RETROSPECTIVE ANALYSIS OF USE OF WHOLE LUNG IRRADIATION FOR PATIENTS WITH NEWLY DIAGNOSED EWING SARCOMA AND PULMONARY METASTASES

Hadeel Halalsheh[1]*; Sue Kaste*[2]*; Matthew J. Krasin*[3]*; April Sykes*[4]*; Natasha Sahr*[4]*; Sheri Spunt*[5]*; Sara Federico*[1]*; Alberto Pappo*[1]*; **Michael W. Bishop***[1]
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Paper 033 3042780

WHOLE-LUNG IRRADIATION AFTER HIGH-DOSE BUSULFAN/MELPHALAN CONDITIONING THERAPY IN EWING SARCOMA WITH LUNG METASTASES: A MULTICENTRIC STUDY

Massimo E. Abate[1]*; Letizia Ronchi*[2]*; Barbara Diletto*[14]*; Lorenza Gandola*[14]*; Nadia Puma*[15]*; Angela Tamburini*[3]*; Maurizio Mascarin*[4]*; Elisa Coassin*[4]*; Arcangelo Prete*[5]*; Sebastian Asaftei*[6]*; Carla Manzitti*[7]*; Luca Coccoli*[8]*; Mariella Capasso*[9]*; Tiziana Venesio*[13]*; Emilia Pecori*[14]*; Marta Pierobon*[16]*; Anna Paioli*[1]*; Elisa Carretta*[10]*; Giovanni Piero Frezza*[11]*; Alessio Giuseppe Morganti*[2]*; Stefano Ferrari*[1]*; Piero Picci*[12]*; Alessandra Longhi*[1]*; Silvia Cammelli*[2]*; Roberto Luksch*[15]
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Discussion – *Rick Haas*

Paper 034 3042627

THE WNT-DEPENDENT SECRETOME ALTERS TUMOR: TUMOR MICROENVIRONMENT CROSSTALK TO PROMOTE INVASION AND ANGIOGENESIS IN EWING SARCOMA

Allegra Hawkins; Elisabeth Pedersen; Sonja Konzen; Colin Sperring; Sydney Treichel; ***Elizabeth Lawlor***
University of Michigan, Ann Arbor, MI, USA

Paper 035 3042245

A PHASE I STUDY OF THE POLY-ADP RIBOSE POLYMERASE (PARP) INHIBITOR, NIRAPARIB (NIR), IN COMBINAITON WITH IRINOTECAN (IRN) IN PATIENTS WITH ADVANCED EWING SARCOMA: RESULTS OF SARC025 ARM 2

Sandra J. Strauss[1]*; Karla V Ballman*[2]*; Kam Zaki*[1]*; Lee Helman*[3]*; Brigitte Widemann*[4]*; Douglas Hawkins*[5]*; Leo Mascarenhas*[3]*; J.W Glod*[4]*; Jay Ji*[6]*; Ziping Zhang*[6]*; Birgit Geoerger*[7]*; Jeremy Whelan*[1]*; Denise Reinke*[8]*; Shreyaskumar Patel*[9]*; Rashmi Chugh*[10]

[1]University College London Hospitals NHS Trust, London, United Kingdom; [2]Weill Cornell Medicine, New York, NY, USA; [3]Children's Center for Cancer and Blood Diseases, Los Angeles, CA, USA; [4]National Cancer Institute Centre for Cancer Research, Bethesda, MD, USA; [5]Seattle Children's Hospital, Seattle, OR, USA; [6]National Clinical Target Validation Laboratory, Bethesda, MD, USA; [7]Institut Gustave Roussy, Paris, France; [8]SARC, Ann Arbor, MI, USA; [9]MD Anderson, Houston, TX, USA; [10]University of Michigan, Ann Arbor, MI, USA

Paper 036 3035962

SLFN11 IS A SIGNIFICANT DETERMINANT OF PARP INHIBITOR SENSITIVITY IN PEDIATRIC SARCOMAS

Jessica Gartrell*; Marcia M. Mellado-Largarde; Jia Xie; Brandon Bianski; Kaley Blankenship; Michael Clay; Armita Bahrami; Sara Federico; Christopher L. Tinkle; Elizabeth Stewart; Anang Shelat*

St. Jude Children's Research Hospital, Memphis, TN, USA

Paper 037 3027426

INNOVATIVE TARGETED THERAPY FOR EWING SARCOMA

Shunya Ohmura[1]*; Martin F. Orth*[1]*; Aruna Marchetto*[1]*; Stefanie Stein*[1]*; Julia S. Gerke*[1]*; Giuseppina Sannino*[1]*; Julian Musa*[1]*; Fabienne Wehweck*[1]*; Maximilian M. Knott*[1]*; Jing Li*[1]*; Tilman Hölting*[1]*; Laura Romero-Pérez*[1]*; Florencia Cidre-Aranaz*[1]*; Horacio Bach*[2]*; Wolfgang Hartmann*[3]*; Uta Dirksen*[4]*; Thomas Kirchner*[5]*; Thomas G. Grünewald*[6]

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Discussion – *Stephen Lessnick*

7:00 pm - 10:00 pm **Gala – Reception and Dinner at the beautiful Villa Miani next door to the Cavalieri Hotel. Cocktail Attire** *Villa Miani*

Saturday, 17 November, 2018

6:30 am - 5:30 pm	Registration	*Salon de Cavalieri 1 & Gallery*
7:00 am - 8:00 am	**Coffee and Posters**	*Salon de Cavalieri 1 & Gallery*
8:00 am - 9:00 am	– POSTER DISCUSSION – Abstracts within Poster Abstract Section	*Salon del Cavalieri 2,3,4*

Circulating Tumor DNA – *Brian Crompton*

Poster 127 3042631

PILOT STUDY EVALUATING THE CONCORDANCE OF CIRCULATING TUMOR DNA ALTERATIONS WITH TUMOR-BASED SEQUENCING IN SOFT TISSUE SARCOMA

Bryce Demoret[1]; Sherri Z. Millis[2]; Gabriel Tinoco[1]; David Liebner[1]; ***James L. Chen***[1]

[1]The Ohio State University, Columbus, OH, USA; [2]Foundation Medicine, Cambridge, MA, USA

Poster 128 3042674

CIRCSARC; NON-INVASIVE MONITORING OF SARCOMAS PATIENTS BY CIRCULATING TUMOUR DNA IN PLASMA

Heidi M. Namløs[1]; Seyed Hossein Moosavi[1]; Bodil Bjerkehagen[2]; Olga Zaikova[3]; Susanne Lorenz[4]; Lars Aasheim[4]; Eivind Hovig[1]; Nina L. Jebsen[5]; Ola Myklebost[6]; Boye Kjetil[7]; ***Leonardo A. Meza-Zepeda***[1]

[1]Department of Tumor Biology, Oslo University Hospital, Oslo, Norway; [2]Department of Pathology, Oslo University Hospital, Oslo, Norway; [3]Department of Surgery, Oslo University Hospital, Oslo, Norway; [4]Department of Core Facilities, Oslo University Hospital, Oslo, Norway; [5]Department of Oncology, Haukeland University Hospital, Bergen, Norway; [6]Department of Clinical Science, University of Bergen, Bergen, Norway; [7]Department of Oncology, Oslo University Hospital, Oslo, Norway

Poster 129 3042933

ULTRA-SENSITIVE DETECTION OF TRANSLOCATIONS IN THE CELL-FREE DNA OF PEDIATRIC SARCOMA PATIENTS

Avanthi T. Shah[1]*; Tej Azad[2]; Jake Chabon[3]; Stan Leung[1]; Aviv Spillinger[1]; Heng-Yi Liu[1]; Marcus Breese[1]; Maximilian Diehn[3]; Ash A. Alizadeh[3]; Alejandro Sweet-Cordero[1]*

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Poster 130 3043078

NONINVASIVE MOLECULAR PROFILING AND RESPONSE MONITORING BY CELL-FREE DNA ANALYSIS IN OSTEOSARCOMA

Emily Slotkin[1]*; Julie Yang[2]; Dana Tsui[2]*

[1]Pediatrics, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]Memorial Sloan Kettering Cancer Center, New York, NY, USA

Poster 132 3042854

TREATMENT MONITORING IN PATIENTS WITH PEDIATRIC SARCOMAS USING CIRCULATING \ TUMOR DNA ANALYSIS: A FEASIBILITY STUDY

Jun Zhao[1]*; Braden McDonald[2]; Tania Contente-Cuomo[2]; Ahuva Odenheimer[2]; Michelina de la Maza[1]; Pooja Hingorani[1]; Muhammed Murtaza[2]*

[1]Pediatric Hematology/Oncology, Phoenix Children's Hospital, Phoenix, AZ, USA; [2]Center for Non-invasive Diagnostics, Translational Genomics Research Institute, Phoenix, AZ, USA

Geonomics – *Roberta Maestro*

Poster 182 3042599

DISCOVERY AND CHARACTERIZATION OF RECURRENT, TARGETABLE ALK FUSIONS IN LEIOMYOSARCOMA

Lara E. Davis[1]*; Kevin Nusser*[1]*; Joanna Przybyl*[2]*; Janet Pittsenbarger*[1]*; Nicolle Hofmann*[1]*; Sushama Varma*[2]*; Sujay Vennam*[2]*; Maria Debiec-Rychter*[3]*; Matt van de Rijn*[2]*; Monika Davare*[1]
[1]Oregon Health & Science University, Portland, OR, USA; [2]Stanford University, Stanford, CA, USA; [3]KU Leuven, Leuven, Belgium

Poster 183 3014793

GENOME INFORMED THERAPY FOR OSTEOSARCOMA

Leanne Sayles[1]*; Marcus Breese*[1]*; Amanda Koehne*[1]*; Stan Leung*[1]*; Avanthi T. Shah*[1]*; Sheri Spunt*[2]*; Steven DuBois*[4]*; Douglas Hawkins*[3]*;* ***Alejandro Sweet-Cordero***[1]
[1]Pediatrics, University of California San Francisco, San Francisco, CA, USA; [2]Pediatrics, Stanford University, San Francisco, CA, USA; [3]Pediatrics, University of Washington, Seattle, WA, USA; [4]Pediatrics, Dana Farber Cancer Institute, Boston, MA, USA

Poster 185 3042669

COMPREHENSIVE GENOMIC PROFILING OF SYNOVIAL SARCOMAS IDENTIFIES GENOMICALLY DEFINED SUBGROUPS WITH CHARACTERISTIC ALTERATION PATTERNS

Sherri Z. Millis[1]*; Peter Vorenkamp*[3]*; Petra Vorenkamp*[3]*; Jeffrey Ross*[1]*; Siraj Ali*[1]*; Sally Trabucco*[1]*; James L. Chen*[2]
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Poster 186 3042566

THE FUSION LANDSCAPE AND ACTIONABLE ALTERATIONS OF SARCOMA REVEALED BY "REAL WORLD" GENOMIC SEQUENCING

Jason Roszik[1]*; Anthony P. Conley*[1]*; Roman Groisberg*[1]*; Roberto Carmagnani Pestana*[1]*; Shiraj Sen*[1]*; Vivek Subbiah*[1]
[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Poster 188 3042711

UTILITY OF FOUNDATIONONE HEME PROFILING IN SARCOMA: INSTITUTIONAL EXPERIENCE AND CLINICAL OUTCOMES

Adrienne Victor[1]*; Deepak Sahasrabudhe*[1]*; Megan Baumgart*[1]
[1]Medical Oncology, University of Rochester, Rochester, NY, USA

Immunotherapy – *Sandra D'Angelo*

Poster 216 3014823

NEOADJUVANT THERAPY INDUCES A POTENT INFLAMMATORY AND CORRESPONDING REGULATORY RESPONSE WITHIN THE SARCOMA IMMUNE MICROENVIRONMENT

Teresa Kim[1]*; Matthew Spraker*[3]*; Y. David Seo*[1]*; Kimberly Smythe*[2]*; Robert Pierce*[2]*; Taylor Hain*[2]*; Edward Y. Kim*[3]*; Gabrielle Kane*[3]*; Isaac Jenkins*[5]*; Qianchuan (Chad) He*[4]*; Seth Pollack*[2]
[1]Surgery, University of Washington, Seattle, WA, USA; [2]Clinical Research Division, Immunology, Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [3]Radiation Oncology, University of Washington, Seattle, WA, USA; [4]Biostatistics Program, Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [5]Clinical Biostatistics, Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA, USA

Poster 229 3042851

RESPONSE TO SUBSEQUENT THERAPY IN NY-ESO-1 POSITIVE SOFT TISSUE SARCOMA PATIENTS TREATED WITH CMB305 THERAPY

Sant P. Chawla[1]; *Seth Pollack*[2]; *Matthew Block*[7]; *Mihaela Druta*[3]; *Khanh Do*[4]; *John C. Morris*[5]; *Joseph W. Kim*[6]; *Chet Bohac*[8]; *Hailing Lu*[9]; *Sacha Gnjatic*[10]; *Robin L. Jones*[11]; *P. Hwu*[12]; *Neeta Somaiah*[13]
[1]*Medical Oncology, Sarcoma Oncology Center, Santa Monica, CA, USA;* [2]*Medical Oncology, Fred Hutchinson Cancer Center, Seattle, WA, USA;* [3]*Medical Oncology, Moffitt Cancer Center, Tampa, FL, USA;* [4]*Medical Oncology, Dana Farber Cancer Institute, Boston, MA, USA;* [5]*Medical Oncology, University of Cincinnati, Cincinnati, OH, USA;* [6]*Medical Oncology, Yale University, New Haven, CT, USA;* [7]*Medical Oncology, Mayo clinic, Rochester, MN, USA;* [8]*Clinical Development, Immune Design, South San Francisco, CA, USA;* [9]*Science, Immune Design, Seattle, WA, USA;* [10]*Immunology, Mt. Sinai, New York City, NY, USA;* [11]*Medical Oncology, Royal Marsden, London, United Kingdom;* [12]*Medical Oncology, MD Anderson Cancer Center, Houston, TX, USA;* [13]*Medical Oncology, MD Anderson Cancer Center, Houston, TX, USA*

Poster 230 3042145

IMMUNE RESPONSE, SAFETY, AND OVERALL SURVIVAL OF NY-ESO-1+ SOFT TISSUE SARCOMA PATIENTS TREATED WITH CMB305 THERAPY

Sant P. Chawla[1]; ***Seth Pollack***[2]; *Matthew Block*[11]; *Mihaela Druta*[3]; *Khanh Do*[4]; *John C. Morris*[5]; *Joseph W. Kim*[6]; *Chet Bohac*[7]; *Hailing Lu*[7]; *Sacha Gnjatic*[8]; *R. L. Jones*[9]; *P. Hwu*[10]; *Neeta Somaiah*[10]
[1]*Medical Oncology, Sarcoma Oncology Center, Santa Monica, CA, USA;* [2]*Medical Oncology, Fred Hutchinson Cancer Center, Seattle, WA, USA;* [3]*Medical Oncology, Moffitt Cancer Center, Tampa, FL, USA;* [4]*Medical Oncology, Dana Farber Cancer Institute, Boston, MA, USA;* [5]*Medical Oncology, University of Cincinnati, Cincinnati, OH, USA;* [6]*Medical Oncology, Yale University, New Haven, CT, USA;* [7]*Science, Immune Design, Seattle, WA, USA;* [8]*Immunology, Mt. Sinai, New York City, NY, USA;* [9]*Medical Oncology, Royal Marsden Hospital NHS Foundation Trust, London, United Kingdom;* [10]*Medical Oncology, MD Anderson Cancer Center, Houston, TX, USA;* [11]*Medical Oncology, Mayo Clinic, Rochester, MN, USA*

Poster 238 3042673

ACTIVITY OF TREMELIMUMAB AND DURVALUMAB IN ADVANCED SARCOMAS: PRELIMINARY RESULTS OF A SIGNAL-SEEKING PHASE 2 TRIAL

Maya Kansara[1]; *Subotheni Thavaneswaran*[1]; *John Grady*[1]; *Mark Cowley*[1]; *Audrey Silvestri*[1]; *Mandy L. Ballinger*[1]; *Elektra Hajdu*[1]; *Emily Collignon*[1]; *Lucille Sebastian*[2]; *Katrin Sjoquist*[2]; *Wendy Hague*[2]; *Amy Prawira*[1]; *Anthony Joshua*[1]; *Charles Bailey*[3]; *Ulf Schmitz*[3]; *Trevor Pugh*[4]; *Torsten O. Nielsen*[5]; *Amanda R. Dancsok*[5]; *Chee Lee*[2]; *John Simes*[3]; *David M. Thomas*[1]
[1]*Cancer Genomic Medicine, Garvan Institute, Sydney, NSW, Australia;* [2]*NHMRC Clinical Trials Centre, Sydney, NSW, Australia;* [3]*Gene and Stem Cell Therapy Program, Centenary Institute, Sydney, NSW, Australia;* [4]*Department of Medical Biophysics, University of Toronto, Toronto, ON, Canada;* [5]*Vancouver Coastal Health Research Institute and Faculty of Medicine, Department of Pathology and Laboratory Medicine, Vancouver, BC, Canada*

Poster 240 3042810

INTERFERON GAMMA MAKES "COLD" SYNOVIAL SARCOMA AND MYXOID/ROUND CELL LIPOSARCOMA "HOT": RESULTS OF A PHASE 0 TRIAL

Shihong Zhang[1]; *Venu Pillarisetty*[2]; *Lee D. Cranmer*[1]; *Stanley Riddell*[1]; *R. L. Jones*[3]; ***Seth Pollack***[1]
[1]*Fred Hutchinson Cancer Research Center, Seattle, WA, USA;* [2]*Surgery, University of Washington, Seattle, WA, USA;* [3]*Royal Marsden Hospital, London, United Kingdom*

Vascular Tumors – *Silvia Stacchiotti*

Poster 002 3042315

PITFALLS IN ANGIOSARCOMA DIAGNOSIS: LESSONS LEARNED FROM CENTRAL REVIEW OF 657 DUTCH CASES

Marije Weidema[1]*; Melissa Hillebrandt-Roeffen*[1]*; Ingrid Desar*[1]*; Yvonne Versleijen-Jonkers*[1]*; Winette van der Graaf*[1]*; Uta Flucke*[2]

[1]*Medical Oncology, Radboud University Medical Center, Nijmegen, Netherlands;* [2]*Pathology, Radboud University Medical Center, Nijmegen, Netherlands*

Poster 005 3037976

THE ANGIOSARCOMA PROJECT: GENERATING THE GENOMIC LANDSCAPE OF A RARE SARCOMA THROUGH A NATIONWIDE PATIENT-DRIVEN INITIATIVE

Michael Dunphy[1]*; Esha Jain*[1]*; Elana Anastasio*[1]*; Mary McGillicuddy*[1]*; Rachel Stoddard*[1]*; Beena Thomas*[1]*; Sara Balch*[1]*; Kristin Anderka*[2]*; Katie Larkin*[2]*; Niall Lennon*[2]*; Yen-Lin E. Chen*[3]*; Andrew Zimmer*[4]*; Esme O. Baker*[4]*; Simone Maiwald*[4]*; Jen Lapan*[4]*; Jason L. Hornick*[5]*; Chandrajit Raut*[5]*; George Demetri*[6]*; Eric S. Lander*[7]*; Todd Golub*[1]*; Nikhil Wagle*[6]*;* ***Corrie Painter***[1]

[1]*Cancer Program, Broad Institute of MIT and Harvard, Cambridge, MA, USA;* [2]*Genomics Platform, Broad Institute of MIT and Harvard, Cambridge, MA, USA;* [3]*Massachusetts General Hospital, Boston, MA, USA;* [4]*Data Sciences Platform, Broad Institute of MIT and Harvard, Cambridge, MA, USA;* [5]*Brigham and Women's Hospital, Boston, MA, USA;* [6]*Dana-Farber Cancer Institute, Cambridge, MA, USA;* [7]*Broad Institute of MIT and Harvard, Cambridge, MA, USA*

Poster 006 3042503

A RETROSPECTIVE REVIEW OF PATIENTS WITH ANGIOSARCOMA TREATED IN BRITISH COLUMBIA

Alannah Smrke[1]*; Jeremy Hamm*[1]*; Anand Karvat*[1]*; Christine Simmons*[1]*; Amirrtha Srikanthan*[1]

[1]*BC Cancer , Vancouver, BC, Canada*

Poster 008 3042562

NEOADJUVANT CHEMOTHERAPY ASSOCIATED WITH ENHANCED LOCAL CONTROL IN RADIATION-INDUCED ANGIOSARCOMA OF BREAST AND CHEST

Audrey Michot[1]*; Marie Karanian*[2]*; Maryck Lae*[11]*; Romuald Wernert*[3]*; Marie-Pierre Sunyach*[4]*; Dimitri Tzanis*[5]*; Jean-Marie Guilloit*[6]*; Maria Rios*[7]*; Antoine Giraud*[8]*; François Le Loarer*[9]*; Jean-Yves Blay*[10]*; Eberhard Stoeckle*[1]

[1]*Surgery, Institut Bergonié, Bordeaux, France;* [2]*Pathology, Leon Berard, Lyon, France;* [3]*Surgery, Institut de Cancerologie de l'Ouest, Angers, France;* [4]*Radiotherapy, Centre Leon Berard, Lyon, France;* [5]*Surgery, Institut Curie, Paris, France;* [6]*Surgery, Centre Francois Baclesse, Caen, France;* [7]*Medical Oncology, Institut de Cancerologie de Lorraine, Nancy, France;* [8]*Epidemiology and Clinical Research Unit, Institut Bergonié, Bordeaux, France; 9. Pathology, Institut Bergonié, Bordeaux, France;* [10]*Medical Oncology, Centre Leon Berard, Lyon, France;* [11]*Pathology, Institut Curie, Paris, France*

9:00 am - 10:30 am — – SESSION 7 – — *Salon del Cavalieri 2,3,4*

Osteosarcoma/Chondrosarcoma/Chordoma

Moderators: **Vicki Keedy** and **Kirsten Sundby Hall**

Paper 038 — 3042790

STRESS MEDIATED TRANSLATIONAL CONTROL OF CHILDHOOD BONE SARCOMA METASTASIS

*Amal M. EL-Naggar[1]; Syam Somasekharan[2]; Hongwei Cheng[2]; Gian Luca Negri[3]; Didier Surdez[4]; Olivier Delattre[4]; **Poul H. Sorensen**[1]*
[1]Molecular Oncology, BC Cancer & University of British Columbia , Vancouver, BC, Canada; [2]Vancouver Prostate Centre, Vancouver, BC, Canada; [3]Canada's Michael Smith Genome Sciences Centre, Vancouver, BC, Canada; [4]Centre de recherche de l'Institut Curie, Paris, France

Paper 039 — 3035462

PROSPECTIVE PHASE II STUDY OF SCANNED BEAM PROTON THERAPY FOR SPINE SARCOMAS

***David J. Konieczkowski**[1]; Yen-Lin E. Chen[1]; Karen De Amorim Bernstein[1]; Beow Yeap[2]; Matthew DiMaria[3]; Wenquin Jiang[2]; Nannette Thomas[1]; Suzanne L. McGovern[4]; John T. Mullen[5]; Joseph H. Schwab[6]; Francis Hornicek[7]; Thomas F. DeLaney[1]*
[1]Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA, USA; [2]Biostatistics Center, Massachusetts General Hospital, Boston, MA, USA; [3]Cancer Center Protocol Office, Massachusetts General Hospital, Boston, MA, USA; [4]Department of Radiation Oncology, MD Anderson Cancer Center, Houston, TX, USA; [5]Department of Surgical Oncology, Massachusetts General Hospital, Boston, MA, USA; [6]Department of Orthopaedic Surgery, Massachusetts General Hospital, Boston, MA, USA; [7]Department of Orthopedic Surgery, University of California Los Angeles, Los Angeles, MA, USA

Paper 040 — 2993960

APATINIB FOR ADVANCED OSTEOSARCOMA AFTER FAILURE OF STANDARD MULTIMODAL THERAPY: AN OPEN LABEL PHASE 2 CLINICAL TRIAL(NCT02711007)

***Lu Xie**; Jie Xu; Xin Sun; Xiaodong Tang; Taiqiang Yan; Rongli Yang; Wei Guo*
Musculoskeletal Tumor Center, Peking University People's Hospital, Beijing, China

Paper 041 — 3042511

SARC024: REGORAFENIB IN PATIENTS WITH REFRACTORY OSTEOSARCOMA

***Lara E. Davis**[1]; Christopher Ryan[1]; John Crowley[2]; Kristen Ganjoo[3]; Elizabeth Loggers[4]; Sant P. Chawla[5]; Mark Agulnik[6]; Michael B. Livingston[7]; Damon Reed[8]; Vicki Keedy[9]; Daniel A. Rushing[10]; Scott Okuno[11]; Denise Reinke[12]; Richard F. Riedel[13]; Steven Attia[14]; Leo Mascarenhas[15]; Robert Maki[16]*
[1]Oregon Health and Science University, Portland, OR, USA; [2]Cancer Research and Biostatistics, Seattle, WA, USA; [3]Stanford Cancer Institute, Stanford, CA, USA; [4]Seattle Cancer Care Alliance, Seattle, WA, USA; [5]Sarcoma Oncology Research Center, Santa Monica, CA, USA; [6]Northwestern University Feinberg School of Medicine, Chicago, IL, USA; [7]Levine Cancer Institute, Atrium Health, Charlotte, NC, USA; [8]H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA; [9]Vanderbilt University Medical Center, Nashville, TN, USA; [10]Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN, USA; [11]Mayo Clinic, Rochester, MN, USA; [12]SARC, Ann Arbor, MI, USA; [13]Duke University Medical Center, Durham, NC, USA; [14]Mayo Clinic, Jacksonville, FL, USA; [15]Children's Center for Cancer and Blood Diseases, Children's Hospital Los Angeles, Univ. of Southern California, Los Angeles, CA, USA; [16]Monter Cancer Center, Northwell Health and Cold Spring Harbor Laboratory, Lake Success, NY, USA

Paper 042 3042857

CABOZANTINIB IN PATIENTS WITH ADVANCED OSTEOSARCOMAS AND EWING SARCOMAS: A FRENCH SARCOMA GROUP (FSG)/ US NATIONAL CANCER INSTITUTE PHASE II COLLABORATIVE STUDY

Antoine Italiano[1]*; Nicolas Penel*[2]*; Emmanuelle Bompas*[3]*; Sophie Piperno-Neumann*[4]*; Marina Pulido*[1]*; Natacha Entz-Werle*[5]*; Axel Le Cesne*[6]*; Christine Chevreau*[7]*; Florence Duffaud*[8]*; Isabelle Ray-Coquard*[9]*; Maud Toulmonde*[1]*; Carine Bellera*[1]*; Jean-Yves Blay*[9]

[1]*Institut Bergonié, Bordeaux, France;* [2]*Centre Oscar Lambret, Lille, France;* [3]*Institut Cancerologie de l'Ouest, Nantes, France;* [4]*Institut Curie, Paris, France;* [5]*CHU de Strasbourg, Strasbourg, France;* [6]*Institut Gustave Roussy, Villejuif, France;* [7]*Oncopole Toulouse, Toulouse, France;* [8]*APHM Marseille, Marseille, France;* [9]*Centre Leon Berard, Lyon, France*

Discussion – *Katherine Janeway*

10:30 am - 11:00 am **Morning Coffee Break** *Salon de Cavalieri 1 & Gallery*

11:00 am - 12:00 pm – NINA AXELRAD LECTURE – *Salon del Cavalieri 2,3,4*

Academic Clinical Trials in Sarcomas at the Time of Genomic Revolution

Jean-Yves Blay

(Centre Léon BERARD Lyon, France)

12:00 pm - 1:00 pm **Lunch** *Belle Arti & Garden Lobby*

1:00 pm - 1:30 pm *Salon del Cavalieri 2,3,4*

Liddy Shriver Early Career Research Award

Cigall Kadoch

1:30 pm - 3:30 pm – SESSION 8 – *Salon del Cavalieri 2,3,4*

Soft Tissue Sarcoma: Biology

Moderators: **Torsten Nielsen** and **Poul Sorensen**

Paper 043 3042288

WHOLE GENOME SEQUENCING OF 1,111 SARCOMA PROBANDS REVEALS POT-1 AS A SARCOMA PREDISPOSITION GENE

Mandy L. Ballinger[1]*; Mark Pinese*[1]*; Emma Rath*[1]*; Paul James*[2]*; Ajay Puri*[3]*; Nicolas Isambert*[4]*; Martin Tattersall*[5]*; Beatrice Seddon*[6]*; Ian Judson*[7]*; Winette van der Graaf*[7]*; Nicolas Penel*[8]*; Axel Lecesne*[9]*; Coonoor Chandrasekar*[10]*; Jean-Emmanuel Kurtz*[11]*; Joshua Schiffman*[12]*; R. Lor Randall*[12]*; Florence Duffaud*[13]*; Jin-Hee Ahn*[14]*; Rory Rickard*[15]*; Jean-Yves Blay*[16]*; Isabelle Ray-Coquard*[16]*; David M. Thomas*[1]

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Paper 044 3042786

SEQCOMPLEX UNRAVELLING OMICS LANDSCAPE AND TARGETING ONCOGENIC PATHWAYS IN UNDIFFERENTIATED PLEOMORPHIC SARCOMAS - AN INTEGRATED APPROACH

Maud Toulmonde[1]*; Damien Geneste*[1]*; Stephanie Verbeke*[1]*; Julien Adam*[2]*; Fabiola Cecchi*[3]*; Banafshe Larijani*[4]*; Francois Bertucci*[6]*; Florent Petitprez*[5]*; Audrey Laroche*[1]*; Carlo Lucchesi*[1]*; Antoine Italiano*[1]*; Todd Hembrough*[3]

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Paper 045 3010210

RATIONALES FOR TARGETING/CO-TARGETING LEIOMYOSARCOMA PATHWAYS: BIOLOGIC PROFILES IN 712 UTERINE OR SOFT-TISSUE LMS

Inga-Marie Schaefer[1]*; Elizabeth G. Demicco*[2]*; Magdalena Matusiak*[3]*; Sebastian Bauer*[4]*; Frédéric Chibon*[5]*; Davis Ingram*[6]*; Jason L. Hornick*[1]*; Wei-Lien Wang*[6]*; Alexander J. Lazar*[6]*; Matt van de Rijn*[3]*; Jonathan A. Fletcher*[1]

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Paper 046 3042897

CHROMATIN STATE TRANSITIONS ASSOCIATED WITH PRC2 FUNCTIONAL LOSS DRIVE A DE-DIFFERENTIATED PHENOTYPE IN MALIGNANT PERIPHERAL NERVE SHEATH TUMORS

Veena Kochat[1]*; Ayush Raman*[2]*; Sharon Landers*[1]*; Christopher Terranova*[2]*; Chia-Chin Wu*[2]*; Xizeng Mao*[2]*; Davis Ingram*[3]*; Zachary Mulder*[1]*; Michelle Yeagley*[1]*; Hannah Beird*[2]*; Angela Bhalla*[1]*; John Slopis*[4]*; Ian McCutcheon*[5]*; Jianhua Zhang*[2]*; Phillip Futreal*[2]*; Wei-Lien Wang*[3]*; Alexander J. Lazar*[3]*; Kunal Rai*[2]*; Kiela E. Torres*[1]

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Paper 047 3042069

TWIST BRIDGES P53 AND MDM2 AND REDUCES THE EFFICACY OF MDM2 INHIBITORS

Sara Piccinin[1]*; Elena Doriguzzi Breatta*[1]*; Sara Lombardi*[1]*; Mattia Lombardi*[1]*; Flavia Pivetta*[1]*; Michela Armellin*[1]*; Camillo Rosano*[2]*;* ***Roberta Maestro***[1]

[1]CRO Aviano, Aviano, Italy; [2]San Martino National Cancer Institute, Genova, Italy

Discussion – *Judith Bovee*

3:30 pm - 4:00 pm **Afternoon Coffee Break** *Salon de Cavalieri 1 & Gallery*

4:00 pm - 5:30 pm | – SESSION 9 – | *Salon del Cavalieri 2,3,4*

Soft Tissue Sarcoma: Local Therapy

Moderators: **Kenneth Cardona** and **Alessandro Gronchi**

Paper 048 3042386

LONG-TERM COMPARISON OF LOCAL RECURRENCE AFTER CONVENTIONAL AND INTENSITY-MODULATED RADIATION THERAPY FOR PRIMARY SOFT TISSUE SARCOMAS OF THE EXTREMITY

Joanna C. Yang[1]*; Michael Folkert*[2]*; Aimee M. Crago*[3]*; Sam S. Yoon*[3]*; Sam Singer*[3]*; Kaled Alektiar*[1]
[1]*Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA;* [2]*Radiation Oncology, UT Southwestern Medical Center, Dallas, TX, USA;* [3]*Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA*

Paper 049 3028760

CAN WE CURE PATIENTS WITH ABDOMINAL DESMOPLASTIC SMALL ROUND CELL TUMOR? RESULTS OF A RETROSPECTIVE MULTICENTRIC STUDY ON 100 PATIENTS

Charles Honoré[1]*; Jean-Baptiste Delhorme*[2]*; Elise Nassif*[3]*; Gwenael Ferron*[4]*; Emmanuelle Bompas*[5]*; Olivier Glehen*[6]*; Antoine Italiano*[7]*; Francois Bertucci*[8]*; Daniel Orbach*[9]*; Axel Le Cesne*[3]*; Jean-Yves Blay*[10]*; Christine Chevreau*[11]*; Olivier Mir*[3]
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Paper 050 3027816

ENHANCED RECOVERY AFTER SURGERY (ERAS) IN PATIENTS UNDERGOING SURGERY FOR SOFT TISSUE SARCOMA (STS): EARLY RESULTS OF A PROSPECTIVE QUALITY IMPROVEMENT PROTOCOL

Heather Lyu[1]*; Lily V. Saadat*[1]*; Elizabeth H. Baldini*[2]*; Jiping Wang*[1]*; Matthias Stopfkuchen-Evans*[1]*; Ronald Bleday*[1]*; Monica Bertagnolli*[1]*; Chandrajit Raut*[1]
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Paper 051 3042593

DEVELOPMENT OF A DYNAMIC PROGNOSTIC NOMOGRAM TO PREDICT OVERALL SURVIVAL DURING FOLLOW-UP IN PRIMARY EXTREMITY SOFT TISSUE SARCOMA PATIENTS TREATED WITH SURGERY

Dario Callegaro[1]*; Rosalba Miceli*[2]*; Sylvie Bonvalot*[3]*; Peter Ferguson*[4]*; Dirk Strauss*[5]*; Antonin Levy*[6]*; Anthony M. Griffin*[4]*; Andrew J. Hayes*[5]*; Silvia Stacchiotti*[7]*; Cécile Le Péchoux*[6]*; Myles J. Smith*[5]*; Marco Fiore*[1]*; Angelo Paolo Dei Tos*[8]*; Henry Smith*[5]*; Charles Catton*[9]*; Paolo Casali*[10]*; Jay Wunder*[4]*; Alessandro Gronchi*[1]
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Paper 052 3042509

THE IMPACT OF UNPLANNED EXCISIONS OF SOFT TISSUE SARCOMAS: A MULTI-INSTITUTIONAL PROPENSITY SCORE ANALYSIS FROM THE US-SARCOMA COLLABORATIVE

Mohammad Zaidi[1]; *Cecilia G. Ethun*[1]; *Yuan Liu*[2]; *Thuy B. Tran*[3]; *George Poultsides*[3]; *Valerie P. Grignol*[4]; *J. H. Howard*[4]; *Meena Bedi*[5]; *Harveshp Mogal*[6]; *Jennifer Tseng*[7]; *Kevin K. Roggin*[7]; *Konstantinos Chouliaras*[8]; *Konstantinos Votanopoulos*[8]; *Darren Cullinan*[9]; *Ryan C. Fields*[9]; *Shervin Oskouei*[1]; *Nickolas Reimer*[1]; *David Monson*[1]; *Kenneth Cardona*[1]

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Discussion – *Rebecca Gladdy*

5:30 pm - 6:00 pm **CTOS Business Meeting** *Salon del Cavalieri 2,3,4*

11:30 am – 1:00 pm
– SESSION 1 –
Sarcoma of the Year: Intimal Sarcoma

Paper 001 3042623

SYSTEMIC TREATMENTS IN MDM2 + INTIMAL SARCOMA: A MULTICENTRE EXPERIENCE WITH ANTHRACYCLINE, GEMCITABINE AND PAZOPANIB WITHIN THE WORLD SARCOMA NETWORK (WSN)

Anna Maria Frezza[1]*; Tarek Assi*[2]*; Luigi Mariani*[3]*; Armelle Dufresne*[4]*; Siontis Brittany*[5]*; Kan Yonemori*[6]*; Emi Noguchi*[6]*; Eytan Ben-Amy*[7]*; Mrinal Gounder*[8]*; Robin Jones*[9]*; Pawel Teterycz*[10]*; Florence Duffaud*[12]*; Maria Abbondanza Pantaleo*[11]*; Vinod Ravi*[13]*; Bruno Vincenzi*[14]*; Giacomo Giulio Baldi*[15]*; Alexander Fedenko*[16]*; Hans Gelderblom*[17]*; Robert Maki*[18]*; Jean-Yves Blay*[4]*; Axel Le Cesne*[2]*; Scott Schuetze*[5]*; Paolo Casali*[1]*; Katherine Thornton*[7]*; Silvia Stacchiotti*[1]

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Objective: Intimal sarcoma (IS) is an exceedingly rare neoplasm, marked by *MDM2* and *CDK4* amplification, for which new potentially active treatments are under development. The outcome for IS patients (pts) is unfavourable, with a reported median survival of approximately one year. Data on the activity of currently available systemic therapies are limited. We report a multi-institution retrospective analysis on the activity of anthracycline-based and gemcitabine-based regimens as well as pazopanib in pts with IS treated across 16 sarcoma reference centres in Europe, US and Japan within the WSN.

Methods: Adult pts with a histologically confirmed diagnosis of MDM2+ IS treated with anthracycline-based, gemcitabine-based regimens and pazopanib were selected. Diagnoses were reviewed and confirmed by institutional sarcoma pathologists. MDM2 status was evaluated by immunohistochemistry or FISH. Response was assessed by RECIST 1.1. Progression-free survival (PFS), time to progression (TTP) and overall survival (OS) were computed by Kaplan-Meier method.

Results: Eighty-three pts with IS treated between Oct 2001 and May 2018 were retrospectively identified. MDM2 status was positive in 60 pts, under assessment in 23. The median age at diagnosis was 48 years (IQR: 35-59); 36 (43%) pts were males, 47 (57%) females. The primary sites were pulmonary artery (51; 61%), heart (27, 33%; left side 19, 70%; UKN 8, 30%) and other sites (5, 6%). Twenty-eight (34%) pts had localized disease treated with curative intent, 55 (66%) advanced disease treated with palliative intent (locally advanced: 15, 27%; metastatic: 40, 73%). Seventy-six (92%) received an anthracycline-based regimen, 29 (35%) gemcitabine-based regimens and 10 (12%) pazopanib; 20 (24%) pts received more than one treatment. The median follow up was 38.3 months (IQ range: 17-64). No toxic deaths were reported.

1. In the anthracycline group, 27 (36%) pts were treated for localized disease with a curative intent, 49 (64%) pts for advanced disease. Twenty-two (29%) treated with anthracyclines had cardiac IS., The median number of prior lines in this group was 0 (IQR 0-0). Fifty-seven (75%) pts over 76 were evaluable for response. Best response was complete response (CR) in 3 pts (5%), partial response (PR) in 18 (32%), stable disease (SD) in 27 (47%) and progressive disease (PD) in 9 (16%) (overall response rate, ORR = 37%). For pts with localized disease, the median TTP and OS were 14 (IQR: 9-35) and 51 (IQR: 33-136) months, respectively. For pts with advanced disease, the median PFS and OS were 8 (IQR: 4-17) and 22 (IQR: 9-62) months, respectively. The progression-free rate (PFR) at 12 months was 38%.
2. In the gemcitabine group, 2 (7%) pts were treated for localized disease with curative intent, 27 (93%) pts for advanced disease. The median number of prior lines in this group was 1 (IQR 1-1).Twenty-eight pts were

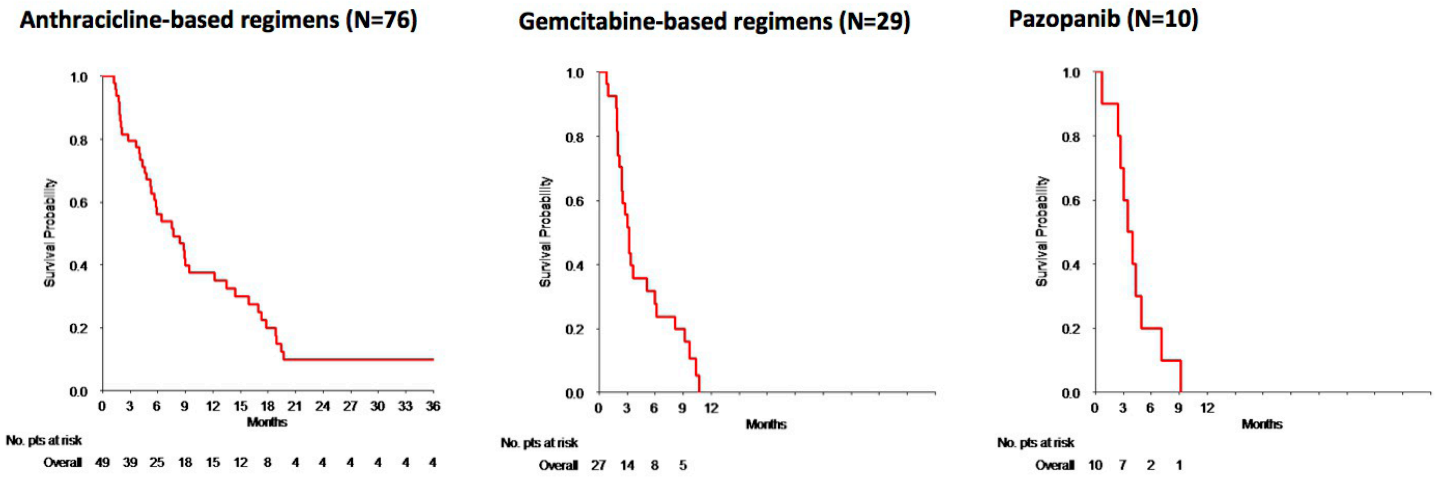
evaluable for response. Best response was PR in 3 (11%), SD in 8 (29%), PD in 17 (61%) (ORR = 11%). For pts with advanced disease, the median PFS and OS were 3 (IQR: 2-6) and 13 (IQR: 10-21) months respectively. 3. In the pazopanib group, all pts had advanced disease and were evaluable for response. Best response was PR in 1 (10%) pt, SD in 3 (30%), PD 6 (60%) (ORR = 10%). The median number of prior lines in this group was 2 (IQR 2-3).The median PFS and OS were 4 (IQR: 3-5) and 12 (IQR: 4-19) months respectively.

Conclusion: This retrospective series confirms the activity of anthracycline-based regimens in IS, with a 12-month PFR of 38%. Of note, anthracycline were used in 22 patients with cardiac IS, with no toxic deaths reported. The outcome with gemcitabine and pazopanib was less favourable, and they could be exploited as further-line therapies or in pts unfit for anthracycline. The prognosis in patients with IS remains poor and new active drugs are urgently needed, including MDM2/CDK4 inhibitors.

Table 1. Population characteristics.

	Anthracycline-based group (N= 76)	Gemcitabine-based group (N=29)	Pazopanib (N=10)
Median age (IQR)	47 years (35 – 58)	44 years (16 – 75)	49 years (38 – 55)
Gender (%) - M - F	- 35 (46%) 41 (54%)	- 14 (48%) 15 (52%)	- 4 (40%) 6 (60%)
Primary site (%) - Pulmonary artery - Heart Left heart - Other	- 49 (65%) 22 (29%) 18 (81%) 5 (6%)	- 19 (66%) 8 (28%) 6 (75%) 2 (7%)	- 7 (70%) 2 (20%) 2 (100%) 1 (10%)
Stage at treatment start (%) - Localized - Advanced	- 27 (36%) 49 (64%)	- 2 (7%) 27 (93%)	- 0 10 (100%)
Regimen used (%)	A: 25 (33%) AI/EI: 45 (59%) Other: 6 (8%)	G: 9 (31%) GD: 16 (55%) Other: 4 (14%)	-
Median number of prior lines (IQR)	0 (0 - 0)	1 (1 - 1)	2 (2 - 3)

A: adriamycin; AI: adriamycin and ifosfamide; EI: epirubicin and ifosfamide; G: gemcitabine; GD: gemcitabine and docetaxel.



Paper 002 3026957

PRIMARY MALIGNANT SARCOMAS OF THE HEART AND GREAT VESSELS: A RETROSPECTIVE ANALYSIS OF PRESENTATION, MANAGEMENT AND OUTCOMES

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Objective: Primary malignant sarcomas of the heart and great vessels are rare (<1% of all sarcomas) with a poor prognosis. These highly aggressive malignancies lead to progressive heart failure and death without treatment. Here, we review the presentation and management of these patients treated at a national centre for cardiothoracic surgery and its associated hospital in Cambridge, UK.

Methods: Medical records of patients diagnosed with sarcomas of the heart or great vessels at the Royal Papworth and Addenbrooke's Hospitals between 2000 and 2018 were reviewed.

Results: 28 patients were diagnosed with either pulmonary artery sarcoma (PAS; 20) or cardiac sarcoma (CS; 8) (14 males, 14 females); median age of presentation 49.5 years (range 18 to 77 years). CS tended to present at a younger age than PAS (median age of 26 vs 57 years, respectively). Presenting symptoms included breathlessness (24), chest pain/tightness (8), cough (6), peripheral oedema (6), constitutional symptoms (6), haemoptysis (3) and TIA (1). Cardiac function was often preserved: 16 had normal left ventricular ejection fraction (LVEF ≥ 55%), 10 had moderate impairment (LVEF ≥ 30%), and 1 had LVEF of <30%. Histological findings were intimal sarcoma (13), high-grade sarcoma NOS (9 – one had previous whole-body irradiation for childhood leukaemia), angiosarcoma (4, all CS), and synovial sarcoma (1 CS). Median overall survival (OS) was 17 months. 19 patients underwent surgery: 14 PAS patients had pulmonary endarterectomy and 4 CS patients underwent resection or maximal debulking of their tumours. There were three peri-operative deaths. The remaining 10 patients had metastatic and/or inoperable disease. Patients who underwent surgery had a better survival compared to those who did not (median OS of 20 vs 9 months, respectively; P = 0.0142). Nine patients received post-surgical chemotherapy, and after completion five also had radiotherapy. The 3 CS patients who had surgical resection with curative intent were treated with adjuvant ifosfamide-based chemotherapy (with close monitoring of fluid balance), and showed no evidence of disease on last follow-ups. One patient received post-operative paclitaxel following maximal debulking of a cardiac angiosarcoma. Post-surgical anthracycline ± ifosfamide were used in patients with PAS with no clinical cardiotoxicity. Although the median OS for patients who received post-operative chemo- and radio-therapy was greater than surgery alone (28 vs 9 months), the difference was not statistically significant (P = 0.2010). In the palliative setting, partial responses were observed with paclitaxel and anthracycline (including liposomal doxorubicin) in cardiac angiosarcoma. For PAS, partial responses were achieved with anthracycline ± ifosfamide for intimal sarcoma. Radiotherapy provided good locoregional control. The longest surviving PAS patient (103 months) has had pulmonary artery endarterectomy, followed by adjuvant epirubicin and radiotherapy. She developed lung metastases 7 years later, treated with radiofrequency ablation. The longest surviving CS patient (24 months) had surgery to resect a high-grade undifferentiated sarcoma (involved margins), followed by adjuvant ifosfamide and radiotherapy to the right atrium. He remains disease-free.

Conclusion: Cardiac and great vessel sarcomas often present with symptoms mimicking heart failure, pulmonary hypertension or thromboembolic disease. Patients who underwent surgical resection of their primary tumours have much longer survival than those who did not, although this may just be a reflection of the more advanced disease in inoperable patients. However, surgery still offers the best chance of long-term survival and can provide significant symptomatic relief. The use of adjuvant chemo- and radio-therapy was safe and may lead to better outcomes, but further studies are warranted. Active chemotherapy regimens in the palliative setting include paclitaxel (angiosarcoma) and anthracycline ± ifosfamide.

Paper 003 3042337

CLINICAL "REAL WORLD" NEXT GENERATION SEQUENCING REVEALS UNIQUE ABERRATIONS IN INTIMAL SARCOMA

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The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Objective: Intimal sarcomas are very rare sarcomas arising from the pulmonary artery. The genomics of intimal sarcoma are poorly elucidated. Identifying potentially targetable genomic alterations is a rational approach to improving treatment options. We sought to catalog these alterations in intimal sarcoma and assess their clinical utility.

Methods: We queried the AACR project Genomics Evidence Neoplasia Information Exchange (GENIE) database. The GENIE registry derives existing CLIA-/ISO-certified genomic data. We searched all published records in Pubmed/Medline for genomic data from several different platforms. Retrospective records were abstracted to appraise the benefit of using a targeted therapy approach in a large Phase 1 clinic.

Results: Among the 11 patients analyzed in AACR GENIE median age was 46 (range 26-76), 4 were males (36 %). Eight patients had sampling from the primary tumor and three pts had genomics from the metastatic site. Copy number alterations available for ten patients included amplifications in MDM2 (n=8), CDK pathway (n=5), PDGFRA gain (n=4) and CDKN2A copy number loss in three pts. Druggable mutations included ALK, ATM/ATR, PTCH1 and PDGFRB. Unique genomic rearrangement events included PDE4DIP-NOTCH2 and MRPS30-ARID2 fusions. Co-occurring alterations included a NOTCH2 copy number gain in the PDE4DIP-NOTCH2 fusion tumor, and PDGFRB mutations in both fusion-positive cases. A case of whole-exome sequencing (WES) and array-comparative genomic hybridization (aCGH) in an autopsy case of cardiac intimal sarcoma (Virchows Arch. 2017 Sep;471(3):423-428) identified concurrent *PDGFRα* amplification and *PDGFRβ* mutation in intimal sarcoma. There was no patient with intimal sarcoma among the 406 sarcoma pts enrolled on clinical trials. Intimal sarcomas were not eligible for any clinical trial given location of the tumors in major blood vessels.

Conclusion: Inclusion of genomic profiling to management of intimal sarcoma adds a potential line of therapy that have little or no standard of care. The somatic mutations and DNA copy number alterations in the PDGFR pathway relevant to the pathogenesis and potential targeted therapy of cardiac intimal sarcoma may be targeted by Imatinib or Olaratumab. Inclusion of such rare tumors in targeted therapy basket trials with a waiver for inclusion criteria is warranted.

Paper 004 3042847

OUTCOMES OF MULTIMODALITY TREATMENT WITH INDUCTION CHEMOTHERAPY, MAXIMAL RESECTION, AND PROTON BASED RADIATION THERAPY FOR CARDIAC AND PULMONARY VESSEL SARCOMAS

Yen-Lin E. Chen[1]*; Rouyu Miao*[1]*; Edwin Choy*[2]*; Gregory M. Cote*[2]*; Thomas F. DeLaney*[1]
[1]Radiation Oncology, Massachusetts General Hospital, Boston, MA, USA; [2]Hematology Oncology, Massachusetts General Hospital, Boston, MA, USA

Objective: Sarcomas arising from the pericardium, myocardium, valves, pulmonary veins or pulmonary arteries are extremely rare with limited experience on clinical outcomes. Median survival is reported to be 9 to 12 months in the literature with 2 year survival of 10-15%. We report the results of largest experience using multimodality therapy with proton based local therapy.

Methods: 38 patients with sarcomas arising from the pericardium, myocardium, valves, pulmonary veins, or pulmonary arteries were queried from an intitutional sarcoma data repository of 13,950 patients. Cliniopathologic, treatment, outcomes and toxicities were recorded. Kaplan Meier analysis and Cox proportional hazards regression were used to analyze survival outcomes and prognostic factors.

Results: 38 patients with pericardial, cardiac, or pulmonary vessel sarcoma were treated the the following characteristics: 12 female, 26 male; 15 < 40 and 23 >= 40 years old; including 9 UPS/MFH, 8 angiosarcoma, 4 spindle cell sarcoma, 4 sarcoma NOS, 3 leiomyosarcoma, 2 osteosarcoma, 2 Ewing sarcoma, and 1 each of chondrosarcoma, MPNST, rhabdomosarcoma, synovial sarcoma, and intimal sarcoma; 18 were <5 cm and 18 >= 5 cm; 34 N0 and 4 N+; 33 M0, and 5 M1 on presentation. 65% received induction and/or maintainence chemotherapy (adriamycin, ifosfamide, taxol being most common). 65% received RT. 33 underwent resection, of which 11 were R2, 3 R1, and 9 R0. The 1, 3, and 5 year oveall survival was 64%, 37%, and 28%. Median survival is 28 months. The 1, 3, and 5 years local failure free survival were 80%, 64%, and 52% respectively for patients receiving proton based RT to a median dose of 64.8 GyRBE (range 63-72 GyRBE, 3 with additional intraoperative electrons) versus 13%, 10%, 10% treated without RT (p=0.05). The 1, 3, and 5 year metastatic free survival were 25%, 14%, and 14%. Patients with tumors < 5 cm (p=0.036), age > 40 (p=0.028), surgical resection (p=0.011), and non-angiosarcoma histologies (p= 0.002) had better survival on Log Rank test.

Conclusion: Despite high metastasis rate, an aggressive strategy combining induction chemotherapy with maximally safe surgical resection, and high dose proton therapy, we report median survival double of that seen in the literature and long-term survivors. Patients able to receive high dose local therapy with protons and/or surgical resection, < 5 cm tumor, age > 40, and non-angiosarcoma appear to do best. A multidisciplinary approach to this extremely rare and complex sarcoma is recommended.

Paper 005 3042630

THE IMPACT OF CHEMOTHERAPY ON SURVIVAL OF PATIENTS WITH EXTREMITY AND TRUNK WALL SOFT TISSUE SARCOMA: REVISITING THE RESULTS OF THE EORTC-STBSG 62931 RANDOMISED TRIAL USING SARCULATOR, A VALIDATED NOMOGRAM-BASED RISK ASSESSMENT TOOL

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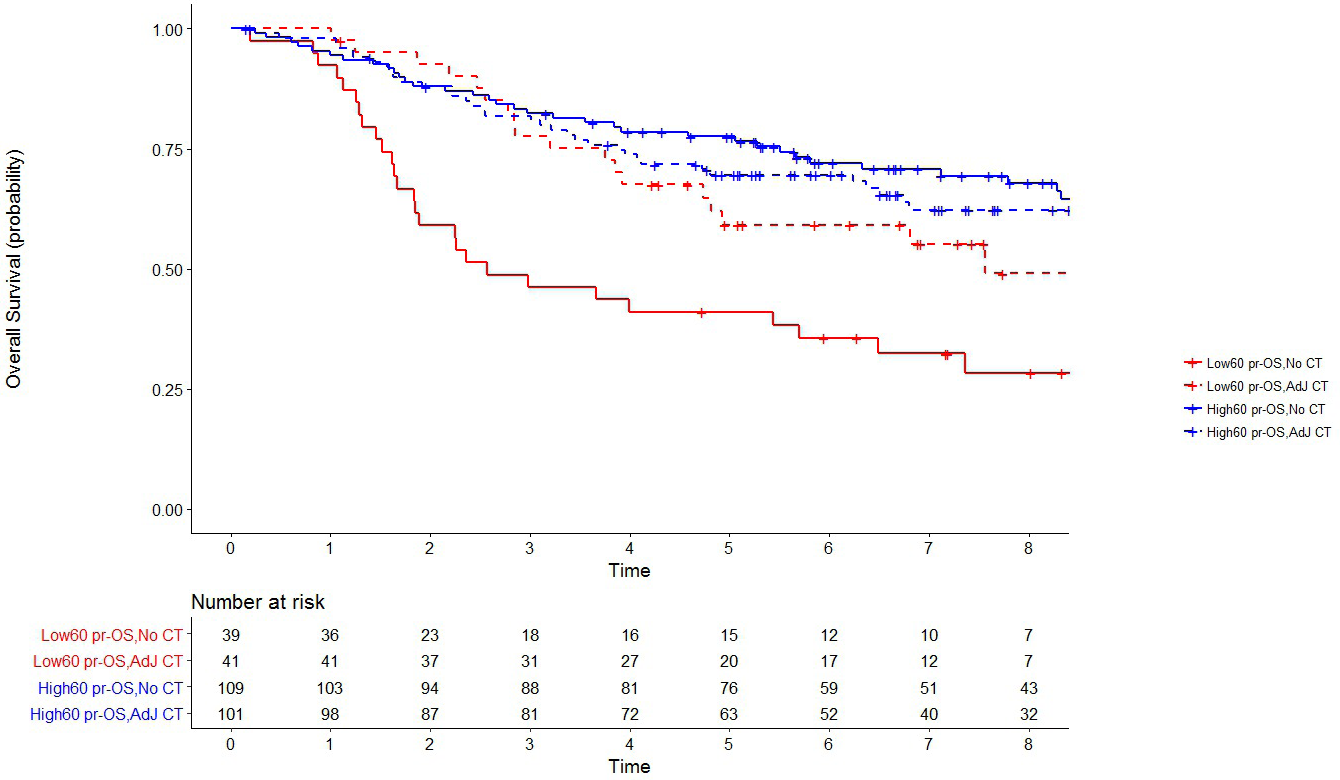
Objective: Conflicting results have been reported for perioperative chemotherapy for adult with high-risk soft tissue sarcoma (STS) in randomised controlled trials (RCT) conducted to date. Variations in treatment schedules that have been tested and inclusion of low-risk tumours may have diluted the effect of chemotherapy in these patients. This study sought to determine whether patients with high-risk STS as identified using the nomogram Sarculator (Lancet Oncol 2016;17:1045-54) did better when treated with adjuvant chemotherapy in the EORTC-STBSG 62931 RCT (Lancet Oncol 2012;13:1045-54), which failed to detect an impact for adjuvant doxorubicin plus ifosfamide over observation.

Methods: This was a retrospective analysis of the EORTC-STBSG 62931 RCT performed on individual data of enrolled patients with extremity and trunk wall STS. The prognostic nomogram Sarculator was used to calculate 10-year predicted probability of overall survival (pr-OS) for each patient. Patients were grouped in two categories of predicted pr-OS: high (pr-OS > 60%) and low (pr-OS ≤ 60%). OS and disease-free survival (DFS) were calculated at the study median follow-up (8-year).

Results: 351 participants were randomised in the EORTC-STBSG 62931 trial and were followed up for a median time of 96 months [interquartile range (IQR) 70 – 118 months]. The 8-year probability of OS and DFS was 58% [95% confidence interval (CI): 52–63%] and 51% (95% CI: 46–57%), respectively. In patients with extremity and trunk wall STS (N=290/351) adjuvant chemotherapy was not associated with an OS benefit [Hazard ratio (HR) = 0.91, 95%CI 0.63–1.31]. Nomogram predicted pr-OS ranged between 5% and 96%, with a median value of 72% (IQR 57-83%). Patients with a low predicted pr-OS (N=80) were at greater risk of death compared to patients with higher predicted pr-OS (N=210, HR=2.13, 95%CI 1.47-3.09). There was a statistically significant reduction of the risk of death when adjuvant chemotherapy was used in the group at low predicted survival (HR=0.50, 95%CI 0.30-0.90) while this difference was not detected in patients with high OS (HR=1.20, 95%CI 0.75-1.91). Consistently, there was a statistically significant reduction of the risk of recurrence when adjuvant chemotherapy was used in the group at low predicted pr-OS, <60% (HR = 0.49, 95%CI 0.28-0.85) while this difference was not observed in patients with high pr-OS (HR = 0.95, 95%CI 0.62-1.44).

Conclusion: Patients treated in the EORTC-STBSG 62931 RCT with extremity and trunk wall STS and a low predicted pr-OS (i.e., high-risk patients) had better OS and DFS when treated with adjuvant chemotherapy. This analysis offers a possible explanation for the conflicting results between the lack of a beneficial effect of chemotherapy in EORTC-STBSG study 62931 and the recent interim report of the ISG-1001 (Lancet Oncol 2017;18:812-822), which showed a survival benefit for patients who underwent neoadjuvant anthracycline-based chemotherapy.



Overall survival (OS) according to two categories of predicted probability of 10-year OS (pr-OS) based on a cut-off value of 60% identified in a previous study (Eur J Cancer 2018;93:28-36) and EORTC-STBSG 62931 study treatment arms (adjuvant chemotherapy vs observation).

Paper 006 3042737

PROPENSITY SCORE MATCHING ANALYSIS OF DOXORUBICIN PLUS DACARBAZINE, DOXORUBICIN PLUS IFOSFAMIDE OR DOXORUBICIN ALONE AS FIRST-LINE TREATMENT FOR ADVANCED, METASTATIC OR UNRESECTABLE LEIOMYOSARCOMA: A RETROSPECTIVE STUDY FROM THE EORTC SOFT TISSUE AND BONE SARCOMA GROUP

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Objective: First-line treatment for advanced leiomyosarcoma is still based on doxorubicin alone or in combination. Previous retrospective data suggested limited activity of ifosfamide in this histological type (Sleijfer S, et al. Eur J Cancer 2010), whereas dacarbazine showed interesting anti-tumor activity in limited series. We retrospectively evaluated doxorubicin+dacarbazine (DoDa), doxorubicin+ifosfamide (DI) and doxorubicin alone (Do) as first-line treatment in advanced leiomyosarcoma.

Methods: Inclusion criteria: confirmed histological diagnosis, treatment between 1/2010 and 12/2015, measurable disease (RECIST 1.1), ECOG performance status (PS) ≤2, age ≥18 years, absence of major comorbidities. Endpoints: progression-free survival (PFS), overall survival (OS), overall response rate (ORR). PFS was analyzed using methods for interval-censored data as the last progression-free assessment prior to progressive disease was collected. Due to the absence of

randomization, propensity scores were estimated as the probability of each patient to receive one of the three treatments using a logistic regression model accounting for histology, site of primary, age, gender, PS, tumor extent, and tumor grade. Patients were then matched across the different groups by their propensity score.

Results: 303 patients, 216 females (71%), median age 58 (range 20-87), were enrolled from 18 EORTC STBSG sites. Treatments were distributed as follows: 117 patients received DoDa (39%), 71 DI (23%), and 115 Do (38%). No significant differences were detected among regimens in terms of dose reductions >10%, delays >72h, or G-CSF use. In the whole population, unadjusted median PFS was 9.4 (95% CI 6.1-9.7), 6.8 (4.5-9.5), 5.4 months (3.8-6.8), and observed ORR was 36.8%, 21.5%, and 25.9%, for DoDa, DI and Do, respectively. When trying to adjust for lack of randomization by balancing baseline characteristics among arms by means of propensity scores, in the 2:1:2 (DoDa:DI:Do) matched population, DoDa showed a significantly longer PFS when compared to Do [median 9.2 months (95%CI 5.2-9.7) *vs.* 4.8 (2.3-6.0); HR 0.72 (0.52-0.99)], but not when compared to DI [8.2 months (5.2-10.1), HR 1.01 (0.68-1.50)]. PFS did not differ significantly between DI and Do [HR 0.71 (0.48-1.06)]. In the same matched population, ORR was 30.9%, 19.5%, and 25.6% for DoDa, DI, and Do, respectively. Shorter median follow-up was observed in DoDa (32 months; IQR 23-47) compared to DI (50; 37-73) and Do arms (46; 31-58), weakening a direct comparison of OS. With this limit, in the pairwise comparison of the 2:1:2 matched population, patients in DoDa arm showed longer OS [median 36.8 (27.9-47.2) months] when compared to both DI and Do arms [21.9 (16.7-33.4), HR 0.65 (0.40-1.06); and 30.3 (21.0-36.3) months, HR 0.66 (0.43-0.99); respectively]. Subsequent treatments were well balanced across arms. None of the selected factors for multivariate analysis (age, sex, ECOG PS, histotype, site of primary tumor, tumor grade, and tumor extent) had significant interaction with the received treatment for both PFS and OS.

Conclusion: To our knowledge, this is the largest retrospective study on the first-line treatment of advanced leiomyosarcoma. Potential biases may be related to: 1) retrospective nature of the study; 2) center-specific preference in treatment and protocol; 3) discrepancies in follow-up across treatment arms. This said, in the propensity score-adjusted population, DoDa favorably compared with both DI and Do showing interesting activity in terms of both ORR and PFS. Consistency of both DI and Do outcomes with prospective data from EORTC 62012 trial (median PFS for leiomyosarcoma: 6.6 and 6.1 months, respectively) strengthens the reliability of these results. DoDa warrants further evaluation in prospective trials in leiomyosarcoma.

Paper 007 3042520

PHASE 1B STUDY OF OLARATUMAB PLUS DOXORUBICIN AND IFOSFAMIDE IN PATIENTS WITH ADVANCED OR METASTATIC SOFT TISSUE SARCOMA: INITIAL RESULTS

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Objective: Olaratumab is a recombinant, fully human monoclonal antibody that binds platelet-derived growth factor receptor alpha (PDGFRα). In a randomized phase 2 study, olaratumab in combination with doxorubicin (Dox) demonstrated a significant improvement of overall survival over Dox alone in patients with advanced or metastatic soft tissue sarcoma (STS). Based on these data, olaratumab was granted accelerated approval by the Federal Drug Administration and conditional approval by the European Medicines Agency in 2016. Dox plus ifosfamide (Dox-Ifos) is an alternative standard first-line regimen for the treatment of STS that is widely used in patients with symptomatic disease and in the neoadjuvant and adjuvant settings. However, more toxicities are observed with Dox-Ifos compared with Dox alone. Here we report the initial results from a Phase 1b study (JGDR; NCT03283696) examining olaratumab (15 mg/kg) plus Dox-Ifos.

Methods: Adult patients with advanced or metastatic STS, no prior lines of systemic therapy, ECOG PS 0-1, and suitable to receive Dox-Ifos treatment were enrolled. Patients received olaratumab on Days 1 and 8 at 15 mg/kg in combination with Dox (75 mg/m2; D1-3) and Ifos (10 g/m2; D1-4) followed by mandatory granulocyte-colony-stimulating factor therapy in cycles 1-6 on a 21-day cycle. Dox was allowed to be administered by continuous infusion or bolus administration and with cardiac protection, per institutional standard. Mesna dosing was at least 60% of the Ifos dose, per local standard. The primary objective was to characterize the safety profile of the olaratumab plus Dox-Ifos combination and to determine the recommended phase 2 dose. Secondary objectives included pharmacokinetics and antitumor activity. Considering the known toxicities of the Dox-Ifos backbone, a pre-specified dose limiting toxicity (DLT) rate of <60% (ie, ≤8 of 15 patients) during Cycle 1 was deemed acceptable for the olaratumab plus Dox-Ifos combination.

Results: Sixteen patients have been enrolled and treated with olaratumab plus Dox-Ifos since study start on 19-Oct-2017. As of data cutoff, 10 patients have received treatment with olaratumab plus Dox-Ifos and completed the DLT period. Two of the 10 patients had DLTs (one with Grade 4 febrile neutropenia and the other with both Grade 3 febrile neutropenia and Grade 3 mucositis). Common related adverse events (all grades/≥Grade 3) occurring in >30% of patients included fatigue (60%/0%), anemia (50%/30%), neutropenia (40%/40%), thrombocytopenia (40%/10%), constipation (40%/0%), and nausea (40%/0%). One patient discontinued study treatment due to progressive disease, and all others were on study treatment as of data cutoff. Among 7 patients evaluated for tumor response assessment, 3 patients had a partial response according to RECIST and 3 further patients had stabilized disease as best overall response for a disease control rate of 86%. Updated results will be presented at the meeting.

Conclusion: With 8 of 10 evaluable patients having completed the DLT period without DLTs, the cohort has already met the pre-specified safety criterion (<60% of patients with DLTs). Therefore, the 15 mg/kg dose level of olaratumab plus Dox-Ifos is considered safe and tolerable thus far. The safety profile observed to-date for this combination is consistent with the known side effect profile for Dox-Ifos. Based upon the tolerability of the 15 mg/kg dose level of olaratumab, the study has proceeded to the next cohort evaluating an olaratumab loading dose of 20 mg/kg in Cycle 1, followed by 15 mg/kg of olaratumab in subsequent cycles with the same doses of Dox and Ifos.

Paper 008 3042717

ANTHRACYCLINE-BASED VERSUS GEMCITABINE-BASED ADJUVANT CHEMOTHERAPY IN FIGO STAGE 1 UTERINE LEIOMYOSARCOMA

Roberta Sanfilippo[1]*; Rosanna Mancari*[2]*; Sara Manglaviti*[1]*; Giorgio Bogani*[1]*; Domenica Lorusso*[1]*; Elena Fumagalli*[1]*; Rossella Bertulli*[1]*; Angelo Paolo Dei Tos*[3]*; Paola Collini*[1]*; Francesco Raspagliesi*[1]*; Nicoletta Colombo*[2]*; Paolo Casali*[1]
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Objective: Uterine leiomyosarcoma (U-LMS) is a rare disease with a high recurrence rate even when diagnosed at an early stage. A recent retrospective study showed that women treated with adjuvant gemcitabine and docetaxel had no improvement in disease-free survival (DFS) compared to women who received no additional treatment to surgery. We wished to retrospectively review the outcome of patients treated on an adjuvant basis with an anthracycline-based regimen as compared to gemcitabine and docetaxel in uterine leiomyosarcoma.

Methods: We retrospective reviewed all patients with FIGO stage I uterine leiomyosarcoma who underwent hysterectomy with or without oophorectomy and then treated with adjuvant chemotherapy with anthracycline-based or gemcitabine-based chemotherapy at two Italian referral centres from 1997 up to now.

Results: We identified 145 pts: 97 were treated with an anthracycline based regime and 48 with gemcitabine and docetaxel. Median number of cycles of anthracycline based regimen was 4 (range 2-6), while it was 5 (range 3-7) with gemcitabine and docetaxel. DFS was 31 months in pts treated with anthracycline-based chemotherapy versus 19 in pts treated with gemcitabine and docetaxel.

Conclusion: In this retrospective and purely explorative case series analysis, DFS was not the same by using an anthracycline-based chemotherapy or gemcitabine and docetaxel. This parallels a recent randomized trial in limb and superficial trunk soft tissue sarcomas (including leiomyosarcoma), in which a difference was seen in favor of an anthracycline-based regimen. At the moment, at the best of currently available evidence, future trials to assess the efficacy of adjuvant chemotherapy in uterine leiomyosarcoma should incorporate anthracyclines.

Paper 009 3042702

EUROPEAN PHASE I/II TRASTS TRIAL OF TRABECTEDIN PLUS RADIOTHERAPY IN PATIENTS WITH METASTATIC SOFT TISSUE SARCOMA (STS): A COLLABORATIVE SPANISH (GEIS), ITALIAN (ISG) AND FRENCH (FSG) SARCOMA GROUPS STUDY

Javier Martín-Broto[1]*; Antonio Lopez-Pousa*[2]*; Nadia Hindi*[1]*; Josefina Cruz*[3]*; Javier Peinado*[1]*; Carlo Morosi*[4]*; Josep Isern Verdun*[2]*; Maria Carmen Dolado*[5]*; Rosa Maria Alvarez Alvarez*[5]*; Ana Alvarez González*[5]*; Tiziana Venesio*[6]*; Marco Gatti*[6]*; Pablo Luna Fra*[7]*; Ignacio Alastuey*[7]*; Jean-Yves Blay*[8]*; Marie-Pierre Sunyach*[8]*; Inmaculada Rincon*[10]*; Alessandro Gronchi*[4]*; Jesus Romero*[9]

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Objective: Patients with advanced STS who require tumor shrinkage beyond first line, have very limited options since the approved drugs exhibit less than 10% of RECIST response. Trabectedin (Yondelis®) had shown preclinical synergy with radiotherapy (RT). Low-dose RT concurrent with trabectedin was given in a phase I/II trial as a proof-of-concept of synergy. Herein, we present data from the phase I in the cohort of patients with lung metastases.

Methods: Patients received trabectedin along with RT (30 Gy) in 10 fractions (3Gy/fr). Three dose levels of trabectedin were administered: -1 (1.1 mg/m^2), 1 (1.3 mg/m^2) and 2 (1.5 mg/m^2). Dose level 1 was expanded for a better cardiotoxicity assessment. Dose-limiting toxicity (DLT) were defined as grade ≥3 events excluding grade (G) 3/4 neutropenia lasting <5 days, G3 transaminitis if not led to trabectedin delay and G3/4 nausea/vomiting due to inadequate prophylaxis. Primary endpoint of the Phase I part was to assess safety and tolerability of the combination and to find recommended dose for the Phase II part. Primary end-point of the trial was response rate according to RECIST.

Results: From 04/2015 to 06/2017, 18 patients were enrolled. Most patients had synovial sarcoma in (n=10, 56%) followed by undifferentiated pleomorphic sarcoma (n=3, (17%), and myxoid liposarcoma, dedifferentiated liposarcoma, G3 not otherwise specified sarcoma, leiomyosarcoma and malignant peripheral nerve sheath tumors (n=1 each, 5.5%). Patients received a median of 1 prior line of chemotherapy (range: 0-3). Twelve patients received trabectedin at dose level 1 and 6 patients at dose level 2. Overall, G 3/4 adverse events (AEs) were: neutropenia (n=8), alanine aminotransferase (ALT) elevation (n=2), gamma-glutamyl transferase (GGT) elevation (n=2), anemia (n=2), febrile neutropenia and pneumonitis (n=1 each). There were two DLTs: transient G4 ALT elevation in level 1 and G4 neutropenia (>5 days) in level 2. Based on central radiological review of 17 evaluable patients, 2 patients achieved complete response (12%), 3 partial response (18%), 6 stable disease (35%), and 6 had progressive disease (35%) (Table 1). The local review reported CR in 2 patients (12%), 5 PR (29%), 4 SD (24%), 6 PD (35%). On the irradiated lesions, 4 CR (24%), 8 PR (47%), 4 SD (24%) and 1 PD (5%) were found. With a median follow-up of 18 months, median progression-free survival (PFS) was 2.83 (95%CI: 2.3-3.3). Thirteen patients (72%) have died, with a median overall survival (OS) of 8.77 months (95%CI: 3.6-13.9) and 12-month OS rate of 48%.

Conclusion: Trabectedin concurrent with RT was feasible in patients with pulmonary metastatic STS regardless of histologic subtype. Trabectedin at 1.5 mg/m^2 is the recommended dose for phase II part. Our results have confirmed the synergy of trabectedin plus low-dose RT, with 71% of the irradiated lesions showing long-lasting dimensional responses. Clinical trial information: NCT02275286.

Table 1. Responses assessment according to RECIST

Response	Central review	Local review	Irradiated lesions
	n (%)	n (%)	n (%)
Complete response (CR)	2 (12)	2 (12)	4 (24)
Partial response (PR)	3 (18)	5 (29)	8 (47)
Stable disease (SD)	6 (35)	4 (24)	4 (24)
Progressive disease (PD)	6 (35)	6 (35)	1 (5)

Evaluable patients, n=17.

4:00 pm – 6:00 pm
– SESSION 3 –
GIST

Paper 010 3042567

MULTICENTRIC RETROSPECTIVE ANALYSIS OF PATIENTS WITH *KIT* EXON 9 MUTATED GIST

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Objective: Patients (pts) with advanced gastrointestinal stromal tumors (GIST) harbouring the *KIT* exon 9 mutation have a better progression-free survival (PFS) on a higher daily dose level, i.e. 800 mg of imatinib (IM), which is therefore held as standard treatment in this subgroup. This schedule in the adjuvant setting has been subsequently proposed despite the lack of any controlled trials.

Methods: We retrospectively evaluated characteristics of pts with *KIT* exon 9 mutated GIST in seven different centers in France and Spain, treated with a daily dose of 400 mg of IM. Pts with localized and advanced GIST were separately analyzed: Kaplan-Meier and Cox proportional hazards model analyses were used to compare median relapse-free survival (RFS) and OS (mOS) in the adjuvant setting, and overall response rate (ORR), median PFS to IM 400 mg (mPFS), median time to IM failure (mTIF) defined as time to 2nd progression (PD) or death, and mOS in the advanced setting.

Results: We identified 45 pts (47% of males) with a median age of 60 yrs (16-78). 66.7% of GIST were originated in the small bowel and 20% in the stomach. In adjuvant situation (31 pts), 42% of pts had a high risk (HR) of relapse (Miettinen classification) and 29% an intermediate risk (IR). 17 out of 31 pts received adjuvant 400 mg/d of IM for a median duration of 21 months (m). The mRFS of pts receiving adjuvant IM was 82 m vs 21 m for those who did not. In the advanced setting, 24 pts were treated with 400 mg of IM. The ORR was 34.7% (3 CR and 5 PR), with additional 9 stabilizations (benefit in 73.8% of pts). At PD, 75% of pts received the higher dose IM regimen (800 mg). The mPFS was 13.99 m (CI 95% 9.9-18.1) and the mTIF was 20.63 m (CI 95% 14.2-27). The mOS was 42.9 m (27.2-58.6). No prognostic variable (gender, age, PS, site of primary disease, diameter of largest lesion, prior surgery of primary) was significantly related with mOS or mTIF.

Conclusion: Despite the limitations of retrospective analysis and the small number of pts, benefit of adjuvant IM (400 mg/d) in pts with localized GIST harbouring *KIT* exon 9 mutations seems relevant. Pts with advanced GIST initially treated with 400 mg of IM have a similar outcome in terms of mTIF (20 m) than those receiving high-dose IM upfront (19 m in the initial MetaGIST trial, M.V. Glabbeke et al, JCO 2010).

Paper 011 3041313

A WEB-BASED SURVEY OF PERCEIVED COGNITIVE IMPAIRMENTS AND OTHER PATIENT-REPORTED OUTCOMES IN GIST PATIENTS

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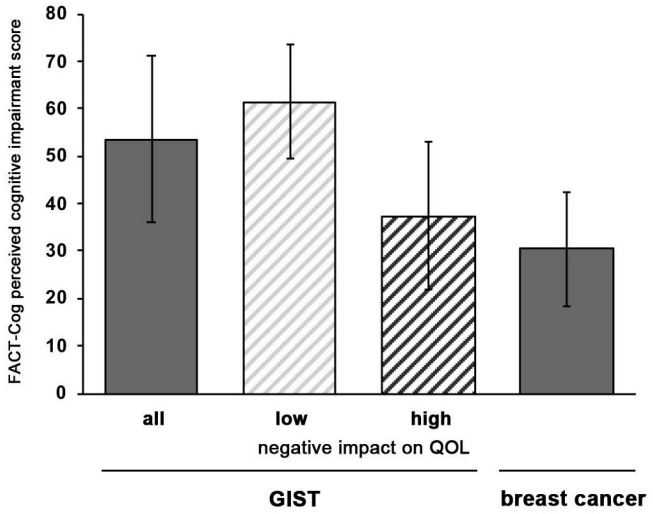
Objective: Cognitive problems including impairments of memory, attention, and processing information have been well-documented among survivors of a number of different cancers, particularly breast cancer. Even moderate or mild cognitve problems have been found to interfere with daily life. Cognitive problems are also often associated with disturbances of mood, anxiety and fatigue that can contribute to further negative effects on quality of life. Little is known about cognitive impairment in gastrointestinal stromal tumor (GIST) patients/survivors, the vast majority of whom are maintained on long-

term therapies, most prominently the tyrosine kinase inhibitor imatinib mesylate (Gleevec). Anecdotally, these therapies have been associated with cognitive complaints, including problems with attention, concentration and memory. Our aims for the present research are to (1) investigate the prevalence of perceived cognitive impairment among GIST patients, to (2) examine relationships with self-reported health-related quality of life (HRQOL), and to (3) explore possible differences in these patient-reported outcomes among GIST patients who received different treatment regimens.

Methods: We have developed a web-based survey to collect de-identified information about GIST patient demographics (e.g., age, gender, education), medical/cancer history and treatment regimens. Perceived cognitive problems, sleep/fatigue, mood, anxiety, QOL and general health were assessed using validated self report measures, including the FACT-Cog (Functional Assessment of Cancer Therapy - Cognitive) V3, PROMIS (Patient-Reported Outcomes Measurement Information System) Short Forms 8a and SF-36. The study was approved by the Institutional Review Board of the University of Pittsburgh (#PRO17060551). The survey was distributed through email, websites and Facebook with the help of GIST Support International, the GIST Cancer Research Fund, Sarcoma Patients EuroNet and the Life Raft Group. The research is ongoing, and we report on results of the first 200 respondents with complete data.

Results: Fifty-five (27.5%) male and 145 (72.5%) female GIST patients completed the survey with a mean age of 56.9 (sd=11.1) years and an average of 6.8 (sd=5.4) years since diagnosis. One-hundred-eighty-five (92.5%) patients were Caucasian and 62% had completed college and/or graduate school. The mean FACT-Cog Perceived Cognitive Impairment (PCI) score (a measure of cognitive problems in dailiy life) was 53.64 (sd=17.44) with an Impact on QOL (IQOL; a measure of perceived negative effects that cognitive symptoms have on QOL) score of 11.64 (sd=4.28). On both scales, higher scores denote better function/QOL. The prevalence of substantial negative impact on QOL (IQOL≤10) was 32.5% (n=65). Individuals with strong negative IQOL scored significantly lower on PCI (mean=37.40) than individuals with little negative impact (mean=61.51; $p<0.001$). Results are comparable to FACT-Cog outcomes in previous breast cancer research (Figure 1;Ferguson RJ, et al. Cancer. 2016;122:1782-91). Age, type of TKI therapy and time since diagnosis were not associated with PCI, whereas fatigue (r=-0.57), depression (r=-0.43), pain (r=-0.45), anxiety (r=-0.42) and poor sleep (r=-0.32) were significantly associated with PCI. GIST survivors with higher education had significantly better self-reported cognitive function (PCI; p=0.044).

Conclusion: Approximately one third of GIST patients report significant QOL effects of long-term cognitive impairment. Self-reports of cognitive impairment appear to be independent of age, type of TKI therapy, and time since diagnosis, while fatigue, pain, sleep difficulty and emotional distress are associated. Results are comparable to research with breast cancer survivors. Further investigation with objective neurocognitive testing is warranted to quantify the neurocognitive impact of disease and TKI therapy.



Perceived Cognitive Impact (PCI) scores in GIST patients.

Paper 012 3027631

AVAPRITINIB IS HIGHLY ACTIVE AND WELL-TOLERATED IN PATIENTS (PTS) WITH ADVANCED GIST DRIVEN BY DIVERSE VARIETY OF ONCOGENIC MUTATIONS IN KIT AND PDGFRA

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Objective: Oncogenic KIT/PDGFRA mutations drive >85% of GIST, and most patients (pts) initially respond to imatinib and other kinase inhibitors. However, nearly all pts become resistant to all approved kinase inhibitors, largely due to primary and acquired resistance mutations, particularly those involving the kinase activation loop (KIT Exon 17/18; PDGFRα D842V). We initiated NAVIGATOR (NCT02508532) a phase 1 study to define the clinical activity of avapritinib (Ava, formally BLU-285), a potent and highly-selective small molecule inhibitor with broad activity against activated KIT/PDGFRA mutants, including activation loop resistance mutants.

Methods: Adult pts with unresectable GIST were enrolled following a 3+3 dose escalation to the maximum tolerated dose (MTD) followed by expansion. The expansion part of the study enrolled adult pts with unresectable GIST who had a PDGFRα D842V mutation regardless of prior therapy, and pts who had received ≥2 tyrosine kinase inhibitors (TKIs) including imatinib, who were primarily pts with KIT mutant GIST. A third group of pts without a PDGFRα D842V mutation who had only received imatinib (2nd line) was added later during the study. Pts were given Ava orally, once daily (QD) on a 4-week cycle. We serially assessed adverse events (AE) per CTCAE v4.03, circulating tumor DNA (ctDNA) via next generation sequencing and BEAMing and response by central radiology review using mRECIST 1.1 and Choi criteria every 8 weeks.

Results: As of the January 11, 2018 cutoff, 160 pts (108 *KIT* mutant, 50 *PDGFRA* mutant, 1 wildtype, and 1 pending mutation assessment) were treated with Ava at doses of 30-600 mg QD, including 114 in the expansion part (85 *KIT,* 27 *PDGFRA*). Pts with *KIT and PDGFRA*-driven GIST had received a median of 4 prior TKI regimens (range 2-11) and 1 prior TKI regimen (range 0-6), respectively. Substantial activity was seen among 52 response-evaluable pts with heavily pre-treated (median of 5th line) *KIT*-driven GIST initiating treatment at 300-400 mg QD. ORR by central review was 13% (7 PR [1 pending confirmation]); 31 (60%) pts had tumor reduction, and DCR was 63% by mRECIST. ORR by Choi criteria was 52%. Tumor size reduction and response were seen across a broad range of KIT mutations. Among 37 response-evaluable pts with D842 mutant PDGFRα (across all dose levels including escalation and expansion) all but 1 had tumor size reduction, and ORR by central review was 70% (2 CR, 24 PR); 10 (27%) pts had best response of SD, 1 had PD. Disease control rate (DCR) was 97% by mRECIST. ORR by Choi criteria was 97%, including CR in 5%. Antitumor activity was durable with an estimated PFS at 1 year of 80% (median not reached). Data from the 2nd line expansion cohort and mutational analysis of ctDNA will be available at the time of the meeting. Most AEs (regardless of attribution to Ava) were grade 1 or 2, most commonly nausea (58%), fatigue (53%), periorbital edema (45%), vomiting (39%), anemia (37%), cognitive effects (37%), peripheral edema (35%), diarrhea (32%), decreased appetite (32%). Treatment-related Gr 3 AEs occurring in ≥5% of pts were anemia (11%) and fatigue (6%). AEs were manageable and only 14 (9%) patients discontinued Ava due to a treatment-related AE.

Conclusion: Avapritinib has important clinical activity in advanced GIST with unprecedented response rate and PFS in PDGFRα D842-GIST and substantial activity in heavily pretreated *KIT* mutant GIST patients with diverse genotypes. Further development in both GIST subtypes is warranted and underway.

Paper 013 3033840

INITIAL RESULTS OF PHASE 1 STUDY OF DCC-2618, A BROAD-SPECTRUM KIT AND PDGFRAINHIBITOR, IN PATIENTS (PTS) WITH GASTROINTESTINAL STROMAL TUMOR (GIST) BY NUMBER OF PRIOR REGIMENS

Suzanne George[3]*; Michael Heinrich*[10]*; Ping Chi*[4]*; Albiruni Razak*[5]*; Margaret von Mehren*[6]*; Michael Gordon*[7]*; Kristen Ganjoo*[2]*; Neeta Somaiah*[8]*; Jonathan Trent*[11]*; Julie Wolf*[9]*; Rodrigo Ruiz-Soto*[1]*; Oliver Rosen*[1]*; Filip Janku*[8]
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Objective: DCC-2618, a kinase switch control inhibitor, broadly inhibits mutations in KIT exons 9, 11, 13, 14, 17 and 18. Based on clinical activity observed in heavily pretreated GIST pts in a Phase 1 study, DCC-2618 is being evaluated in a Phase 3 study, INVICTUS (NCT03353753), in ≥4th line patients. Given the breadth of inhibition of KIT mutations and safety profile, the Phase 1 study included expansion cohorts to assess clinical benefit in 2nd and 3rd line GIST pts prior to initiation of a second Phase 3 study in 2nd line GIST patients by the end of 2018.

Methods: The Phase 1 study includes dose-escalation testing of oral DCC-2618 dosed QD or BID in 28 day cycles followed by an expansion phase using the RP2D of 150 mg QD in 6 cohorts, including cohorts for GIST patients based on prior regimens (2nd/3rd, 4th/>4th). Local RECIST response assements were performed every 2 cycles. Patients who progressed per RECIST in the expansion cohorts, were allowed to dose escalate to 150 mg BID.

Results: At cut off of April 18, 2018, 150 GIST patients were enrolled at dose levels of ≥100 mg/d with KIT (141 patients) or PDGFRa- (8 patients) -driven GIST. One patient had SDH-deficient GIST. 114 GIST patients were treated at the 150 mg QD dose, including 19, 27, and 68 pts who previously received 1, 2 or ≥3 prior lines of therapy, respectively. For the 114 GIST patients, ORR was 14%, 3-month DCR was 70%, mPFS was 24 weeks; 56% of pts were censored. For the 46 evaluable patients in 2nd/3rdline, ORR was 22%, 3-month DCR was 81% and mPFS was 36 weeks; 61% of pts were censored. Updated ORR, DCR and mPFS will be presented. Grade (G) 3/4 adverse effects (regardless of attribution, in >1 patient) for all 114 patients treated at 150 mg QD included asymptomatic lipase increase 11,anemia 4, hypertension 3, blood bilirubin increased 3, diarrhea 2, abdominal pain 2, back pain 2, hypophosphatemia 2, hyponatremia 2, hyperkalemia 2.

Conclusion: DCC-2618 demonstrated encouraging clinical benefit and a favorable tolerability profile in GIST patients treated in the 2nd line or later. Clinical benefit as measured by ORR, DCR and mPFS was greater in 2nd / 3rd line patients compared to more heavily pretreated patients. Preliminary data from the Phase 1 expansion supports further testing in the planned Phase 3 study in 2nd line GIST.

Paper 014 3041747

NON-INVASIVE DETECTION OF CTDNA REVEALS INTRATUMOR HETEROGENEITY AND IS ASSOCIATED WITH TUMOR BURDEN IN GASTROINTESTINAL STROMAL TUMOR

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Objective: Molecular analysis of circulating tumor DNA (ctDNA) has a large potential for clinical application by capturing tumor-specific aberrations through non-invasive sampling. In gastrointestinal stromal tumor (GIST), analysis of *KIT* and *PDGFRA* mutations is important for therapeutic decisions, but the invasiveness of traditional biopsies limits the possibilities for repeated sampling. The objective of the present study was to explore the clinical utility of ctDNA in GIST.

Methods: Circulating cell-free DNA was isolated from plasma from 50 GIST patients. Targeted next-generation sequencing was performed using the Archer Reveal ctDNA 28 kit for Illumina, and data was processed using the Archer Analysis (v5.1) pipeline. Associations between ctDNA detection and clinical and histopathological parameters were analyzed.

Results: Tumor-specific mutations in ctDNA were detected in 16 of 44 plasma samples (36%) from treatment-naïve patients, and in 3 of 6 (50%) patients treated with tyrosine kinase inhibitors. A significant association between detection of ctDNA and the modified National Institutes of Health risk classification was found. All patients with metastatic disease had detectable ctDNA. Tumor burden was the most important detection determinant in localized disease. Median tumor size was 13.4 cm for patients with detectable mutation in plasma compared to 4.4 cm in patients without detectable mutation (p=0.006). ctDNA

analysis of a patient with disease progression on imatinib revealed that multiple resistance mutations were synchronously present, and detailed analysis of tumor tissue showed that these were spatially distributed in the primary tumor, revealing a high degree of intratumor heterogeneity. Plasma samples taken throughout the course of treatment demonstrated that clonal evolution can be monitored over time.

Conclusion: We have shown that detection of GIST-specific mutations in plasma is particularly feasible for patients with high tumor burden. In such cases, mutational analysis by use of liquid biopsies can capture the molecular heterogeneity of the whole tumor, and may guide treatment decisions during progression. Analyses of repeated samples from a cohort of patients with metastatic GIST are ongoing.

Paper 015 3042824

UTILITY OF CIRCULATING TUMOR DNA (CTDNA) IN THE MANAGEMENT OF PATIENTS WITH GASTROINTESTINAL STROMAL TUMOR (GIST): ANALYSIS OF 184 PATIENTS

Junaid Arshad[1]; Breelyn A. Wilky[1]; Ali Roberts[2]; Becky Nagy[2]; ***Jonathan Trent[1]***
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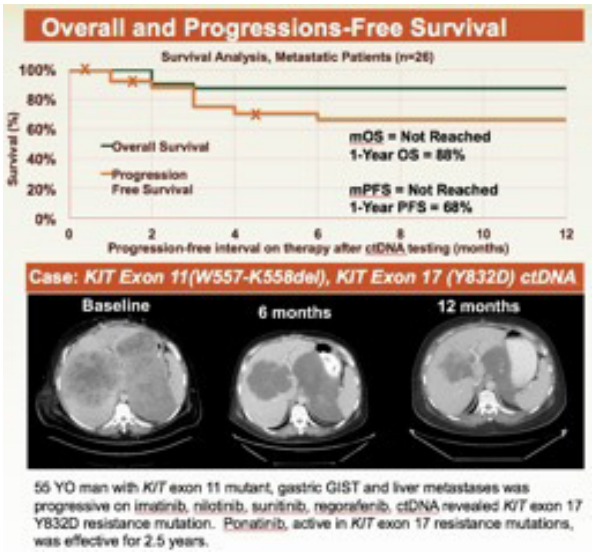
Objective: GIST is the most common sarcoma of the GI tract. Systemic therapy of GIST is determined by *KIT*, *PDGFR*, RAF, or other genomic alterations. Tissue-based next generation sequencing (NGS) has been the primary method to identify driver mutation and selection of systemic therapy (imatinib 400mg daily for KIT exon 11 and 800mg daily for KIT exon 9, avapritinib for PDGFR D842V, larotrectinib for NTRK fusion, and vemurafenib for RAF mutant GIST). Moreover, secondary resistance mutations in KIT commonly occur in exon 13 or exon 17 which display differential sensitivity to post-imatinib tyrosine kinase inhibitors (TKI). Circulating tumor DNA (ctDNA) is a novel and non-invasive alternative to multiple percutaneous biopsies. ctDNA may be identified in plasma of GIST patients and used to quantify, amplify, and sequence driver mutations. We performed a retrospective analysis of 184 GIST to determine the sensitivity, specificity, predictive value, and survival after ctDNA testing.

Methods: Sequencing of ctDNA was performed on blood from 184 GIST patients (152 de-identified-Guardant Health and 32-institutional with IRB-approval). Patient data were abstracted from the EMR and stored in a HIPAA-compliant database. Formalin-fixed paraffin embedded (FFPE) tissue was collected for all Sylvester patients (n=32). Peripheral blood samples were collected, shipped at room temperature and centrifuged to isolate plasma. DNA was extracted, concentrated, and quantified. Analysis of 73 genes, copy number (18 genes), fusions (6 genes), and insertions/deletions (23 genes) was performed with 15,000x avg. depth and algorithmic reconstruction of fragments.



55 YO man with *KIT* exon 11 mutant, gastric GIST and liver metastases was progressive on imatinib, nilotinib, sunitinib, regorafenib. ctDNA revealed *KIT* exon 17 Y832D resistance mutation. Ponatinib, active in *KIT* exon 17 resistance mutations, was effective for 2.5 years.

Results: Of 184 patients, 87 (47%) were female and median age 59 (range, 28-90). Serial testing was performed in 22 patients resulting in 208 samples. Patients with only variations of uncertain significance (VUSs) were excluded. Of the 94 patients with pathogenic mutations, 62% had KIT, 29%(TP53), 11% (NF1), 9%(KRAS), 8% (PDGFRA), 8% (PIK3CA), 6%(PTEN), 4% (EGFR), 4% (MYC), 3% (FGFR1). The median number of alterations per sample was 2(Range, 1-12) excluding VUSs. The number of samples with actionable KIT or PDGFRA mutation was 68(66%). The most common types of mutation were missense (46%), insertion/deletion (25%) followed by amplification (8%). Our institutional cohort of patients (n=32 had a median age of 62(Range33-90) with 17(53.1%) females, 5 (16%) Hispanics and 27 caucasian (84%). Metastatic disease was present in 26(81%) patients where as 6(19%) had localized disease. Of 32 patients, 18(64%) had exon 11, 5(18%) had exon9, 4(12%) had no KIT or PDGFR mutation, 1(2%) had primary exon 13, 2(7%) had primary exon 17, 2(7%) had PDGFRA exon 18 mutations. There were 3 (11%) patients with secondary Kit exon17, 1(3%) with secondary exon 13 and 1(3%) with both secondary exon 13 and exon 17 mutations. Our comparison of ctDNA testing with NGS testing of FFPE tumor tissue revealed a specificity of 100%, sensitivity of 56%, and a **positive predictive value (PPV) of 100%**. Failure of concordance was observed in patients with localized, small-volume, or no evidence of disease. Median lines of treatment was 3(Range0-6). From the time of ctDNA testing, neither the the median overall survival (OS) nor progression-free survival were reached. Moreover, **88% of patients were alive and 68% progression-free at 12 months** after ctDNA testing (Figure).

Conclusion: Most alterations (85%) occurred in kinase signaling pathways. The **very high PPV of ctDNA** results in potentially clinically useful information when a mutation is detected. **The OS and PFS rates are higher than expected in heavily pretreated GIST patients** suggesting a benefit in clinical use of ctDNA. Future directions include increasing sensitivity of ctDNA assays as well as prospectively studying the effectiveness of ctDNA testing to determine subsequent therapy in patients with metastatic, resistant, GIST.

Paper 016 3030004

CLINICAL VALUE OF CT-DNA IN LOCALIZED AND ADVANCED GIST: CROSS-VALIDATION OF AMPLICON-BASED NGS WITH DD-PCR IN MATCHED TISSUE AND PLASMA SAMPLES

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Objective: Gastrointestinal stromal tumor (GIST) initiation and evolution is usually framed by KIT/PDGFRA oncogenic activation, and in later stages by the polyclonal expansion of resistant subpopulations harboring KIT secondary mutations (muts) after the onset of imatinib (IM) resistance. Thus, GIST is expected to be an informative model for circulating tumor (ct)DNA determination as a non-invasive dynamic biomarker. Although ctDNA evaluations by next generation sequencing (NGS) approaches are compelling, their clinical value in GIST is unclear, given the paucity of studies incorporating cross-validations by droplet digital PCR (ddPCR) and in matched tissue-plasma samples.

Methods: Cohort A (n=13) were pts with localized (n=5) or metastatic (n=8) GIST in which matched tissue and plasma samples were either IM-naïve or progressing on IM, sunitinib (SU) or regorafenib (RE). Matched tissue in metastatic pts included resections of single lesion (n=5) or surgery of several lesions for R0 disease (n=3). In all cases plasma samples were collected while on drug 7-14 days before tumor resection. Cohort B (n=9) were pts with metastatic, IM-resistant GIST with archival tumor tissue followed with CT-scans in which serial plasma samples were collected while on SU or RE. An Amplicon panel covering 60 genes involved in cancer was used to sequence tumor (1,000x) and plasma (5,000x) samples in an Illumina MiSeq platform. NGS diagnostic accuracy in plasma was validated by ddPCR and by NGS evaluations of tumor.

Results: Cohort A: the localized GISTs had *KIT* Ex 11 mut (n=2) or *PDGFRA* mut (n=3) in tumor tissue. The metastatic GISTs (n=8) had *KIT* Ex 11 mut. No muts, including KIT/PDGFRA, were detected in matched plasma for the localized GISTs. ctDNA muts were detected in 3/8 metastatic GIST pts (37.5%), but only found in 2nd and 3rd line: 0/2 in IM-naïve, and 0/1 after failure of IM, 2/3 after SU, and 1/2 after RE. No other clinicopathological features were associated with presence/absence of muts in ctDNA. Interestingly, only primary *KIT* ex 11 muts were identified in matched tissue and plasma from 3 pts progressing on SU or RE. Loss of CD117 expression was observed in progressing lesions compared to pre-treatment biopsy, thus consistent with unidentified mechanisms of resistance. IM-resistance *KIT* ex 17 mutations (D816V, D820Y, N822K) were found in the tumor tissue from the 3 remaining, ctDNA-silent GIST pts progressing on IM, SU or RE. Cohort B: 29 plasma samples were analyzed from these 9 pts in cohort B while on treatment with SU or RE. 8 pts had *KIT* ex 11 mut in archival tissue, and 1 pt had *PDGFRA* ex 12 mut. 5/9 pts (55.6%) had ctDNA muts at one or more time points. Primary muts in *KIT* ex 11 (n=4) and *PDGFRA* ex 12 (n=1) were detected in each of these 5 pts. *KIT* ex 17 resistance muts (D816V, N822K, Y823D) were detected in 2 pts. In all cases, emergence/decrease of *KIT* primary or secondary muts correlated, respectively, with progression/stabilization, as assessed by CT-scan. Plasma ctDNA NGS determinations in cohorts A and B had a concordance rate of 82.8% with ddPCR. Allele frequency comparison with plasma samples from other epithelial cancers using ddPCR revealed low shedding in GIST pts.

Conclusion: ctDNA evaluation with amplicon-based NGS detects *KIT* primary and secondary muts in ~50% of GIST pts after IM progression. The main mechanism of resistance is the emergence of *KIT* secondary muts in the activation-loop (ex 17). ctDNA monitoring, when positive, reflects tumor dynamics in GIST pts. Based on this series, GISTs appear to have low ctDNA shedding, which might hamper plasma monitoring of GIST muts.

8:00 am – 10:00 am
– SESSION 4 –
Soft Tissue Sarcoma: Targeted Therapy

Paper 017 3016595

PROSPECTIVE TRIAL OF CRIZOTINIB (C) IN PATIENTS (PTS) WITH ADVANCED, INOPERABLE INFLAMMATORY MYOFIBROBLASTIC TUMOR (IMFT) WITH AND WITHOUT ALK ALTERATIONS: EORTC PHASE II STUDY 90101 "CREATE"

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Objective: The multi-tumor phase 2 trial EORTC 90101 (NCT01524926) assessed the activity and safety of the ALK/MET/ROS1 inhibitor C in IMFT, an orphan malignancy associated with ALK rearrangement or copy number changes.

Methods: Pts with local diagnosis of advanced/metastatic IMFT consented for shipment of a tumor tissue block and were screened for treatment after central confirmation of the diagnosis by reference pathology. Eligible ALK positive (+) and negative (-) pts received oral C 250 mg bid until RECIST 1.1 progression (PD). ALK+ was defined as at least 15% of tumor cells with rearrangement on FISH (Vysis LSI ALK Dual Color Break Apart Probe, Abbott Molecular) and/or immunohistochemical positivity (ALK MAb Clone CD246, DAKO). A Simon's optimal 2 stage design was implemented. If at least 2 out of the first 12 eligible and evaluable ALK+ pts achieved a confirmed RECIST 1.1 partial or complete response (PR, CR), a maximum of 35 pts were enrolled. If at least 6 had a confirmed PR/CR, the trial would be deemed successful.

Results: Between 10/2012 and 04/2017, 13 sites in 8 European countries recruited 35 pts with a local diagnosis of IMFT, of whom only 20 had centrally confirmed IMFT and were treated with C. Among 12 eligible and evaluable ALK+ pts, 6 achieved a confirmed PR or CR, 1 a non-confirmed PR and 5 had stable disease (SD) as best response (ORR 50.0%, 95% confidence interval: 21.1-78.9%). Further efficacy endpoints in ALK+ pts: disease control rate (DCR = CR/PR/SD as best response) 100.0% (73.5-100.0%), 1-year (y) progression free rate (PFR) 73.3 % (37.9-90.6%), 1-y OS rate (OSR) 81.8% (44.7-95.1%). Among 7 eligible and evaluable ALK- pts, 1 achieved a PR, 5 had SD and 1 PD (ORR 14.3%, 0.0-57.9%). Further data in ALK- cases: DCR 85.7% (59.8-100.0%), 1-y PFR 53.6 % (13.2-82.5%), 1-y OSR 83.3% (27.3-97.5%). One additional ALK- case was non evaluable (no measurable disease at baseline). Common related adverse events were nausea (11/20 [55%]), fatigue (9/20 [45%]), blurred vision (9/20 [45%]), vomiting (7/20 [35%]), diarrhea (7/20 [35%]).

Conclusion: EORTC can perform precision medicine phase II trials in ultra-rare cancers such as IMFT, with mandatory collection of tissue, real time reference pathology and genetic profiling. With an ORR of 50% and a DCR of 100% in ALK+ disease, C met pre-specified response rate criteria in this trial. The drug achieves long-lasting disease control in the vast majority of ALK+ pts. Sporadic responses and disease stabilization in ALK- cases either suggest limitations of the assays and their cut-offs for target positivity, or the presence of other oncogenic drivers/alternative fusions that may be sensitive to C. Based on the findings of this prospective trial, C should be considered as systemic treatment standard of care for this orphan disease.

Paper 018 3006132

ACTIVITY AND SAFETY OF CRIZOTINIB IN PATIENTS WITH ADVANCED CLEAR CELL SARCOMA (CCSA) WITH *MET* ALTERATIONS. EUROPEAN ORGANIZATION FOR RESEARCH AND TREATMENT OF CANCER PHASE 2 TRIAL 90101 "CREATE"

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Objective: Clear cell sarcoma (CCSA) is an orphan and very treatment-resistant malignancy characterised by a specific t(12;22) translocation, which leads to rearrangement of the *EWSR1* gene and overexpression of MET. We prospectively investigated the efficacy and safety of the MET/ALK/ROS1 tyrosine kinase inhibitor crizotinib in patients with advanced or metastatic CCSA.

Methods: Patients with CCSA received oral crizotinib 250 mg twice daily. Primary endpoint was the objective response rate (ORR; RECIST 1.1), secondary endpoints included duration of response, disease control rate (DCR), progression-free survival (PFS), progression-free rate (PFR), overall survival (OS), overall survival rate (OSR), and safety. The study design focused on *MET*+ disease with documented rearrangement of the *EWSR1* gene by fluorescence *in situ* hybridization (FISH).

Results: Among 43 consenting patients with the local diagnosis of CCSA, 36 had centrally confirmed CCSA, 28 of whom were eligible, treated and evaluable. 26/28 patients had *MET*+ disease, of whom one achieved a confirmed partial response and 17 had stable disease (SD) (ORR 3.8%, 95% CI: 0.1-19.6). Further efficacy endpoints in *MET*+ CCSA were a DCR of 69.2% (48.2-85.7%), a median PFS of 131 days (49-235), and a median OS of 277 days (232-442). The 3, 6, 12 and 24 month PFR was 53.8% (34.6-73.0), 26.9% (9.8-43.9), 7.7% (1.3-21.7) and 7.7% (1.3-21.7), respectively. Half of the *MET*+ CCSA cases had a measurable reduction of target lesions. Among two evaluable *MET*- patients, one had SD and one had progression as best response. The most common treatment-related adverse events were nausea (18/34 [52.9%]), fatigue (17/34 [50.0%]), vomiting (12/34 [35.3%]), diarrhea (11/34 [32.4%]), constipation (9/34 [26.5%] and blurred vision (7/34 [20.6%]).

Conclusion: While objective RECIST responses to crizotinib are uncommon in patients with CCSA with rearrangement of the *EWSR1* gene, shrinkage of target lesions and disease control was observed in a considerable proportion of patients. The outcome of crizotinib treatment in CCSA is similar to results achieved in soft tissue sarcoma with single-agent doxorubicin in first line or with pazopanib in subsequent lines of treatment. Given the long follow-up in this trial, our series will serve as an important resource for further prospective research in this rare and hard to treat malignancy.

Paper 019 3025592

MILADEMETAN, AN ORAL MDM2 INHIBITOR, IN WELL-DIFFERENTIATED/DE-DIFFERENTIATED LIPOSARCOMA: RESULTS FROM A PHASE 1 STUDY IN PATIENTS WITH SOLID TUMORS AND LYMPHOMAS

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Objective: The MDM2 gene is amplified in almost all well-differentiated/de-differentiated liposarcomas (WD/DD LPS), resulting in inactivation of tumor suppressor p53. Therefore, MDM2 may represent a therapeutic target for WD/DD LPS.

Milademetan (DS-3032b) is an oral small-molecule drug that disrupts the MDM2-p53 interaction, resulting in reactivation of wild-type p53 and inducing cell cycle arrest or apoptosis. This phase 1, first-in-human study (NCT01877382) evaluated milademetan in patients with advanced solid tumors or lymphomas, particularly WD/DD LPS.

Methods: Eligible patients had a histologically or cytologically confirmed, relapsed or refractory advanced solid tumor or lymphoma. Patients received milademetan orally at the assigned dose and schedule (Table 1). The primary objectives of this study were to assess the safety and tolerability of milademetan and to determine the maximum tolerated dose (MTD) and tentative recommended phase 2 dose. Secondary objectives included pharmacokinetics (PK), pharmacodynamics (PD), and preliminary efficacy.

Results: 103 patients were enrolled: WD/DD LPS (48 [46.6%]), other sarcomas (7 [6.8%]), melanoma (21 [20.4%]), lymphoma (4 [3.9%]), and other malignancies (23 [22.3%]). Median age was 61 years, 50.5% were male, and 62.1% had ≥ 3 prior cancer therapies. 46/47 (97.9%) patients tested had wild-type *TP53*. Four dosing schedules were evaluated (Table 1). The most common drug-related treatment-emergent adverse events (TEAEs) included hematologic TEAEs (thrombocytopenia, anemia, neutropenia), gastrointestinal TEAEs (nausea, vomiting, diarrhea, anorexia), and fatigue (Table 2). The TEAE profile is consistent with that of previously investigated MDM2 inhibitors. Schedule D (once daily for first 3 d of every 14 d [qd 3/14]) was associated with the lowest incidence of drug-related TEAEs (all grades and grade ≥ 3) and no dose-limiting toxicities (DLTs) at doses up to 260 mg qd 3/14, suggesting that an intermittent dosing schedule may be advantageous in alleviating severe TEAEs, compared with a continuous dosing schedule. In 86 efficacy-evaluable patients, 4 (4.7%) achieved partial response (PR; 1 confirmed and 3 unconfirmed) and 52 (60.5%) achieved stable disease (SD) as the best response. Median duration of SD was 7.2 months (95% CI, 5.4-10.1). Among 39 patients with WD/DD LPS who were evaluable for response, 1 (2.6%) patient achieved PR and 30 (76.9%) patients had SD as the best overall response. Median progression-free survival in patients with WD/DD LPS was 6.3 months (95% CI, 3.8-10.1). PK of milademetan were evaluated. Milademetan exposure (C_{max} and $AUC_{0\text{-}24h}$) generally increased with ascending dose. PD biomarker assessment included serum macrophage inhibitory cytokine 1 (MIC-1) and immunohistochemistry of p53 and MDM2 on paired biopsy samples, showing evidence of p53 activation after milademetan exposure. MDM2 gene amplification data were collected by selected sites and will be presented.

Conclusion: Milademetan given on an intermittent schedule had an acceptable safety profile. Objective responses and durable SD were observed in patients with WD/DD LPS. The preliminarily identified dose and schedule for future studies are 260 mg qd 3/14. Further evaluation of milademetan in WD/DD LPS is warranted.

Table 1. Dosing Schedule and Dose Escalation Cohorts

Schedule, days	Doses, mg	Patients N = 103	Histology	MTD, mg
A: qd 21/28	15, 30, 60, 90, 120, 160, 240	60	Solid tumor or lymphoma	120
B: qd 28/28	90	9		90
C: qd 7/28	120, 200	9	Progressing WD/DD LPS and MDM2-amplified solid tumor	Not achieved
D: qd 3/14-3/14	120, 200, 260, 340	25		260

Table 2. Select Drug-Related Treatment-Emergent Adverse Events of Interest

System Organ Class, Preferred Term, n (%)	Schedule A, B, and C Cohorts (n = 78)		Schedule D Cohorts (n = 25)	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
All drug-related TEAEs	**74 (94.9)**	**42 (53.8)**	**21 (84.0)**	**5 (20.0)**
Blood and lymphatic system disorders				
Thrombocytopenia	30 (38.5)	17 (21.8)	4 (16.0)	3 (12.0)
Anemia	32 (41.0)	12 (15.4)	4 (16.0)	0
Neutropenia	9 (11.5)	7 (9.0)	0	0
Gastrointestinal disorders				
Nausea	57 (73.1)	2 (2.6)	16 (64.0)	0
Vomiting	22 (28.2)	2 (2.6)	9 (36.0)	0
Diarrhea	26 (33.3)	0	8 (32.0)	0
General disorders				
Fatigue	36 (46.2)	3 (3.8)	8 (32.0)	0
Metabolism and nutrition disorders				
Anorexia	27 (34.6)	1 (1.3)	6 (24.0)	0

Paper 020 3042882

PHASE 2 STUDY OF THE CDK4 INHIBITOR ABEMACICLIB IN DEDIFFERENTIATED LIPOSARCOMA

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Objective: The oncogene cyclin-dependent kinase 4 (CDK4) is amplified in >90% of dedifferentiated liposarcomas (DDLS). We previously demonstrated that treatment with the CDK4 inhibitor palbociclib results in favorable progression-free survival (PFS) in DDLS. Abemaciclib is a newer and more potent CDK4 inhibitor. This single-arm phase 2 study was designed to test the activity of abemaciclib in DDLS.

Methods: Participants were adults with advanced DDLS, measurable disease by RECIST 1.1, any (or no) prior therapy, and progression by RECIST in the 6 months prior to study entry. The primary endpoint was PFS at 12 weeks. Based on historical data, promising drugs have 12-week PFS of ≥ 40% and not promising ≤ 20%. This study would be positive if 12-week PFS was ≥ 60%. The study was approved by the Institutional Review Board of Memorial Sloan Kettering Cancer Center and all patients provided written informed consent. The study was registered at Clinicaltrials.gov (NCT02846987) and study drug was provided by Eli-Lilly.

Results: Treatment was abemaciclib 200 mg by mouth twice daily continuously. 22 patients were treated and 21 were evaluable for the primary endpoint. Patient characteristics: Median age 61 (range 39-88), 59% male. Lines of prior therapy: 0 (59%); 1 (23%); ≥ 2 (18%). The observed PFS at 12 weeks was 71% (95% CI 48-89%). There was one partial response. A further 3 patients had > 10% decrease in tumor size by RECIST but did not meet the criterion for partial response. Grade 3-4 toxicity included anemia (36%), neutropenia (23%), thrombocytopenia (18%) and diarrhea (9%).

Conclusion: This study met its primary endpoint. In patients with advanced progressive DDLS, abemaciclib treatment results in favorable PFS and objective tumor response with manageable toxicity. Updated response data and results of correlative studies will be presented.

Paper 021 3042818

PHASE II STUDY OF ATEZOLIZUMAB IN PATIENTS WITH ALVEOLAR SOFT PART SARCOMA

Geraldine O'Sullivan Coyne[1]*; Elad Sharon*[2]*; Nancy Moore*[1]*; Robert Meehan*[3]*; Naoko Takebe*[1]*; Lamin Juwara*[4]*; Laurence Rubinstein*[2]*; William Read*[5]*; Richard F. Riedel*[7]*; Priscilla Merriam*[8]*; James Hu*[6]*; Melissa Burgess*[9]*; James Doroshow*[1]*; Alice Chen*[1]
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Objective: Alveolar soft part sarcoma (ASPS) is a rare disease that occurs most frequently in young adult patients (pts). Data from the NCI Pediatric Preclinical Testing Consortium (PPTC) have shown consistent programmed death ligand 1 (PD-L1) gene expression in ASPS xenograft models, and immunohistochemical analysis of clinical specimens has demonstrated PD-1-expressing CD8 T cells and PD-L1-expressing sarcoma cells present in metastatic ASPS lesions. This trial evaluates the activity of single agent atezolizumab, a human monoclonal antibody directed against PD-L1, in adult and pediatric pts with advanced ASPS (NCT03141684, on behalf of the Experimental Therapeutics Clinical Trials Network-ETCTN). The primary objective of the study is to determine the objective response rate using RECIST v 1.1. Secondary objectives include comparison of RECIST v 1.1 with immune RECIST (iRECIST) criteria, and correlation of response with expression of immune biomarkers in paired biopsies. Here we report results for adult pts.

Methods: This is an open-label study in which atezolizumab is administered intravenously at a fixed dose of 1200 mg once every 21 days. Patients ≥6 years of age are eligible (pediatric patients receive atezolizumab at 15 mg/kg, with a maximum dose of 1200 mg). Simon 2-stage design with 9 pts being enrolled in stage I; if at least one partial responses (PR) is observed in stage I, enrollment will proceed to stage II for a total of 24 evaluable pts. Tumor biopsies will be collected in up to 15 adult pts at baseline and post-treatment (prior to cycle 3 day 1, or at any point where there is evidence of clinical response) for evaluation of exploratory biomarkers. Biomarker analyses will include assessment of immune status (measurements of

CD8 cells, CD4 cells, Tregs, levels of TCR and ZAP70 activation), epithelial-mesenchymal transition, and intrinsic apoptosis signaling.

Results: Eighteen pts have been enrolled as of June 1st, 2018. Stage I met its objective and enrollment on stage II is ongoing. The average age on study is 33 years (range, 22-45). PRs was observed in 7/18 pts (39%) with 5/7 pts (28%) having a confirmed PR. Three pts have come off study to date for the following reasons: progressive disease (1 pt, 1 cycle), patient choice (1 pt, unconfirmed PR after 2 cycles), and physician's discretion (1 pt, 5 cycles). The median time to first response was 5 cycles (range, 1-17), and the median time on study is 4.5 cycles (range, 1-19). Drug-related adverse events reported to date include: grade 3 extremity pain (1 pt), grade 2 hypoxia (2 pts), lymphopenia (2 pts), fever (1 pt), anemia (1 pt), fatigue (1 pt). No grade 4 or higher events have been reported.

Conclusion: Atezolizumab is safe and clinically active in pts with ASPS, with a manageable toxicity profile reported to date. Exploratory biomarker analysis in tumor specimens is ongoing.

Paper 022 3033993

EZH2 INHIBITOR TAZEMETOSTAT (TAZ) INTERIM DATA IN ADULTS AND PEDIATRIC PATIENTS WITH INI1-NEGATIVE SOFT-TISSUE SARCOMAS (STS) INCLUDING EPITHELIOID SARCOMA (ES) (NCT02601950, NCT02601937)

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Objective: STS are a heterogeneous group of malignancies and current treatments can have significant toxicities and limited clinical activity. Tumor INI1 loss can occur in STS, including >90% of ES cases. Loss of INI1, a critical subunit of the SWI/SNF complex, leads to oncogenic dependence on EZH2 through transcriptional repression caused by aberrant H3K27me3. TAZ, a potent, selective, oral EZH2 inhibitor has demonstrated tumor regression in INI1-negative preclinical models and clinical activity in phase 1 and 2 trials in INI1-negative sarcomas.

Methods: Data from two open-label multicenter trials (phase 1 pediatric and phase 2 adult) of patients with INI1-negative tumors, including ES, evaluating safety and efficacy of TAZ are reported. Primary and secondary endpoints included ORR by RECIST 1.1, disease control rate (DCR; objective confirmed response of any duration or stable disease [SD] lasting ≥32 weeks), duration of response, PFS, OS, safety/tolerability, PK response biomarkers, and recommended phase 2 dose (RP2D) (phase 1 only).

Results: As of April 6, 2018, 75 STS patients (62 ES and 13 other INI1-negative STS) were enrolled in the phase 2 adult study and as of Jan 16, 2018, 6 ES patients were enrolled in the phase 1 pediatric study. Adults were treated at RP2D of 800 mg BID and ES pediatric patients were treated at 300 (n=1), 700 (n=1) and 1200 (n=4) mg/m^2 BID. The median number of prior lines of therapy in all patients was 1. In adults, there were 10 confirmed partial responses (PRs) (2 with STS, not otherwise specified [NOS] with spindle cell morphology, and 8 with ES) with an ORR of 13% and DCR of 25%. Of the 2 sarcoma NOS patients, 1 remains on treatment at 2 years with an ongoing PR of 48 weeks, and the other remains on treatment at 1 year with an ongoing PR of 16 weeks. Median duration of response of the 10 patients was 41 weeks (range 8-70). The best responses observed in the 6 pediatric ES patients was 1 CR (700 mg/m^2) lasting 20 weeks, 3 SD (1 at 300 mg/m^2, 2 at 1200 mg/m^2), and 2 PD (1200 mg/m^2). Further, 1 pediatric patient with SD (1200 mg/m^2) achieved a CR which is ongoing. TAZ was generally well tolerated in the adult population; no patients discontinued due to an adverse event (AE). AEs were generally mild to moderate with the most frequently reported AEs regardless of attribution being fatigue (36%), nausea (33%), and cancer pain (28%), which is consistent with AEs reported in pediatric patients. However, subsequent

to the data cut, one pediatric patient with INI1-neg poorly differentiated chordoma treated with TAZ at 900 mg/m2 BID developed T-cell lymphoblastic lymphoma after 15 months of treatment.

Conclusion: TAZ demonstrated clinical activity in children and adults with INI1-negative STS, including ES. AEs were mild to moderate in this population, allowing patients to continue on study long term. However, a pediatric patient with a confirmed PR developed T-cell lymphoblastic lymphoma after 15 months of treatment with TAZ. These data support previously reported clinical activity in patients with INI1-negative STS.

Paper 023 3029169

ACTIVITY OF LAROTRECTINIB IN SARCOMA PATIENTS WITH TRK FUSION CANCER

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Objective: Tropomyosin receptor kinases (TRKs) are encoded by **n**eurotrophic **t**yrosine **r**eceptor **k**inase genes (*NTRK*s). Aberrant genomic translocations involving *NTRK* genes have been shown to give rise to constitutively active, oncogenic TRK fusion proteins. Larotrectinib is a potent and highly selective TRK inhibitor. In a recent pooled analysis from three studies involving 55 patients (pts) with TRK fusion cancer, an objective response rate (ORR) of 75% and 80% (per independent and investigator assessment, respectively) was reported (Drilon et al., *NEJM* 2018). Here, we summarize the activity and safety of larotrectinib in pts with TRK fusion sarcomas.

Methods: Pediatric and adult pts with cancers harboring *NTRK* gene fusions (identified by local testing) were enrolled on one of 3 clinical trials (NCT02122913, NCT02637687, and NCT02576431). Most patients received the dose equivalent of 100 mg BID on a continuous 28-day schedule. Efficacy was assessed by an independent review committee using RECIST v1.1. Patients enrolled on NCT02637687 were allowed to have on-study surgery and to re-start larotrectinib if the surgery did not result in clear margins, and were able to undergo adjuvant radiation. These pts had "best response" data censored at time of surgery. Patients could be called a surgical complete response (sCR) if they had no viable tumor cells on pathology review of the surgical specimen.

Results: As of July 17, 2017, 24 pts with TRK fusion sarcoma were enrolled and assessed by IRC, including 13 with soft tissue sarcomas (STS), 8 infantile fibrosarcoma (IFS) and 3 gastrointestinal stromal tumors (GIST). The STS pts ranged in age from 1-61 yr (median 15 yr), the IFS pts ranged from 1 mo to 3 yr (median 9 mo) and the GIST pts from 32-57 yr. Eight distinct *NTRK* gene fusions were detected with the *ETV6-NTRK3* fusion being the most common (11 pts). Other fusions identified included six *TPM3-NTRK1*, two *LMNA-NTRK1*, and one each *LMNA-NTRK3*, *PDE4DIP-NTRK1*, *SQSTM1-NTRK1*, *STRN-NTRK2*, and *TPM4-NTRK3*. The objective response rate was 96% (23/24), with 6 complete responses, 1 sCR, 16 partial responses, and one patient with progressive disease as best response. As of February 19, 2018, eight additional pts (4 STS, 2 IFS and 2 GISTs) have been enrolled. With these expanded numbers of pts, the objective response rate is now 91% overall; 88% in STS (15/17), 90% in IFS (9/10), and 100% in pts with GIST (5/5). Six pts underwent surgical resection, with 3 pts having had R0 resections and stopped larotrectinib without recurrence. Three pts continued therapy with larotrectinib post-surgery due to R1 or R2 resection; the single patient with R2 resection also underwent adjuvant radiation to the surgical bed. Median duration of response has not been reached in any group. Larotrectinib was very well tolerated, with treatment-related adverse events being predominantly grade 1 and 2.

Conclusion: Larotrectinib is highly active and very well tolerated in pts with sarcomas harboring any *NTRK* gene fusions. These results strongly support the inclusion of *NTRK* gene fusions as part of routine molecular testing for pts with advanced sarcoma.

1:30 pm – 3:30 pm

– SESSION 5 –

Benign and Intermediate Grade Bone/Soft Tissue Lesions

Paper 024 3042858

RISK FACTORS IN TENOSYNOVIAL GIANT CELL TUMOURS OF LARGE JOINTS, EVALUATED IN 30 INTERNATIONAL SARCOMA CENTERS

***Monique Mastboom**; Emanuela Palmerini; Floortje Verspoor; Anja Rueten-Budde; Silvia Stacchiotti; Eric Staals; Gerard Schaap; Paul Jutte; Will Aston; Andreas Leithner; Dietmar Dammerer; Akihiko Takeuchi; Quirina Thio; Xiaohui Niu; Jay Wunder; Michiel A. van de Sande*

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Objective: Tenosynovial Giant Cell Tumour (TGCT), previously Pigmented Villonodular Synovitis (PVNS), is a rare, locally aggressive neoplasm. Two types are distinguished: localized- and diffuse-TGCT. A multicenter-pooled database of individual patient data is essential to evaluate individualized risk factors for recurrent disease.

Methods: 2169 (941 localized-, 1192 diffuse-type, 36 unknown) histologically proven TGCT cases of large joints were included, treated between 1990-2017 in one of 30 sarcoma centers globally. Patient inclusion was performed at time of admission at tertiary center. In localized-TGCT, 62% was female with median age at first treatment of 39 years and median follow-up of 34 months. 67% affected the knee and primary treatment at tertiary center was one-staged open synovectomy in 71%. In diffuse-TGCT, 58% was female, median age 35 years and median follow-up 53 months. 64% affected the knee and in 53% primary treatment was one-staged open synovectomy. Proposed risk factors for TGCT were age(continuous), sex(male;female), site(knee;hip;ankle;other), size(≤2;2-5;>5cm), bone-involvement(present;absent), surgical technique(open;arthroscopic) and admission(therapy-naïve;recurrent disease). All were tested in a univariate analyses and significant proposed risk factors subsequently included for multivariate analyses, with endpoint first local recurrence after treatment in the tertiary center. Previous treatments performed elsewhere are regarded a confounder. Recurrent disease was defined as new disease presence after (sub)total synovectomy or growing residual disease.

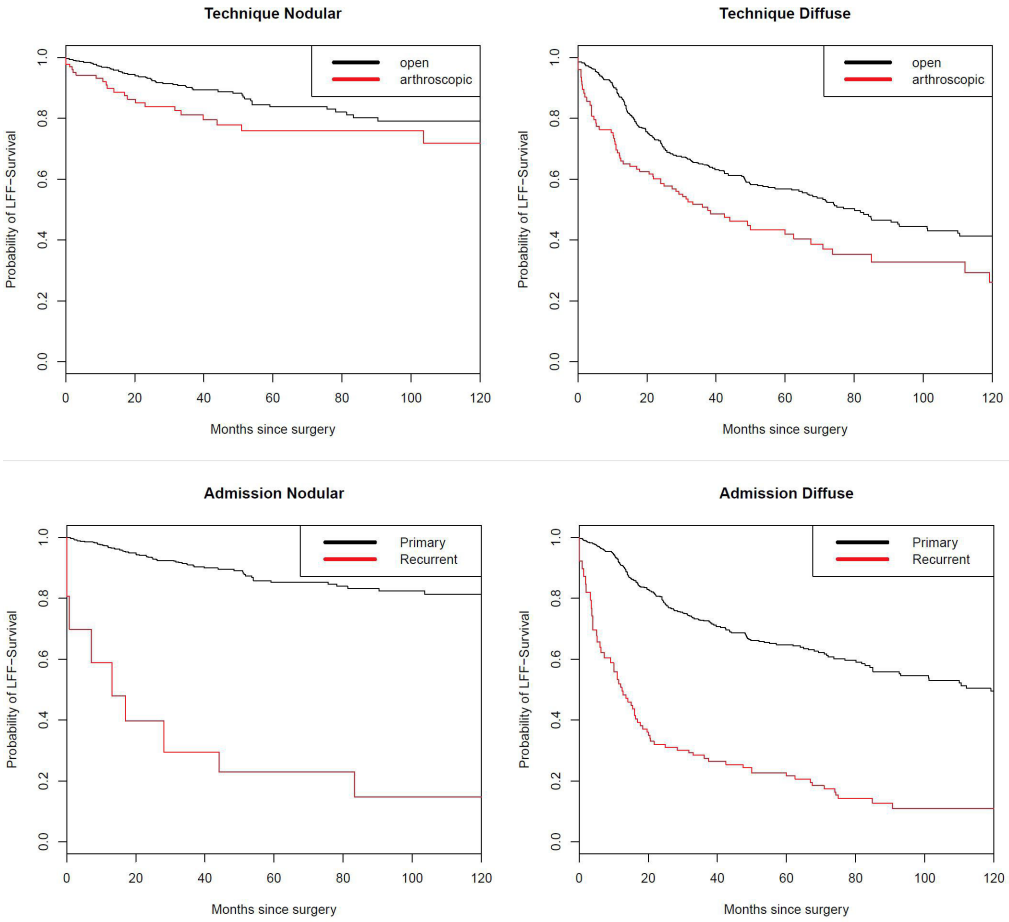
Results: Total number of recurrent disease in localized-TGCT was 14% with local recurrence free survival at 3, 5 and 10 years of 89, 83 and 78 respectively. In diffuse-TGCT, 45% total number recurrences was calculated, accompanied with local recurrence free survival at 3, 5 and 10 years of 62, 54 and 38, respectively. In localized-TGCT, arthroscopic synovectomy HR1.70(95%CI 1.07-2.69) was significantly associated with the outcome in both univariate and multivariate analyses($p<0.024$). In diffuse-TGCT, arthroscopic synovectomy HR1.39(95%CI 1.07-1.80) and recurrent disease admission HR4.02(95%CI 3.18-5.07) was significantly associated in both analyses($p<0.013$). In multivariate analyses of diffuse-type, differences in recurrences were found between knees and the following joints: hip HR1.04(95%CI0.73-1.47;$p=0.83$), ankle HR0.79(95%CI0.56-1.12;$p=0.18$) and other joints HR0.85(95%CI0.61-1.18;$p=0.34$). Complications were noted in 4% for localized and 12% for diffuse disease. At final follow-up, after mean 1 surgery 87% of localized- and after mean 2 surgeries 68% of diffuse-TGCT were disease free.

Conclusion: Surgical treatment of TGCT involves a relatively high risk for postoperative complications and a high risk for local recurrent disease. Risk factors of first local recurrence in both localized- and diffuse-TGCT are initial treatment with arthroscopic synovectomy and in diffuse-type admission with recurrent disease. Identification of risk factors for recurrent disease is necessary to define eligible patients for multimodality (systemic and other (neo)adjuvant) treatment possibilities in TGCT.

	Localized-TGCT	Diffuse-TGCT
Total number	941	1192
Median age at first treatment (IQR) years (L881, D 1121)	39 (27-50)	35 (26-48)
Median duration of symptoms (IQR) months (L 571, D 744)	9 (4-24)	18 (6-36)
Gender		
Male	360 (38%)	499 (42%)
Female	581 (62%)	693 (58%)
Side (L 885, D 1033)		
Left	418 (47%)	460 (45%)
Right	467 (53%)	573 (55%)
Joint		
Knee	633 (67%)	758 (64%)
Hip	37 (4%)	124 (10%)
Ankle	119 (13%)	162 (14%)
Foot*	58 (6%)	63 (5%)
Shoulder	9 (1%)	15 (1%)
Elbow	14 (2%)	17 (1%)
Wrist	24 (3%)	25 (2%)
Hand*	33 (4%)	13 (1%)
Other	14 (2%)	15 (1%)
Bone involvement (L 689, D 847)		
Absent	632 (92%)	588 (70%)
Present	57 (8%)	259 (30%)
Admission (L 941, D 1192)		
Therapy naïve	897 (95%)	910 (76%)
>1 Surgery elsewhere	44 (5%)	282 (24%)
Pain prior to first treatment (L 767, D 969)		
Absent	207 (27%)	231 (24%)
Present	560 (73%)	738 (76%)
Swelling prior to first treatment (L 675, D 775)		
Absent	227 (34%)	196 (25%)
Present	448 (66%)	579 (75%)
Stiffness prior to first treatment (L 663, D 759)		
Absent	598 (90%)	598 (79%)
Present	65 (10%)	161 (21%)
Limited range of motion prior to first treatment (L 667, D 760)		
Absent	557 (84%)	551 (73%)
Present	110 (16%)	209 (27%)
Mean total number surgical treatment (L 747, D 876)	1.1 (range 0-5)	1.8 (range 0-10)
Treatment I (L 941, D 1192)		
Arthroscopy	147 (16%)	207 (17%)
One-staged open synovectomy	669 (71%)	631 (53%)
Two -staged open synovectomy	8 (1%)	175 (15%)
(Tumour)prosthesis	21 (2%)	55 (5%)
Amputation		3 (0.3%)
Wait and see	64 (7%)	67 (6%)
Synovectomy not specified	32 (3%)	54 (5%)
Median tumour volume I (IQR) cm (L 627, D 652)	3.0 (2.0-4.5)	5.4 (3.0-8.8)
Adjuvant therapy I (L 787, D 1033)		
Radiotherapy	8 (1%)	58 (6%)
^{90}Yttrium	21 (3%)	60 (6%)
Systemic	2 (0.3%)	15 (1%)
Other	11 (1%)	11 (1%)
Nothing	745 (95%)	889 (86%)
Complication I (L 763, D 906)		
Superficial wound infection	11 (1%)	15 (2%)
Deep wound infection	1 (0.1%)	10 (1%)
Joint stiffness	5 (0.7%)	32 (4%)
Haemorrhage	1 (0.1%)	7 (1%)
Neurovascular damage	3 (0.4%)	15 (2%)
Thrombosis	2 (0.3%)	1 (0.1%)
Other	11 (1%)	25 (3%)
No complication	729 (96%)	801 (88%)
First recurrence (L 902, D 1131)		
Absent	776 (86%)	624 (55%)
Present	126 (14%)	507 (45%)
Median time to first recurrence (IQR) months (L 96, D 435)	36 (10-50)	24 (12-53)
Median follow-up (IQR) months (L 776, D 978)	34 (10-70)	53 (26-97)
Status last follow-up (L 835, D 1063)		
No evidence of disease	729 (87%)	723 (68%)
Alive with disease - wait and see	71 (9%)	249 (23%)
Alive with disease - awaiting treatment	9 (1%)	42 (4%)
Deceased	5 (0.1%)	19 (2%)
Lost	21 (3%)	30 (3%)

L, localized-TGCT; D, diffuse-TGCT

*digits are excluded



Paper 025 3038487

POSITIVE ASSOCIATION BETWEEN TUMOR RESPONSE AND PATIENT-REPORTED OUTCOMES IN PHASE 3 ENLIVEN STUDY OF PEXIDARTINIB IN TENOSYNOVIAL GIANT CELL TUMOR (TGCT)

*Heather L. Gelhorn[1]; Charles Peterfy[2]; Xin Ye[3]; **Rebecca M. Speck**[1]; Emanuela Palmerini[4]; Silvia Stacchiotti[5]; Jayesh Desai[6]; Andrew Wagner[7]; Thierry Alcindor[8]; Kristen Ganjoo[9]; Javier Martín-Broto[10]; Christopher Ryan[11]; Qiang Wang[3]; Dale Shuster[3]; William D. Tap[12]; Hans Gelderblom[13]*

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Objective: The standard of care for TGCT is tumor surgical resection, but for patients with diffuse or multinodular disease, the tumor may be difficult to completely remove and has a high rate of local recurrence. TGCT is marked by a disease-specific fusion involving the colony-stimulating factor 1 receptor gene (CSF1R). Pexidartinib is a novel investigational CSF1R inhibitor that was evaluated in TGCT within the ENLIVEN study. Results demonstrated significant tumor response as well as improved patient symptoms and function with pexidartinib versus placebo (39% vs 0% by Response Evaluation Criteria in Solid Tumors version 1.1 [RECIST], P < 0.0001; 56% vs 0% by tumor volume score [TVS], P < 0.0001). Serious liver toxicity with increased bilirubin was observed in 4% of patients (Tap et al. 2018 ASCO Annual Meeting). The objective of this analysis was to evaluate the relationship between changes in tumor size and patient-reported outcome (PRO) measures of physical function, stiffness, and pain.

Methods: ENLIVEN was a double-blind, randomized, placebo-controlled phase 3 study of pexidartinib in patients with locally advanced TGCT. The primary endpoint was independent assessment of tumor response rate at week 25 based on central review of MRI scans using RECIST. Secondary endpoints included range of motion, TVS, PRO measures of physical functioning (Patient-Reported Outcomes Measurement Information System−Physical Function scale [PROMIS-PF]),

stiffness (worst stiffness numeric rating scale [NRS]), pain (Brief Pain Inventory [BPI] worst pain NRS and analgesic use), and duration of response. For this analysis, the relationships between maximum percentage change from baseline in tumor size (RECIST and TVS) and percentage change in PRO measures were evaluated through Pearson correlation coefficients (r) for all evaluable patients.

Results: 120 patients were randomized to pexidartinib (n = 61) and placebo (n = 59). Demographics and baseline characteristics include median age 44 years (22-75) for pexidartinib and 45 years (18-79) for placebo. The majority of patients were female, 35 (57%) for pexidartinib and 36 (61%) for placebo. The most prevalent disease location was the knee, 34 (56%) for pexidartinib and 39 (66%) for placebo. Mean greatest change ± standard deviation (SD) in sum of longest diameters (SLD) were −36.6% ± 33.6% and −1.7% ± 6.8% for pexidartinib and placebo, respectively; mean greatest change in TVS were −51.7% ± 31.4% and −1.0% ± 9.5%. Least squares (LS) mean change ± standard error (SE) for PROMIS-PF was improved with pexidartinib (+4.1 ± 1.1) but not with placebo (−0.9 ± 1.0], P = 0.0019); LS mean change in worst stiffness NRS also favored pexidartinib (−2.5 ± 0.3) compared with placebo (−0.3 ± 0.3, P < 0.0001). The prespecified responder analysis of BPI worst pain NRS, defined as ≥ 30% improvement without use of an analgesic, favored pexidartinib (31% vs 15%) but did not reach statistical significance (P = 0.032, 1-sided). However, exploratory analysis of LS mean changes in BPI worst pain NRS favored pexidartinib (−2.5 ± 0.3 vs −0.6 ± 0.3). Reductions in RECIST SLD were moderately correlated with improvements in PROs, with r = −0.36 for PROMIS-PF, r = 0.40 for worst stiffness NRS, and r = 0.41 for worst pain NRS. Correlations of changes in TVS with the 3 PROs tended to be stronger, with r = −0.47 for PROMIS-PF, r = 0.62 for worst stiffness NRS, and r = 0.63 for BPI worst pain NRS.

Conclusion: Reduction in tumor size was correlated with improvement of PROs in the ENLIVEN study of pexidartinib in TGCT.

Paper 026 3042414

PRIMARY VASCULAR TUMORS OF BONE: AN ANALYSIS OF 427 PATIENTS

Marta Sbaraglia[1]*; Alberto Righi*[2]*; Marco Gambarotti*[2]*; Dino Gibertoni*[3]*; Stefania Benini*[2]*; Piero Picci*[2]*; Angelo Paolo Dei Tos*[1]

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Objective: Recently, there have been several important refinements in the classification of vascular tumors of bone also in consideration of newly reported molecular genetic findings.

Methods: To further investigate the clinical relevance a refined classification of vascular tumor of bone, we reviewed all cases of primary bone vascular treated at our Institute. Based on morphology cases were assessed immunohistochemically (FOS-B, CAMTA1 and TFE3) and molecularly (*WWTR1-CAMTA1* and *YAP1-TFE3* genes fusion by RT-PCR, and *CAMTA1, FOS, WWTR1* and *TFE3* gene rearrangements by FISH).

Results: Following morphological, immunohistochemical and/or molecular analysis, 427 primary bone vascular tumors were confirmed as vascular neoplasms based on expression of endothelial markers (CD31 and ERG). Histologies were as follows: 289 hemangiomas, 38 epithelioid hemangiomas, 22 epithelioid hemangioendothelioma, 2 retiform hemangioendothelioma, 1 intraosseous papillary intralymphatic angioendothelioma, 24 pseudomyogenic hemangioendothelioma and 51 angiosarcoma (of these 44 epithelioid angiosarcomas and 7 secondary spindle cells angiosarcoma). Among 289 hemangiomas, 4 patients had a local recurrence after the curettage. All patients were alive without disease at the last follow-up (mean, 92 months). Four out of 38 epithelioid hemangiomas, treated with curettage, recurred with a mean of 76 months, but none of these 38 patients had a fatal outcome or developed distant metastasis. Among 24 pseudomyogenic hemamgioendothelioma 3 recurred locally following curettage, and at the last follow-up (mean 121 months), 3 patients died of other cause, 5 are alive with disease and the remaining 16 patients were alive without disease. Regarding 22 cases of epithelioid hemangioendothelioma, during the follow-up (mean: 65 months), two patients recurred locally after curettage and 6 developed distant metastases to lungs, bone, and soft tissue. Three patients died of disease, with widespread metastases to lungs and bone, three were alive with metastatic disease and five died of unrelated cause. Eleven patients are disease free at the last follow-up. Thirty-seven out of 51 patients with an angiosarcoma died of disease with a mean of 12 months from diagnosis; 3 patients died of other diseases; 5 patients are alive with multicentric diseases and 6 patients are disease-free at last follow-up (mean 112 months). Log-rank test analysis showed significant statistical differences in terms of DFS and OS between epithelioid hemangioma and epithelioid hemangioendothelioma (p=0.004 for DFS and p=0.001 for OS) and between epithelioid hemangioendothelioma and epithelioid angiosarcomas (p<0.001 both for DFS and for OS).

Conclusion: The refined classification of primary vascular neoplasms of bone provides important clinical implications, and the appropriate use of ancillary diagnostic tests increases significantly diagnostic accuracy. Among epithelioid vascular bone tumors, distinguishing hemangioma, hemangioendothelioma, and angiosarcoma translates into statistically significant clinical differences. In our series, pseudomyogenic hemangioendothelioma of bone has an indolent clinical course with a minimal risk of metastasis.

Paper 027 3042427

PHASE II TRIAL OF PAZOPANIB IN ADVANCED EXTRASKELETAL MYXOID CHONDROSARCOMA. A COLLABORATIVE SPANISH (GEIS), ITALIAN (ISG) AND FRENCH (FSG) SARCOMA GROUPS STUDY

Silvia Stacchiotti[1]*; Stefano Ferrari*[2]*; Antonio Redondo*[3]*; Emanuela Palmerini*[2]*; Nadia Hindi*[4]*; Maria A. Vaz*[5]*; Anna Maria Frezza*[1]*; Antonio Gutierrez*[6]*; Antonio Lopez-Pousa*[16]*; Tiziana Venesio*[7]*; Antoine Italiano*[8]*; Sarah N. Dumont*[9]*; Jean-Yves Blay*[10]*; Nicolas Penel*[11]*; Daniel Bernabeu*[12]*; Enrique De Alava*[13]*; Dominique Ranchere-Vince*[10]*; Gian Paolo Dagrada*[1]*; Paola Collini*[1]*; Josefina Cruz*[14]*; Javier Martín-Broto*[15]

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Objective: Extraskeletal myxoid chondrosarcoma (EMC) is an exceedingly rare sarcoma, marked by a specific translocation involving the gene NR4A3 that can be rearranged with different partners. Preliminary retrospective data suggest that sunitinib is active, but no formal prospective studies are available. We report on a multicentric European prospective, investigator-driven, Phase 2 study on pazopanib (P) in NR4A3+ advanced EMC patients (pts), carried out by the Spanish, Italian and French Sarcoma groups.

Methods: From June 2014 to January 2017, 26 advanced adult EMC pts entered this study (median age: 63 yrs; disease extent: metastatic vs locally advanced = 88% vs 12%; prior medical treatment: naive = 21 (81%), fist line = 2 (8%), >1 line = 3 (11%)). Pathological diagnosis and *NR4A3* rearrangement (FISH and/or real-time PCR analysis) were centrally confirmed. In 18 (69.5%) cases NR4A3 was fused with EWSR1, in 2 (7.5%) with TAF 15 while in 6 (23%) case the partner was unknown. Pts had to have evidence of progression in the 6 months before study entry. Pts received P 800 mg/day (relative dose intensity = 0,82%, 658 mg/day), until progression or toxicity. The primary study end-point was objective response rate (ORR) as per RECIST 1.1. Secondary end-points were overall survival, progression-free survival (PFS), clinical benefit rate (CBR) (RECIST CR+PR+SD≥6mos).

Results: Twenty-five/26 pts were evaluable for response (1 early death). 4 pts (16%) had a partial response, 17 (68%) stable disease, 4 (16%) progressed. At the time of this analysis, 5 pts were still under treatment, while 21 interrupted P (18 progression, 1 toxicity, 2 other). In all responsive pts, NR4A3 was fused with EWSR1. At a 27-month median follow-up, the median PFS was 13.5 months (95%CI: 0.6-26.4), with 46% pts being progression-free at 24 months and 65% CBR. 12- and 24-month OS rate for the overall population were 88% and 83%, respectively, while median OS was not reached. 12- and 24-month OS rate for EWSR1-fused cases were 94% and 87%, respectively.

Conclusion: This Phase 2 study shows that pazopanib is active in advanced EMC. Although the RECIST ORR was limited (16%), P was associated with a prolonged disease stabilization in a high proportion of pts, all being progressing at study entry. Interestingly, all responsive patients carried a NR4A3-EWSR1 rearrangement.

Paper 028 3042598

LONGITUDINAL DISTRESS ASSESSMENT AND RESPONSE TOOL (DART) SCREENING IN ADULTS WITH AGGRESSIVE FIBROMATOSIS: HIGH PREVALENCE OF PERSISTENT EMOTIONAL DISTRESS

Abha Gupta[1]*; Nicole Byers*[1]*; Sally Burtenshaw*[2]*; Katrina Ingley*[2]*; Carol Swallow*[2]*; Savtaj Brar*[2]*; Anthony M. Griffin*[2]*; Peter Ferguson*[2]*; Jay Wunder*[2]*; Albiruni Razak*[1]*; Rebecca Gladdy*[2]*; Roberta Klein*[3]*; Madeline Li*[3]

[1]Medical Oncology, Princess Margaret Cancer Center, Toronto, ON, Canada; [2]Surgery, Mount Sinai Hospital, Toronto, ON, Canada; [3]Psychiatry, Princess Margaret Cancer Center, Toronto, ON, Canada

Objective: Clinical experience suggests a high prevalence of emotional distress in patients with aggressive fibromatosis (AF). This is unexpected for a benign tumour, and has not been previously studied. The Distress Assessment and Response

Tool (DART) is a symptom screening program established at the Princess Margaret Cancer Centre (PM). We examined longitudinal DART scores in patients undergoing treatment and follow-up for AF to describe the prevalence and persistence of symptom distress in this population.

Methods: Patients being evaluated at PM for AF complete DART on electronic tablets at every visit as part of routine standard of care. Patients with AF were identified in the DART database through data linkage from the institutional cancer registry, and clinical and demographic data were extracted from the sarcoma database. DART scores corresponding to 4 time-points were analysed: T1: pre-diagnosis to start of treatment, T2: during treatment, T3: < 6 months post-treatment, and T4: ≥6 months post-treatment.

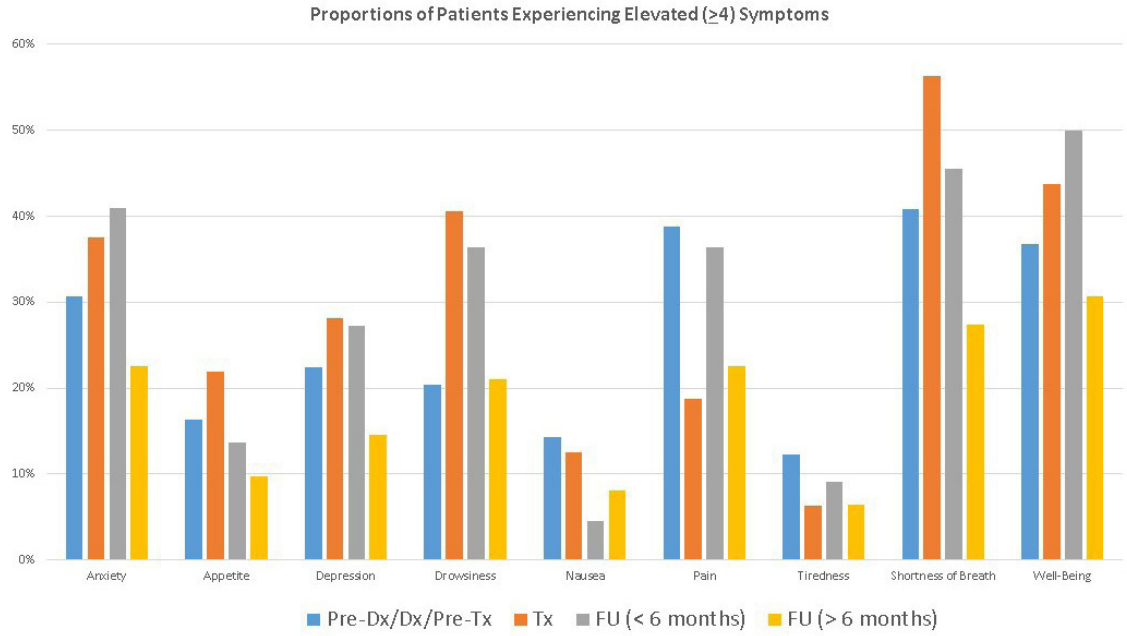
DART includes validated patient-reported outcome measures of physical symptoms (ESAS-r), depression (PHQ-9), anxiety (GAD-7), and social difficulties (SDI-21). An ESAS-r symptom score of ≥4 is considered significant, and threshold ESAS-r scores on anxiety and depression trigger GAD-7 and PHQ-9, respectively. Descriptive symptom distress prevalence data are reported over time, and in comparison to the average annual symptom prevalence in sarcoma patients at PM recorded in the DART database.

Results: From 2010-2018, a total of 165 DART screens from 101 AF patients were completed (n=49 at T1, n=32 at T2, n=33 at T3, n=62 at T4). Patients had a mean age of 40+/-13 years; 75% were female. Site distribution was as follows: abdominal wall: 48%, head/neck: 10%, lower extremity: 11%, mesentery: 12%, and other: 19%. Treatment included medical therapy: 60.5%, observation only: 26%, surgery only: 11%, and other: 2.5%. Overall, mean ESAS-r scores (±SD) were (n=165): anxiety: 2.5 (±2.7), poor appetite: 1.2 (±2.2), depression: 1.9 (±2.6), drowsiness: 2.2 (±2.6), nausea: 0.9 (±1.9), pain: 2.3 (±2.6), dyspnea: 0.8 (±1.7), tiredness: 3.3 (±2.9), and poor well-being: 3.1 (±2.7). PHQ-9 and GAD-7 screening was triggered in 40% and 39%, respectively.

Persistent elevated symptom distress (ESAS-r >=4) was observed for anxiety (T1: 31%, T2: 38%, T3: 41% and T4: 23%), depression (T1: 22%, T2: 28%, T3: 27% and T4: 15%), dyspnea (T1: 41%, T2: 56%, T3: 45% and T4: 27%), and poor well-being (T1:37%, T2: 44%, T3: 50% and T4: 31%). Emotional distress triggering PHQ-9 or GAD-7 was persistent (T1:40%, T2: 38%, T3: 39% and T4:40%). In comparison, among sarcoma patients at PM, the average proportion of patients with ESAS-r >=4 was 19% for anxiety, 15% for depression, 13% for dyspnea and 28% for poor well being.

There was significant correlation between anxiety and depression (R=0.74) for all patients, pain with anxiety (R=0.70) at T3, pain with depression (R=0.71) at T4, and dyspnea with anxiety (R=0.72) at T4.

Conclusion: Adults with AF experience a significant amount of anxiety, depression, dyspnea and poor well-being which persists beyond the end of treatment, and is more prevalent than is observed in adults with sarcoma. Work is ongoing to explore clinical and psychosocial predictors of persistent emotional distress in AF patients. Increased attention to mental health in adults with AF is required at all stages of the treatment journey.



Paper 029 3042617

CAN WAIT AND SEE BE THE STANDARD OF CARE FOR INITIAL APPROACH TO PRIMARY SPORADIC DESMOID TUMORS? PRELIMINARY DATA FROM AN ITALIAN SARCOMA GROUP PROSPECTIVE STUDY

Chiara Colombo[1]*; Marco Fiore*[1]*; Tiziana Venesio*[2]*; Erica Palesandro*[2]*; Paola Boccone*[2]*; Lorenzo D'Ambrosio*[2]*; Alba Bianco*[1]*; Paola Collini*[1]*; Elena Palassini*[1]*; Silvia Stacchiotti*[1]*; Angelo Paolo Dei Tos*[3]*; Paolo Casali*[1]*; Federica Perrone*[1]*; Alessandro Gronchi*[1]

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Objective: In recent years, retrospective evidence of long term disease stabilization and spontaneous regression of sporadic desmoid tumor (SDT) has been provided. As a result, a frontline wait and see approach (W&S) has been more routinely proposed. CTNNB1 coding for β-catenin is mutated in more than 90% of patients. Furthermore, a specific mutation (45F) was found to be correlated with a worse post-surgical local outcome. However, the prognostic role of β-catenin mutations is not fully understood and has never been explored in patients under W&S before any active therapy is performed. The main objective of this study was to prospectively evaluate the role of W&S in patients with primary SDT and to correlate β-catenin mutational status with the clinical outcome.

Methods: This is a prospective, multicenter (Fondazione IRCCS Istituto Tumori Milano and IRCCS Istituto Candiolo) observational study (founded by Ministero della Salute, Ricerca Finalizzata- NCT 02547831), performed among Italian Sarcoma Group centers and aim at evaluating the progression rate in patients affected by primary SDT managed with a front-line conservative approach (W&S). Active treatments were only proposed upon clear disease progression. β-catenin mutational status has been analyzed.

Inclusion criteria were:
-Pathological diagnosis of SDT
-Primary disease at diagnosis or incompletely resected residual disease (R2 resection)
-Intra- and extra-abdominal SDT
-Histological diagnosis confirmed by expert sarcoma pathologists (PC and MB) according to the WHO criteria
-Measurable disease evaluated by on contrast-enhanced MRI (ce-MRI) T1 and T2 weighted images or contrast enhanced CT scan (for intra-abdominal location)

Patient and tumor-related factors, treatment variables, follow up findings, time to progression and status at last follow-up were recorded. Follow-up (FU) schedule required clinical evaluation and ce-MRI (or CT scan) at 3, 6, 9, 12 months, then every 6 months until the third year. Upon progression, defined as tumor growth proven by imaging and/or clinical examination, active treatments were proposed according to physician's preference and registered in the clinical database.

Results: Between 2013 and 2018 a total of 114 patients entered the study (82% female, 18% male); median age 39 (IQ, 35-49) years; sites distribution: abdominal wall (52%), trunk (24%), extremity (18%), intra-abdominal (3%), head/neck (3%). CTNNB1 mutational status was available in 87% of patients. Median follow-up was 11 (IQ, 6-23) months. At the time of last follow up: 4/114 had spontaneous complete regression, 23/114 spontaneous partial regression, 36/114 stable disease, 48/114 progression. For the last 3 patients enrolled status is still unknown. Among patients with stable disease, 6/36 initially experienced a progression and 5/36 initially experienced partial regression, while disease remained stable after that. Among patients with progression, 34/48 needed to start an active treatment. The median time to an active treatment was 6 (IQ range, 4-13) months. A preliminary analysis on the correlation between β-catenin mutational status and outcome revealed that 6/11, 12/51, 4/20 and 5/18 patients with DT harboring 45F, 41A, WT or other mutations had to start an active treatment for progression, respectively. No patient required surgery after enrolment.

Conclusion: This study prospectively confirmed that W&S for primary SDT is safe in light of the high rate of regressions and spontaneous growth arrest. SDT have a favourable course in more than 50% of patients. A higher risk of worse outcome for patients harbouring 45F was observed on the initial analysis but needs further validation on a longer FU. Upon progression, active treatments were considered on an individualized basis, while persisting in the W&S could still pay off.

Paper 030 3042719

INCORPORATION OF *CTNNB1* MUTATION STATUS INTO A PRE-OPERATIVE DESMOID LOCAL RECURRENCE NOMOGRAM IMPROVES PREDICTIVE VALUE

Iris Wei[1]; Anthony Villano[1]; Andrea Knezevic[2]; Bhumika Jadeja[1]; Li-Xuan Qin[2]; Meera Hameed[3]; Sam Singer[1]; ***Aimee M. Crago[1]***

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Objective: Certain *CTNNB1* mutations are associated with greater risk of local recurrence (LR) after resection of desmoid-type fibromatosis. Preliminary reports have suggested that mutation type is associated with validated clinical predictors of recurrence (e.g., tumor site). In this study, we sought to determine whether the extent of such correlation limits the role of preoperative mutation testing and whether incorporation of *CTNNB1* mutation status into a nomogram predicting LR improved performance of the tool.

Methods: Desmoid patients undergoing surgical resection of desmoid tumors from 1986-2016 were identified from a single-institution prospective database. Sanger sequencing, Illumina MiSeq, and droplet digital PCR were used to determine *CTNNB1* exon 3 mutation status in archived tumor samples (canonical S45F, T41A, S45P mutations or none/other). Correlations were examined using Fisher's exact test and local recurrence-free survival (LRFS) by the Kaplan-Meier method and log-rank testing. Cox regression analysis was used to create multivariate models and nomograms predicting LR.

Results: Desmoids were treated surgically in 313 patients; 292 (93%) underwent complete gross resection (R0/R1). Desmoid patients in this cohort were most commonly female (65%), and <46 years old (63%). Extremity, intra-abdominal, and abdominal wall tumors were diagnosed in 33, 26, and 18% of patients, respectively; 72% of lesions were >5 cm in diameter. T41A, S45F, and S45P lesions were identified in 52, 23, and 6.4% of patients, respectively; in 19.5% of patients these canonical mutations were not detected (none/other). Mutation type did not correlate with patient age or tumor size, but S45F mutations were most common in extremity tumors (55%) while GI and abdominal wall tumors almost uniformly (81 and 88%, respectively; p<0.001) associated with T41A mutation or no canonical mutation.

Median follow-up for recurrence-free patients was 3.8 years (range, 4 days to 22.3 years), and 2-year LRFS after R0/R1 resection was 80%. On univariate analysis, presentation status (primary vs. recurrent), tumor site, tumor size, patient age and mutation status were associated with LR (Table). Despite correlation between site and mutation status (p<0.001), both remained significant on multivariate analysis. As in our prior publication, size, site, and patient age were incorporated into an internally validated nomogram to predict LR in patients after complete gross resection; the bootstrap concordance index was 0.707. Addition of mutation status into the model improved concordance to 0.729. A model including mutation status that included only patients treated for primary disease had a concordance of 0.744 (Figure).

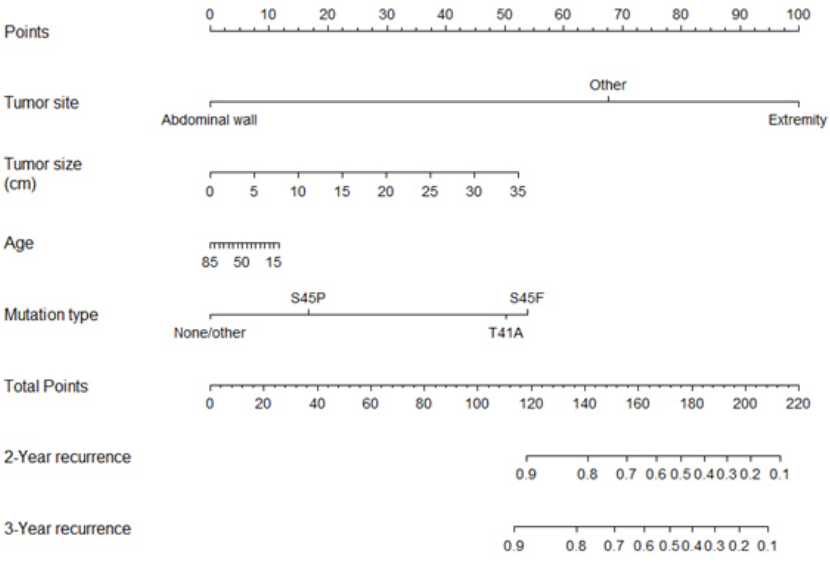

Figure. Nomogram estimating the probability of local recurrence at 2 and 3 years after desmoid resection **for primary presentation tumors**. Bootstrapping concordance index: 0.744.

Conclusion: While *CTNNB1* mutation type associates with tumor site, it remains an independent predictor of LR in multivariate models that include patient age, tumor size, and tumor site. Incorporation of mutation type improved the concordance index of an internally validated nomogram in desmoid patients with primary disease or LR at presentation and for patients treated solely for primary disease.

Analysis of factors predicting local recurrence after desmoid resection (n=292*)

	Univariate		Multivariate	
	Hazard ratio (95% CI)	p	Hazard ratio (95% CI)	p
Margin status (R1 vs. R0)	1.66 (1.04-2.66)	0.03	-	-
Presentation status (recurrent vs primary)	1.96 (1.14-3.39)	0.01	-	-
Depth (deep vs. superficial)	4.25 (0.59-30.6)	0.12	-	-
Sex (female vs. male)	1.11 (0.67-1.83)	0.68	-	-
Location (vs. extremity)				
Abdominal wall	0.03 (0.00-0.23)	<0.001	0.03 (0.00, 0.23)	0.001
Other	0.35 (0.21-0.56)	<0.001	0.37 (0.22, 0.61)	<0.001
Size† (>10 cm vs. ≤10 cm)	1.91 (1.18-3.07)	0.007	1.79 (1.15, 2.76)	0.01
Age (vs. >65 years)				
	4.53 (1.51-13.6)	0.007	1.92 (0.79, 4.68)	0.15
26–65 years	1.86 (0.67-5.14)	0.23	1.38 (0.65, 2.90)	0.40
CTNNB1 mutation type (vs. T41A)				
None/other	0.31 (0.12-0.79)	0.01	0.28 (0.12, 0.65)	0.003
S45F	1.66 (1.01-2.71)	0.04	1.03 (0.61, 1.72)	0.91
S45P	0.16 (0.02-1.16)	0.07	0.31 (0.07, 1.30)	0.11

Covariates found to be statistically significant in the univariate analysis were included in the multivariable model.
*Excluding 21 R2 patients. † Excluding 5 patients with unknown primary tumor size.

4:00 pm – 6:00 pm
– SESSION 6 –
Ewing Sarcoma

Paper 031 3027408

EASY-TO-USE PRACTICAL CLINICAL TOOL FOR SURVIVAL ESTIMATION IN EWING SARCOMA AT DIAGNOSIS AND AFTER SURGERY

Sarah E. Bosma[1]*; Carlo Lancia*[2]*; Anja J. Rüten-Budde*[2]*; Andreas Ranft*[3]*; Hans Gelderblom*[4]*; Marta Fiocco*[2]*; Michiel A. van de Sande*[1]*; Sander Dijkstra*[1]*; Uta Dirksen*[3]
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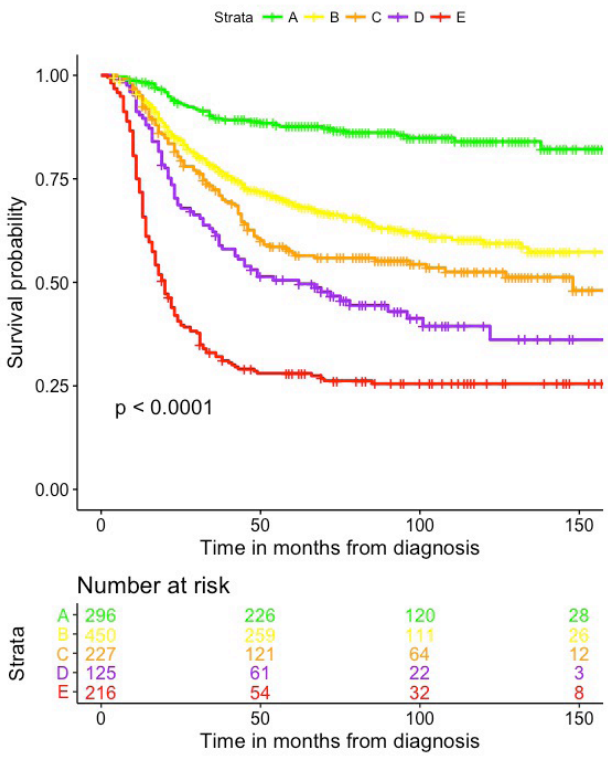
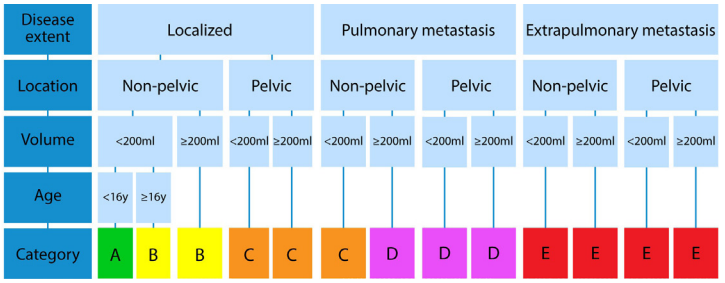
Objective: Accurate estimations of survival in Ewing sarcoma (ES) are necessary to tailor treatment according to the individual patients' risk profile at different time points. Especially in this young population of patients the balance between prognosis and quality of life is essential in our aim to provide the best possible care for our patients. Our aim is to develop an easy-to-use practical clinical tool to predict overall survival from diagnosis. Objectives are to: 1) Identify prognostic factors for overall survival from diagnosis and surgery; 2) Develop an accurate baseline prognostic model; 3) Validate the predictive accuracy of the model by using cross validation; 4) Assess the effect of prognostic factors known at time of surgery on survival.

Methods: A retrospective study of 1314 patients from the EURO.E.W.I.N.G 99 (EE99) database was performed. Associations between prognostic variables known at diagnosis and at surgery, and overall survival, were investigated using Kaplan-Meier's method and multivariate Cox proportional hazard regression model. Cross validation and Harrell C-statistics was performed to evaluate the predictive accuracy of the model.

Results: Median FU was 7,9 years (95% confidence interval [CI] 7,6-8.3). Independent prognostic factors at diagnosis are age, volume, location of the primary tumor and disease extent. Based on these factors 13 prognostic groups were made that were narrowed down to 5 categories (A to E). A flowchart was made to easily stratify patients (Figure 1). 5-year overall survival (5y OS) for categories A to E was 88% (95%CI 86-94), 69% (95%CI 64-74), 57% (95%CI 50-64), 51% (95%CI 42-60) and 28% (95%CI 22-34) respectively (Figure 2). The Harrell C-statistic of the model was 0.70. 982 patients had surgery after neo-adjuvant chemotherapy, 190 had missing data, leaving 792 eligible patients. Independent prognostic factors from surgery were age, volume, disease extent and histological response. There was a significant statistical association between histological response and survival from surgery for all categories A to E (Table 1). For patients in category A (= very favorable survival; 5y OS 85% (95%CI 80-90)) that showed 100% necrosis 5y OS improved even further to 92% (95%CI 87-97), but decreased in case of 90-99% to 77% (95%CI 64-90). In category B (= favorable survival; 5y OS 71% (95%CI 66-76)) patients showed improved 5y OS equal to 79% (95%CI 71-87) in case of 100% necrosis, and decrease 5y OS of 59% (95%CI 49-69) in case of <90% necrosis. 5y OS for patients in category C (= moderate survival; 5y OS 59% (95%CI 50-68)) improved to 68% (95%CI 55-81) in case of 100% necrosis and decreased to 38% (95%CI 22 - 54) in case of <90% necrosis. For patients in category D (= unfavorable survival; 5y OS 52% (95%CI 40-64)) who showed 100% necrosis 5y OS improved to 65% (95%CI 49-81), but decreased drastically in case of <90% necrosis to 11% (95%CI 0-26). In category E (= very unfavourable survival; 5y OS 44% (95%CI 28-56)) the same pattern was seen, with improved 5y OS of 60% (95%CI 41-79) in case of 100% necrosis and a dramatic decrease to 7% (95%CI 0-19) in case of <90% necrosis.

Conclusion: This study presents a practical clinical tool to easily stratify patients with Ewing sarcoma according to risk factors known at the time of diagnosis. Histological response has a strong effect on survival in each risk group. Prognostic classification could assist in developing risk- and response adaptive treatment strategies that allow for early decision making.





Category	At risk	5y OS (95%CI)	Histological response	N	5y OS (95%CI)	Hazard ratio (95%CI)	p-value
A	199	85% (80-90)	100%	107	92% (87 - 97)	Ref	
			90-99%	47	77% (64 - 90)	2,69 (1,13 - 6,33)	0,024
			<90%	45	78% (65 - 91)	3,55 (1.57 - 8,02)	0,002
B	316	71% (66-76)	100%	132	79% (71 - 87)	Ref	
			90-99%	93	66% (55 - 77)	1.85 (1.12-3.06)	0,017
			<90%	91	59% (49 - 69)	2.51 (1.56-4.04)	<0,001
C	135	59% (50-68)	100%	57	68% (55 - 81)	Ref	
			90-99%	44	61% (46 - 76)	1,03 (0,54-1.96)	0,925
			<90%	34	38% (22 - 54)	2,37 (1.30-4,31)	0,005
D	73	52% (40-64)	100%	35	65% (49 - 81)	Ref	
			90-99%	18	58% (34 - 82)	0,94 (0,39-2.28)	0,889
			<90%	20	11% (0 - 26)	5,11 (2.51-10,41)	<0,001
E	69	44 (28-56)	100%	29	60% (41 - 79)	Ref	
			90-99%	22	41% (20 - 62)	2,07 (0,92-4,61)	0,077
			<90%	18	7% (0 - 19)	5,22 (2.35-11.62)	<0,001

Paper 032 3042243

RETROSPECTIVE ANALYSIS OF USE OF WHOLE LUNG IRRADIATION FOR PATIENTS WITH NEWLY DIAGNOSED EWING SARCOMA AND PULMONARY METASTASES

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Objective: Whole lung irradiation (WLI) is used routinely for the treatment of Ewing sarcoma with pulmonary metastases. Patients treated at St. Jude Children's Research Hospital (SJCRH) who demonstrate a complete response (CR) of pulmonary disease with induction chemotherapy often do not receive WLI. In this retrospective analysis, outcomes are reported for patients with newly diagnosed Ewing sarcoma and pulmonary metastases.

Methods: With IRB approval, a comprehensive chart review was performed for patients with newly diagnosed Ewing sarcoma and pulmonary metastases at SJCRH between 1979 and 2015. Therapeutic regimens differed based on era of treatment. All patients were evaluated for response of pulmonary disease following induction chemotherapy. Demographic and treatment characteristics obtained included age, primary site and size (<8cm vs. ≥8cm), laterality of pulmonary metastases, number of pulmonary nodules (≤3 vs. >3), presence of extrapulmonary metastases, receipt of compressed interval chemotherapy, receipt of autologous stem cell transplantation, administration of WLI, and post-induction CR. Event-free survival (EFS) and overall survival (OS) were estimated using Kaplan-Meier methods, and comparisons of groups were calculated using Log-rank test. Cox proportional hazards regression was used to examine effects of demographic and treatment characteristics on EFS and OS.

Results: Fifty-four patients (27 female; median age 12.9 years) were evaluated. Thirty-two patients were <14 years of age at diagnosis. Two thirds had pelvic primary site; tumor size was >8cm in 72%. Pulmonary metastases were bilateral in 42 (78%) patients, and 34 patients (63%) had > 3 lung nodules at diagnosis. Extrapulmonary metastases were present in 26 patients (48%), most commonly involving bone (16), and bone marrow (11). Fifteen patients underwent autologous stem cell transplant and 14 received compressed interval chemotherapy. Thirty-three patients (61%) achieved a pulmonary CR after induction therapy. WLI was delivered to 16 patients (29.6%; 12/21 non-CR patients, 4/33 CR). After a median follow up of 3.6 years (range 0.7-36.7 years) for all patients, twenty-one (38.9%) were alive at last follow up. The estimated overall 5-year event free survival (EFS) and overall survival (OS) were 30.8%±6.4% and 49.6%±7.1%, respectively. There was no significant difference in OS (P=0.6) or EFS (P=0.42) between patients who received WLI with upfront therapy. Among patients with only pulmonary metastases, 5-year OS was 58.5%±11.4% for those who did not receive WLI, and 58.3%±18.6% for those who received WLI (P=0.63). On univariate analysis, pulmonary CR after induction chemotherapy was the only factor correlated with significantly better EFS (P<0.001) and was borderline significant for OS (P=0.069). On multivariate analysis, post induction complete pulmonary remission was the only independent predictor for OS (P=0.013) and EFS (P<0.001) when adjusted for WLI.

Conclusion: Patients with pulmonary CR after induction chemotherapy have prolonged EFS. While WLI use was selective, patients with no extrapulmonary metastases treated without WLI achieved survival outcomes similar to historical patients who received WLI on clinical trials. Prospective clinical investigation of the utility of WLI in patients with post-induction CR is warranted.

Paper 033 3042780

WHOLE-LUNG IRRADIATION AFTER HIGH-DOSE BUSULFAN/MELPHALAN CONDITIONING THERAPY IN EWING SARCOMA WITH LUNG METASTASES: A MULTICENTRIC STUDY

Massimo E. Abate[1]*; Letizia Ronchi*[2]*; Barbara Diletto*[14]*; Lorenza Gandola*[14]*; Nadia Puma*[15]*; Angela Tamburini*[3]*; Maurizio Mascarin*[4]*; Elisa Coassin*[4]*; Arcangelo Prete*[5]*; Sebastian Asaftei*[6]*; Carla Manzitti*[7]*; Luca Coccoli*[8]*; Mariella Capasso*[9]*; Tiziana Venesio*[13]*; Emilia Pecori*[14]*; Marta Pierobon*[16]*; Anna Paioli*[1]*; Elisa Carretta*[10]*; Giovanni Piero Frezza*[11]*; Alessio Giuseppe Morganti*[2]*; Stefano Ferrari*[1]*; Piero Picci*[12]*; Alessandra Longhi*[1]*; Silvia Cammelli*[2]*; Roberto Luksch*[15]

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Objective: To analyze toxicity, outcome and prognostic factors in Ewing sarcoma (ES) patients (pts) with pulmonary and/or pleural metastases (PPM) treated with busulfan and melphalan (BU-MEL), followed by autologous stem cell transplantation (ASCT), and subsequent whole-lung irradiation (WLI).

Methods: Between November 1, 1999, and January 31, 2017, 68 pts with histologically proven diagnosis of Ewing Sarcoma and lung metastases at time of diagnosis or at relapse were enrolled in 10 Italian Centres. Pts underwent chemotherapy and local treatment of the primary tumor followed by BU-MEL with ASCT. WLI 12 Gy for < 14 years old and 15 Gy for ≥ 14 years old pts was applied at least 8 weeks after BU-MEL. Clinical characteristics, treatment protocol, chest CT scan, spirometries, toxicity according to CTCAE and outcome data were retrospectively collected and analyzed. Overall Survival (OS), Event-Free Survival (EFS), Pulmonary Relapse Free Survival (PRFS) and 95% confidence intervals (CI) were estimated according to the Kaplan-Meier method. Prognostic factors were analyzed by log-rank tests and Cox and logistic regression procedures.

Results: On January 31, 2018, with a median follow-up of 34 months, the 3-year EFS, OS, and PRFS were 60.4%(CI:44.3-73.3), 72.5%(CI:55.9-83.7) and 65%(CI:48.2-77.6), respectively. The median age at diagnosis was 14 years (range: 8 months-35 years). Fifty-six of 68 (82%) had pulmonary metastases at time of diagnosis; fifty-two (76%) had metastatic lesions in both lungs. Spirometries collected before and after BU-MEL, after WLI, and during follow-up, showed pulmonary function changes in 6.4%, 25.0%, 38.4%, and 35.9%, respectively. CTCAE grade 1-2 and grade 3 toxicity were reported in 13 (19.1%) and 2 (2.9%) pts, respectively. Grade 3 toxicity was pericarditis/esophagitis/pancreatitis in one and P. Carinii pneumonia in another patient. Risk factors identified in univariate and multivariate analysis were poor response after chemotherapy of the primary tumor, > 10 lung metastatic lesions at diagnosis and incomplete radiological response of lung metastases after chemotherapy.

Conclusion: WLI at recommended doses and time interval after BU-MEL is feasible and could contribute to the disease control in ES patients with PPM and responsive disease, the response to chemotherapy of the primary tumor being the strongest prognostic factor. Treatment intensification strategies in the selected group of patients with poor responsive disease warrant further evaluation.

Figure 1: 3 years Event-Free Survival in patients with only lung metastases at first diagnosis

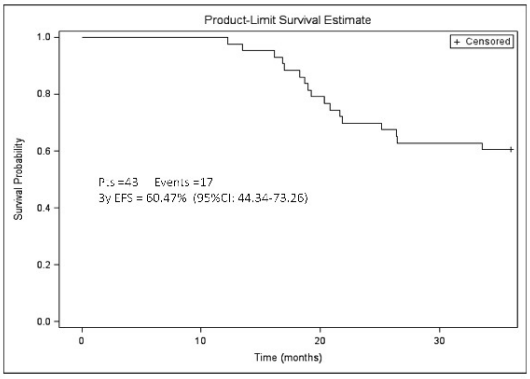

Figure 2: 3 years Overall Survival in patients with only lung metastases at first diagnosis

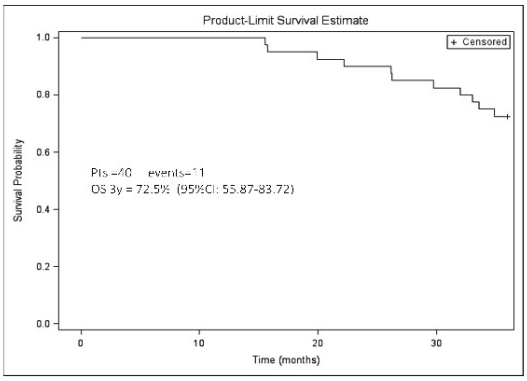

Figure 3: 3 years Pulmonary Relapse-Free Survival in patients with only lung metastases at first diagnosis

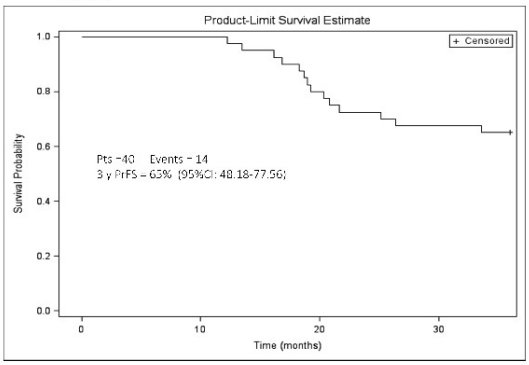

Table 1: Univariate analysis for 3-years PRFS in patients with only lung metastases at first diagnosis

Subgroup	Variable	Pts	Events	3ys PRFS (95% CI)	LOG RANK TEST (p value)
Age	≤ 14 ys	17	4	76.47% (48.83-90.45)	0.1491
	> 14 ys	23	10	56.52% (34.32-73.76)	
Primary site	Pelvic	16	7	56.25% (29.54-76.22)	0.3035
	Other	24	7	70.83% (48.38-84.89)	
Soft tissue response	CR	8	2	75% (31.48-93.09)	0.5070
	PR/SD	32	12	62.5% (43.52-76.68)	
Local therapy	Surgery	15	6	60% (31.76-79.65)	0.0842
	Surgery+RT	13	2	84.62% (51.22-95.91)	
	RT	11	6	45.45% (16.62-70.69)	
Histological necrosis	Good	18	1	94.44% (66.64-99.20)	0.0005
	Poor	10	6	40% (12.27-67.02)	
Lung mets	≤ 10	20	4	80% (55.11-91.98)	0.0397
	> 10	19	10	47.37% (24.44-67.28)	
	Bilateral	34	13	61.76% (43.42-75.71)	0.3453
	Monolateral	6	1	83.33% (27.31-97.47)	
Chest CT response	CR	26	7	73.08% (51.69-86.15)	0.0375
	PR/SD	13	7	46.15% (19.16-69.64)	
Busulfan	IV	24	11	54.17% (32.71-71.43)	0.1396
	OS	14	3	78.57% (47.25-92.54)	
WLI start from SCT	> 90 days	15	8	46.67% (21.23-68.75)	0.0987
	≤ 90 days	24	6	75% (52.61-87.91)	

Table 2: Multivariate analysis for 3-years PRFS in patients with only lung metastases at first diagnosis

Parameter		Hazard Ratio	95% Hazard Ratio Confidence Limits	
Histological necrosis	Poor response vs good response	11.063	2.089	58.594
Lung mets radiological response	PR/SD vs CR	0.542	0.058	5.092
Number of lung mets	>10 vs <=10	3.002	0.624	14.450

Mets = metastases; PR = Partial Response; SD = Stable Disease; CR = Complete Remission

Paper 034 3042627

THE WNT-DEPENDENT SECRETOME ALTERS TUMOR: TUMOR MICROENVIRONMENT CROSSTALK TO PROMOTE INVASION AND ANGIOGENESIS IN EWING SARCOMA

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Objective: Patients with metastatic Ewing sarcoma have dismal survival rates, making it imperative to understand the mechanisms that drive metastasis. We have previously shown that activation of Wnt/beta catenin alters the tumor cell transcriptome, inhibits EWS/FLI1, and promotes a metastatic phenotype (Pedersen, et al. 2016). Moreover, we recently reported that Wnt-activated cells alter their secretome, resulting in increased secretion of extra-cellular matrix proteins that are implicated in metastasis of other tumor types (Hawkins, et al. 2018). In this study we have investigated the impact of the Wnt-dependent secretome on Ewing tumor biology.

Methods: Previously published transcriptome and secretome data were interrogated for pathways of relevance to metastasis and tumor progression. Activation of canonical Wnt and TGF-beta pathways in Ewing cell lines was monitored by western blot and by reporter assays, in the presence and absence of conditioned media from Wnt3a-stimulated tumor cells. Gene and protein expression were quantified by RT-PCR and western blot. Invadopodia assays were used to evaluate matrix degradation and invasive capacity. Angiogenesis was assessed in chorioallantoic membrane (CAM) assays and by evaluating the impact of conditioned media on endothelial cell proliferation.

Results: Analysis of secretome data identified TGF-beta ligands and numerous downstream targets of the TGF-beta pathway, including TNC, COL1A1, TGFBI, and CTGF, in the conditioned media of Wnt3a-treated Ewing sarcoma cells. In addition, the transcriptome of Wnt3a-treated cells showed upregulated expression of *TGFBR2* and other TGF-beta pathway genes. Orthogonal approaches in multiple cell lines validated these unbiased findings and also showed that beta catenin-activated tumor cells become sensitized to TGF-beta pathway activation. Specifically, Wnt-dependent upregulation of *TGFBR2* resulted in *de novo* SMAD phosphorylation and induction of SMAD-reporter activity upon provision of TGF beta ligand. This was associated with formation of invadopodia and enhanced matrix degradation. Exposure to a TGFBR1 inhibitor abrogated induction of *TNC,* as well as other Wnt3a-induced genes, and also blocked invadopodia activity, confirming the functional relevance of Wnt-dependent, TGF-beta pathway sensitization. Significantly, reporter assays showed that this functional cooperation between the canonical Wnt and TGF-beta pathways was restricted to small subpopulations of differentially responsive cells, revealing profound phenotypic heterogeneity at the level of individual cells. Importantly, TNC and other TGF-beta-responsive proteins, serve additional tumor cell non-autonomous roles in the tumor microenvironment (TME), in particular in promotion of angiogenesis. Therefore, we assessed the impact of the Ewing sarcoma secretome on this essential property of expanding tumors. Transcriptomic analysis of primary Ewing tumors identified a direct relationship between beta-catenin activation and angiogenic gene expression. In addition, CAM xenografts showed increased angiogenesis in the context of tumor cells that harbored constitutively active beta catenin. Finally, conditioned media from Wnt3a-activated tumor cells augmented endothelial cell proliferation. Mechanistically, enhanced endothelial cell proliferation was shown to be, at least in part, dependent on increased secretion of TNC.

Conclusion: These studies reveal the key importance of crosstalk between tumor cells and the TME in promoting Ewing sarcoma progression. Moreover, they, for the first time, implicate clonal cooperation between canonical Wnt- and TGF-beta-responsive Ewing sarcoma cells in mediating a pro-invasive, pro-angiogenic tumor phenotype.

Paper 035 3042245

A PHASE I STUDY OF THE POLY-ADP RIBOSE POLYMERASE (PARP) INHIBITOR, NIRAPARIB (NIR), IN COMBINAITON WITH IRINOTECAN (IRN) IN PATIENTS WITH ADVANCED EWING SARCOMA: RESULTS OF SARC025 ARM 2

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Leo Mascarenhas[3]*; J.W Glod*[4]*; Jay Ji*[6]*; Ziping Zhang*[6]*; Birgit Geoerger*[7]*; Jeremy Whelan*[1]*; Denise Reinke*[8]*;*
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Objective: PARP inhibitors are postulated to have potential therapeutic value in Ewing sarcoma via PARP trapping of the EWS-FLI1 complex as well as catalytic inhibition and resultant decrease in DNA damage repair. The co-administration of

PARP inhibitors with the topoisomerase I inhibitor, irinotecan (IRN), exhibits notable synergistic anti-cancer activity *in vitro* and *in vivo*. In ARM 2 of a phase I study of the potent and highly selective PARP-1 and -2 inhibitor niraparib (NIR), we evaluated the combination with IRN to determine the dose-limiting toxicities (DLT) and maximum tolerated dose in patients with pre-treated incurable Ewing sarcoma.

Methods: Using a 3+3 design, eligible patients ≥ 13 yrs with recurrent/relapsed Ewing sarcoma were assigned to cohorts evaluating NIR 100-300mg qd D1-7 and IRN 20-50mg/m^2 D2-6 of a 28 day cycle commencing at 100mg NIR and 25mg/m^2 IRN (Dose level 1). Pre-treatment tumor biopsy was mandated and for those ≥ 18 years on C2D8. RECIST 1.1 response assessment was performed every 2 cycles for first 6 cycles, then every 2-3 cycles.

Results: Between Nov 2016 and May 2018, 12 eligible patients (9 male) with confirmed EWSR1-FLI1 translocation positive Ewing sarcoma were enrolled at 2 dose levels. Median age was 27 years (range 16-50); median prior therapies 4 (range 1-9) with 7 patients having received prior IRN. At time of data cutoff, the median number of cycles was 2 (range 1 - 17). DLTs were observed in all 3 patients at dose level 1 (1 pt each with grade 3 anorexia, grade 3 colitis, and grade 3 transaminitis). No DLTs were reported in 7 evaluable patients treated at NIR 100mg and IRN 20mg/m^2 (dose level -1); 2 patients experienced transient grade 3 neutropenia and 1 patient grade 3 gastro-intestinal toxicity (diarrhea, abdominal pain, nausea and vomiting lasting < 72 hours) and grade 3 thrombocytopenia. In 10 evaluable patients, best response was partial response in 1 patient, stable disease in 4 patients, and progressive disease in 5 patients. Median progression-free survival was 4.9 months (range 1.18-NR). Pharmacodynamic analysis of tumor samples demonstrated > 80% PARP inhibition across all doses of NIR.

Conclusion: NIR 100 mg qd D1-7 in combination with IRN 20mg/m^2 was well tolerated with preliminary evidence of efficacy that warrants further investigation. Patient biopsy was feasible and pharmacodynamic analysis supported the recommended phase 2 dose. Further cohorts incorporating temozolomide are planned and additional correlative analysis is ongoing.

Paper 036 3035962

SLFN11 IS A SIGNIFICANT DETERMINANT OF PARP INHIBITOR SENSITIVITY IN PEDIATRIC SARCOMAS

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Objective: Soft tissue sarcomas include a group of aggressive cancers that disproportionally affect adolescents and young adults. Several of these tumors harbor an *EWSR1* translocation, the most notable of which include: Ewing sarcoma (ES), desmoplastic small round cell tumor (DSRCT), clear cell sarcoma (CCS), angiomatoid fibrous histiocytoma, extraskeletal myxoid chondrosarcoma and myxoid liposarcoma (MLS). Published work suggests that the *EWSR1*-translocation in ES directly impedes the DNA damage repair response by creating a functional deficiency in *BRCA1*. Further, several sarcoma cell lines express high levels of schlafen family member 11 (SLFN11), a protein that directly binds replication protein A1 at stalled DNA replication forks to impede DNA repair checkpoint maintenance and increase sensitivity to DNA-damaging agents. We hypothesize that the presence of an *EWSR1*-translocation and/or high levels of SLFN11 protein expression in sarcomas are independent biomarkers of sensitivity to PARP inhibitor (PARPi) combination therapy involving DNA damaging agents.

Methods: SLFN11 protein expression was profiled by immunohistochemistry (IHC) in tumor samples of patients enrolled in St. Jude sponsored clinical trials for the treatment of pediatric solid tumors. Western blot analysis and qPCR were used to determine SLFN11 status in *EWSR1* translocated cell lines ES8 (ES), JNDSRCT-1 (DSRCT) and SU-CCS-1 (CCS) and non-translocated cell line U20S (osteosarcoma, 'OS'). CRISPR-Cas9 technology was used to knock-out (KO) SLFN11 in ES8 and JN-DSCRT-1. Transfection was used to overexpress SLFN11 in U2OS, SU-CCS-1, JNDSRCT-1 and the ES8 and JNDSRCT-1 SLFN11 KO cell lines. The viability of wild-type and engineered cell lines was quantified following exposure to the PARPi talazoparib (TAL) as a single agent and in combination with DNA damaging agents including ionizing radiation, irinotecan (IRN), and temozolomide (TMZ) using colony formation assays (CFA) and CellTiter Glo (CTG). DNA damage and cell cycle were assessed using immunofluorescence and high content imaging. The sensitivity of wild-type and engineered ES8 to TAL + IRN + TMZ was assessed in orthotopic xenografts.

Results: IHC staining has been completed on 105 different tumor samples thus far. SLFN11 was variably expressed in ES, DSRCT, OS, MLS and a small number of neuroblastomas. CTG and CFA revealed a positive correlation between sensitivity to TAL as single-agent or in combination with DNA damaging agents and SLFN11 expression in pediatric sarcoma cell lines. All ES cells studied expressed SLFN11 and were sensitive to TAL showing >90% decrease in proliferation at drug concentrations <10nM. JN-DSRCT-1 expressed moderate levels of SLFN11 and showed similar sensitivity; U2OS and SU-CCS-1 did not express SLFN11 and showed significantly less sensitivity. ES8 and JN-DSRCT-1 SLFN11 KO cells showed

less sensitivity to TAL and DNA damaging agents compared to the parental cell lines, while overexpression of SLFN11 in U2OS increased sensitivity to these agents. In vivo studies using ES8 SLFN11 KO cells showed resistance to TAL + IRN + TMZ, with median survival of 44 days compared to 77 days for wild-type cell lines.

Conclusion: SLFN11 is variably expressed in pediatric sarcomas. Preliminary results from our engineered cell lines and SU-CCS-1 suggest that SLFN11 protein levels may be more predictive of PARPi drug sensitivity than the presence or absence of an *EWSR1* translocation. Further studies are warranted to understand this phenotype.

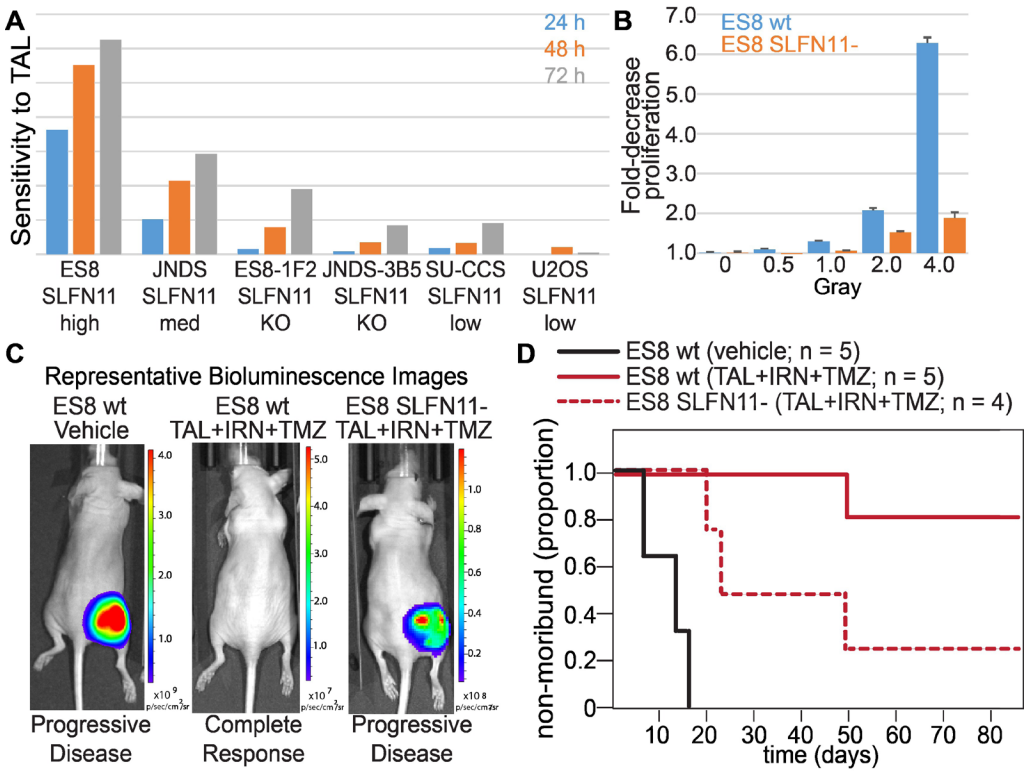

Figure 1. (A) CTG assay revealed a positive correlation between SLFN11 levels and sensitivity to the PARPi TAL. **(B)** ES8 SLFN11 KO cells were more resistant to ionizing radiation, and showed less than a two-fold loss of cell proliferation compared to a greater than six-fold decrease for wild-type cells at 4Gy. **(C)** Representative bioluminescence from in vivo studies demonstrating increased tumor burden in ES8 SLFN11 KO mice xenograft models. **(D)** Kaplan-Meier curve demonstrating decreased survival in ES8 SLFN11 KO mice xenograft models.

Paper 037 3027426

INNOVATIVE TARGETED THERAPY FOR EWING SARCOMA

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Objective: Ewing sarcoma is the second most frequent bone tumor in children and adolescents, characterized by pathognomonic chimeric transcription factors generated through balanced chromosomal translocations fusing the *EWSR1* gene with variable members of the *ETS* family of transcription factors, most commonly *FLI1* (t(11;22)(q24;q12); 85% of cases). Although significant improvements have been achieved in therapy for Ewing sarcoma patients with localized disease, the outcome for patients with relapsed or metastatic disease remains unacceptably low despite the application of highly intensified treatment regimens. Since EWSR1-FLI1 has been shown to be notoriously difficult to target, this study aimed at identifying EWRS1-FLI1-dependent and strongly upregulated 'surrogate' targets which are only lowly expressed in normal tissues and whose inhibition cannot be bypassed in Ewing sarcoma cells as their function is essential for maintenance of tumor cell proliferation and viability.

Methods: To identify such surrogate targets we stepwise crossed several high-throughput 'omics' datasets. First, a transcriptome-profiling dataset derived from Ewing sarcoma cell lines with or without EWSR1-FLI1 knockdown was used to identify genes that are strongly upregulated by EWSR1-FLI1. Second, the resulting list of genes was filtered for those that proved to be also highly expressed in transcriptome datasets of primary Ewing sarcoma tumors. In a third step, we excluded all genes that showed high expression in any of 71 normal tissue types examined. Finally, candidate genes were further screened for those encoding potentially druggable kinases or enzymes and for which small-molecule inhibitors are already available. The biological role of the most promising target was further investigated by cell-based proliferation, clonogenicity and survival assays using RNA interference (RNAi) and specific small-molecule inhibitors.

Results: By screening for druggable EWSR1-FLI1 dependent surrogate targets we found one enzyme involved in cell proliferation, maintenance of DNA integrity and tumor invasion. Knockdown of this enzyme in Ewing sarcoma cell lines using RNAi significantly reduced cell proliferation and clonogenic growth. Similarly, its pharmacological blockade inhibited cell proliferation and clonogenicity of Ewing sarcoma cells, while mesenchymal stem cells derived from Ewing sarcoma patients showed relative resistance toward the applied small molecule inhibitor, possibly due to around 10-fold lower expression levels of this enzyme. Importantly, the observed anti-proliferative effects could be achieved at low micromolar ranges in multiple Ewing sarcoma cell lines.

To examine whether this inhibitor could still halt proliferation of Ewing sarcoma cell lines that are fully resistant toward conventional chemotherapeutics, we established a doxorubicin-resistant Ewing sarcoma cell line by culturing with a serial dose escalation of doxorubicin over a long period, resulting in around 40-fold increase in IC50 compared to the parental cell line. Strikingly, while these doxorubicin-resistant cells could not be killed any more at clinically relevant doxorubicin concentrations, they fully responded to the small-molecule inhibitor directed against the selected target. Interestingly, high expression levels of our surrogate target are significantly associated with poor outcome of Ewing sarcoma patients, which appears to be independent of metastasis.

Conclusion: We identified a functionally relevant and druggable EWRS1-FLI1-dependent target which is overexpressed in Ewing sarcoma tumors and whose high expression is associated with poor patient outcome. As the pharmacological blockade of this enzyme can even kill Ewing sarcoma cells fully resistant toward one of the most effective chemotherapeutics applied in Ewing sarcoma treatment protocols, we launched a series of mechanistic *in vitro* and *in vivo* experiments to further explore its biological relevance in tumor growth and metastasis of Ewing sarcoma tumors.

9:00 am – 10:30 am
– SESSION 7 –
Osteosarcoma/Chondrosarcoma/Chordoma

Paper 038 3042790

STRESS MEDIATED TRANSLATIONAL CONTROL OF CHILDHOOD BONE SARCOMA METASTASIS

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Objective: In aggressive childhood bone sarcomas such as Ewing sarcoma (EwS) and osteosarcoma (OS), the single-most powerful predictor of poor outcome is metastatic disease. This highlights the critical need to identify new factors driving sarcoma metastasis. Sarcoma cells are continually exposed to acute stress in the tumor microenvironment, including oxidative stress and hypoxia. Each is potentially lethal unless tumor cells can acutely adapt to them. Successful adaptation can then lead to emergence of clones with aggressive behaviour, including metastatic capacity. Several recent large-scale genomic sequencing efforts have searched for a genetic basis of clonal selection, but have largely failed to identify genetic drivers of metastasis. We posit that instead, stress-induced cell plasticity acquired through acute changes in mRNA translation drives tumor fitness for metastasis. For example, YB-1, an RNA binding protein (RBP), translationally activates *HIF1A* mRNAs to activate HIF1α synthesis under hypoxia (1), and mRNAs encoding the stress granule (SG) nucleating factor, G3BP1, under oxidative stress to mediate SG formation (2). SGs are cytosolic structures containing stalled translation initiation complexes, RBPs, 40S ribosomes, and silenced mRNAs, induced under diverse stresses to reduce translation. We previously found that blocking YB-1 translational activation of either HIF1α or G3BP1 markedly reduces EwS and OS metastasis *in vivo*. We hypothesize that blocking YB-1 translation of either HIF1α or G3BP1, or both, decreases the fitness of sarcoma cells to metastasize, and that targeting this process has therapeutic potential.

REFERENCES

1. https://www.ncbi.nlm.nih.gov/pubmed/25965573
2. https://www.ncbi.nlm.nih.gov/pubmed/25800057

Methods: We performed small molecule screens to search for inhibitors of YB-1 translational activity, using fluorescent detection of SG formation *in vitro* as a tractable readout. This identified class I HDAC inhibitors including MS-275 as potently blocking SGs. We then confirmed that these agents reduce acute synthesis of HIF1α and G3BP1 under hypoxia and oxidative stress, respectively, as well as SG formation *in vitro*. We then tested effects of MS-275 on metastatic capacity of EwS and OS cell lines and a EwS PDX model *in vivo*, using the mouse renal subcapsular implantation model to generate xenografts.

Results: In mice bearing EwS or OS xenografts, or an EwS PDX model, MS-275 almost completely blocked local invasion and dramatically inhibited metastasis of sarcoma cells to lungs. Mechanistically, MS-275 reduced SG formation, increased local stress, and limited tumor cell survival *in vivo*. Remarkably, tumors in MS-275 treated mice lacked expression of both HIF1α and G3BP1. Unexpectedly, MS-275 also blocked synthesis of NRF2, a master anti-oxidant transcription factor leading to increased tumor oxidative stress, highlighting NRF2 is a new translational target of YB-1, which we confirmed biochemically.

Conclusion: Blocking YB-1 translational activation of key stress adaptive a protein, including HIF1α, G3BP1, and NRF2, has widespread effects on the fitness of sarcoma cells to metastasize. Targeting this process, such as with MS-275, alone or in combination with or other agents, therefore offers a promising strategy to reduce the burden of metastatic disease in childhood bone sarcomas.

Paper 039 3035462

PROSPECTIVE PHASE II STUDY OF SCANNED BEAM PROTON THERAPY FOR SPINE SARCOMAS

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Objective: Pre- and/or post-operative radiation therapy (RT) may improve local control in patients undergoing surgery for spine sarcomas. In addition, definitive-intent RT may have a role in patients who do not undergo surgery. However, delivery of adequate RT doses is challenging due to proximity of normal structures. We previously reported a Phase II trial of passively scattered proton therapy for spine sarcoma. Here, we hypothesized that scanned beam proton therapy would allow high local control with acceptable toxicity.

Methods: We conducted a Phase II, NCI-sponsored clinical trial of scanned beam proton therapy for primary or recurrent chordomas and chondrosarcomas of the spine or sacrum. In patients undergoing surgery, CTV1 (encompassing pre-operative gross tumor plus a margin for microscopic disease) was treated pre-or post-operatively to 45-50.4 GyE, CTV2 (encompassing pre-operative gross tumor) was treated post-operatively to a total of 64.8-70.2 GyE, and GTV (only if residual gross disease) was treated post-operatively to a total of 77.4-79.2 GyE. Surgery consisted of en bloc resection with the goal of microscopically negative margins (R0), although in some cases a microscopic positive margin (R1) was planned with the goal of preserving nerve function. In patients not receiving surgery, the same CTV1 and GTV dose levels were used.

Results: 60 patients (51 chordoma, 9 chondrosarcoma) were enrolled between February 2011 and March 2017. 63% were male, with a median age of 59 (range 18-89). All but one had primary tumors. Tumors were predominantly sacral/coccygeal (58%). 51 patients (85%) underwent surgery, of whom 65% had R0, 29% R1, and 6% R2 resections (all at outside institutions prior to trial enrollment). In surgical patients, RT was most often delivered both pre- and post-operatively (63%; median total dose 68.7 GyE), and less often pre-operatively only (12%; median 50.4 GyE) or post-operatively only (20%; median 70.8 GyE). 9 patients (15%) underwent definitive RT without surgery (median 77.4 GyE). With a median follow-up of 28.3 months among 55 patients still alive, two-year local control was 92%, recurrence-free survival (RFS) 85%, and overall survival 94%. On univariate analysis, post-operative only RT (vs both pre- and post-operative) was associated with shorter RFS (62.9% vs 90.8% at two years, HR 5.86 [1.75-19.7], p=0.005); there was also a trend towards shorter RFS in non-R0 resections (71.6% vs 89.1% at two years, HR 2.65 [0.87-8.01], p=0.074). No local or distant recurrences were observed in the definitive RT arm. Acute and chronic toxicities were mild (3.4% each grade 3 and 4); one patient experienced a late grade 2 sacral insufficiency fracture, and two patients experienced late grade 1 hardware failures. No RT-associated myelopathies were observed.

Conclusion: Scanned beam proton therapy can be given safely for spine chordomas and chondrosarcomas. Although follow-up is limited, these initial results suggest promising outcomes in both the peri-operative and definitive settings.

Paper 040 2993960

APATINIB FOR ADVANCED OSTEOSARCOMA AFTER FAILURE OF STANDARD MULTIMODAL THERAPY: AN OPEN LABEL PHASE 2 CLINICAL TRIAL(NCT02711007)

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Objective: Anti-angiogenesis tyrosine kinase inhibitors (TKIs) have been shown to prolong progression-free survival (PFS) in advanced osteosarcoma. Methylsulfonic apatinib is a TKI that specifically inhibits vascular endothelial growth factor receptor-2 (VEGFR-2). We aimed to assess the activity of apatinib in patients with locally advanced or multiple metastatic high-grade osteosarcoma progressing after standard treatment.

Methods: This phase 2 trial was conducted at Peking University People's Hospital. We enrolled participants (≥16 years of age) with relapsed or unresectable osteosarcoma progressing after chemotherapy. Participants received 750 mg or 500 mg apatinib according to body surface area (BSA) once daily until disease progression or unacceptable toxicity. The primary endpoint was objective response rate and PFS at four months. This trial is registered with ClinicalTrials.gov identifier: NCT02711007.

Results: A total of 37 participants were enrolled between March 17, 2016 and June 9, 2017. Until final follow-up, the objective response rate (CR+PR) was 43.24% (16/37). The four-month PFS rate was 56.76% (95% CI 39.43%–70.84%). However, 13/37 (35.14%, 95% CI 20.21%–52.54%) patients were progression-free at six months. Median PFS and overall survival (OS) were 4.50 (95% CI 3.47–6.27) and 9.87 (95% CI 7.97–18.93) months, respectively. Toxic effects led to dose reductions or interruptions in a total of 25/37 (67.57%) patients. The most common grade 3–4 adverse events were pneumothorax in five (13.51%) patients, wound dehiscence in four (10.81%), abdominal cramps in three (8.11%), hypokalemia in two (5.41%), and bilirubin increase, proteinuria, hypertriglyceridaemia, palmar-plantar erythrodysesthesia syndrome, and anemia each in one (2.70%). No other serious adverse events were reported during the trial. There were no treatment-related deaths.

Conclusion: Apatinib is a sensitive drug for advanced osteosarcoma with a high response rate after failure of chemotherapy, with similar duration of response compared to other TKIs.

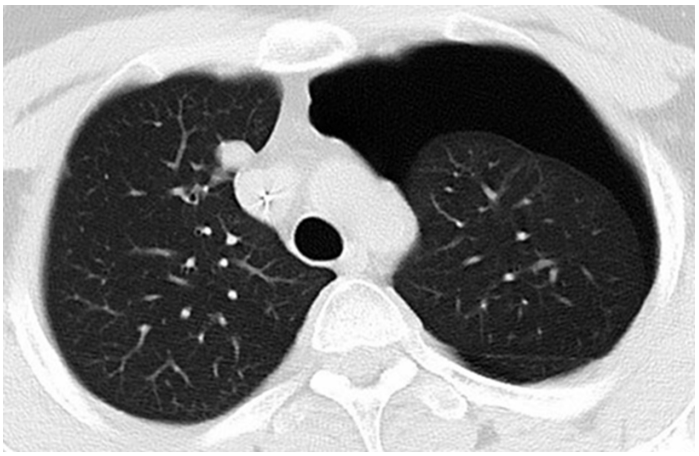
Table 1: Baseline characteristics

	N (percentage)	P (Cox univariate analysis for PFS)
Patients	37 (100%)	
Age (years) Median (Min, Max)	23.4 (16, 62)	
Gender		0.180
Male	26 (70.27%)	
Female	11 (29.73%)	
Nationality		
the Han nationality	35 (94.59%)	
Others	2 (5.41%)	
ECOG performance status1 at enrollment		0.814
0	27 (72.97%)	
1	10 (27.03%)	
High-grade osteosarcoma histosubtypes		0.974
Common(Osteoblastic, Chondroblastic, Fibroblastic)	35 (94.59%)	
Telangiectatic	1 (2.70%)	
Small cell	1 (2.70%)	
Extent of disease get enrolled		
Locally advanced	1 (2.70%)	
Metastatic disease	36 (97.30%)	
Primary tumor location		0.198
Distal Femur	21 (56.76%)	
Proximal Tibia and Fibula	5 (13.51%)	
Proximal Humerus	4 (10.81%)	
Axial skeleton	5 (13.51%)	
Others2	2 (5.41%)	
Sites of target lesions		0.001
Lung only	27 (72.97%)	
Bone only	4 (10.81%)	
Combined with Lung and Bone	6 (16.22%)	
Lines of previous chemotherapy including MAP/I3	37 (100%)	

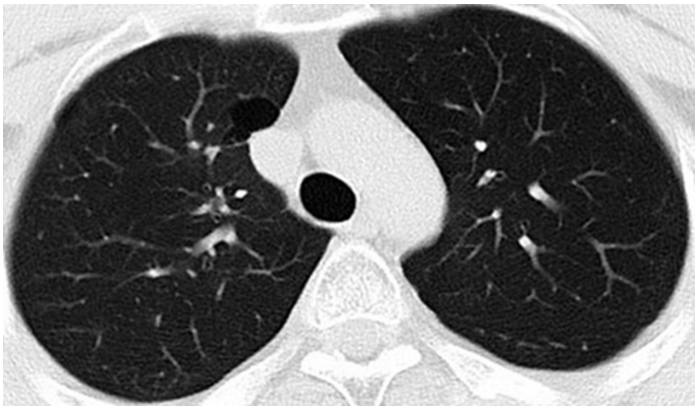
Data are from the intention-to-treat population. 1ECOG=Eastern Cooperative Oncology Group; 2others including metacarpus and distal tibia and fibula 3MAP/I including high-dose methotrexate, doxorubicin, cisplatin and ifosfamide. And we defined those four agents as first-line chemotherapy.

Table 2:Adverse events that arose in at least one participant

Adverse event	All (%)	Grade 1(%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Myalgia/arthralgia	7 (18.92%)	4 (10.81%)	3 (8.11%)	0 (0%)	0 (0%)
Pneumothorax	11 (29.73%)	1 (2.70%)	5 (13.51%)	3 (8.11%)	2 (5.41%)
Wound dehiscence	7 (18.92%)	0 (0%)	3 (8.11%)	4 (10.81%)	0 (0%)
Bladder perforation	2 (5.41%)	0 (0%)	2 (5.41%)	0 (0%)	0 (0%)
Bilirubin increase	3 (8.11%)	0 (0%)	2 (5.41%)	1 (2.70%)	0 (0%)
Proteinuria	7 (18.92%)	4 (10.81%)	2 (5.41%)	1 (2.70%)	0 (0%)
Hypoalbuminemia	2 (5.41%)	1 (2.70%)	1 (2.70%)	0 (0%)	0 (0%)
Hypokalemia	4 (10.81%)	2 (5.41%)	0 (0%)	2 (5.41%)	0 (0%)
Abdominal cramps	8 (21.62%)	0 (0%)	5 (13.51%)	2 (5.41%)	1 (2.70%)
Diarrhea	7 (18.92%)	5 (13.51%)	2 (5.41%)	0 (0%)	0 (0%)
Hypertriglyceridemia	2 (5.41%)	0 (0%)	1 (2.70%)	1 (2.70%)	0 (0%)
Anal fistula	2 (5.41%)	1 (2.70%)	1 (2.70%)	0 (0%)	0 (0%)
Hypertension	10 (27.03%)	5 (13.51%)	5 (13.51%)	0 (0%)	0 (0%)
Hypercholesterolemia	4 (10.81%)	3 (8.11%)	1 (2.70%)	0 (0%)	0 (0%)
Hypothyroidism	5 (13.51%)	1 (2.70%)	4 (10.81%)	0 (0%)	0 (0%)
Oral mucositis	10 (27.03%)	7 (18.92%)	3 (8.11%)	0 (0%)	0 (0%)
Bleeding	2 (5.41%)	0 (0%)	2 (5.41%)	0 (0%)	0 (0%)
Fatigue	12 (32.43%)	5 (13.51%)	7 (18.92%)	0 (0%)	0 (0%)
Weight loss	9 (24.32%)	7 (18.92%)	2 (5.41%)	0 (0%)	0 (0%)
Anorexia	9 (24.32%)	5 (13.51%)	4 (10.81%)	0 (0%)	0 (0%)
Urinary frequency	2 (5.41%)	1 (2.70%)	1 (2.70%)	0 (0%)	0 (0%)
Hoarseness	7 (18.92%)	4 (10.81%)	3 (8.11%)	0 (0%)	0 (0%)
Rash acneiform	13 (35.14%)	10 (27.03%)	3 (8.11%)	0 (0%)	0 (0%)
Anemia	8 (21.62%)	3 (8.11%)	4 (10.81%)	1 (2.70%)	0 (0%)
Palmar-plantar erythrodysesthesia syndrome	8 (21.62%)	2 (5.41%)	5 (13.51%)	1 (2.70%)	0 (0%)
Pleuritic pain	2 (5.41%)	0 (0%)	2 (5.41%)	0 (0%)	0 (0%)
Thrombocytopenia	3 (8.11%)	2 (5.41%)	1 (2.70%)	0 (0%)	0 (0%)
Back pain	3 (8.11%)	2 (5.41%)	1 (2.70%)	0 (0%)	0 (0%)
Anal ulcer	4 (10.81%)	2 (5.41%)	2 (5.41%)	0 (0%)	0 (0%)



A 18-year old advanced osteosarcoma patients with multiple pulmonary metastasis: baseline chest CT with a mass beside the mediastinum (right) and pneumothorax (left)



The same 18-year old advanced osteosarcoma patients with multiple pulmonary metastasis: chest CT one month after taking apatinib with the mass turned into a cavity (right) and pneumothorax absorbed (left)

Paper 041 3042511

SARC024: REGORAFENIB IN PATIENTS WITH REFRACTORY OSTEOSARCOMA

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Objective: There are few effective treatment options for recurrent metastatic osteosarcoma, the most common malignant tumor of bone. Sorafenib led to an improvement in progression free survival (PFS) in a previous small phase 2 trial (Grignani et al, 2011). Regorafenib, a multi-kinase inhibitor of VEGFR1/2/3, RET, KIT, PDGFRβ and others, is a small molecule inhibitor with a similar biochemical profile to sorafenib but is pharmacologically more potent. We hypothesized that regorafenib will improve PFS in advanced osteosarcoma.

Methods: We undertook a randomized, double-blind, placebo-controlled phase 2 trial of regorafenib in osteosarcoma. Eligible subjects were at least 10 years old, ECOG 0-2, with adequate organ function and advanced or metastatic osteosarcoma (primary bone or extraskeletal) with measurable disease by RECIST v1.1, and had progressed within 6 months of registration. Subjects must have received at least 1 prior line of systemic therapy, but no prior treatment with a small molecule kinase inhibitor. The primary endpoint was PFS.
Subjects were randomized 1:1 to receive placebo or regorafenib at a starting dose of 160 mg daily for 3 weeks on, 1 week off. Tumor assessments were obtained every 8 weeks for the first 32 weeks, then every 12 weeks. Subjects randomized to placebo were eligible to crossover to regorafenib upon RECIST progression.
The study design was powered to detect a difference of at least 3 months in median PFS, which was considered a clinically meaningful improvement. Following the release of the REGOBONE trial results (Duffaud et al, 2018) suggesting benefit of regorafenib, an unplanned analysis was conducted after enrollment of 42 of 48 planned subjects and 31 of the required 42 PFS events.

Results: Between September 9 2014 and May 31 2018, 42 subjects from 12 centers were enrolled. Baseline characteristics were balanced (Table 1), although patients randomized to placebo were older and predominately male. Median age was 37 (range, 18-77). Subjects had received an average of 2.6 prior therapy regimens.
At the time of analysis, a statistically significant and clinically meaningful difference in PFS was observed between regorafenib and placebo, and the study was terminated. Median PFS was 5.3 months (95% CI: 2.1-NR) for regorafenib and 1.7 months (95% CI: 1.2-2.6) for placebo (HR=3.25; 95% CI: 1.48-7.13; p=0.003), Figure 1.
At the time of data cutoff, 32 of 42 (76%) patients remained alive. Median follow up among alive patients was 3.4 months. Median overall survival (OS) was 26.7 months (95% CI: 5.1-NR) for patients initially randomized to regorafenib, while median OS could not be estimated for patients initially on placebo (HR=1.82; 95% CI: 0.49-6.78; p=0.37). 11 patients on placebo crossed-over to active drug at time of progression.

Table 2 lists the most common treatment-related adverse events (AE). Grade 1 palmar-plantar erythrodysesthesia was the most common study drug-associated AE, and grade 1-2 gastrointestinal AEs were more frequent in patients receiving regorafenib. . Twenty-nine (69%) patients experienced grade 3 or 4 events. There was one grade 4 colonic perforation attributed to study drug. In the regorafenib arm, there was also one event each for grade 4 thrombocytopenia and grade 4 lymphopenia. In the placebo arm, one patient each experienced grade 4 skin ulceration and grade 4 maculopapular rash.

Conclusion: This randomized study of regorafenib in advanced osteosarcoma met the primary endpoint of PFS, with regorafenib providing a 3.6 month increment in median PFS vs placebo. Cross-over was allowed and there was no statistically significant difference in overall survival between arms.
Notably, regorafenib was well tolerated overall with expected side effects.

These data provide compelling evidence for regorafenib as an effective treatment for advanced osteosarcoma and complement the results of the REGOBONE trial.

Table 1. Baseline Characteristics

	All patients (n=42)	Regorafenib (n=22)	Placebo (n=20)
Median age, years (range)	37 (18-77)	34 (18-70)	48 (19-77)
Sex, M/F	20/22	6/16	14/6
Previous lines of therapy, No. (%)			
1	21 (50)	11 (50)	10 (50)
>1	21 (50)	11 (50)	10 (50)
ECOG performance status, No. (%)			
0-1	41 (98)	22 (100)	19 (95)
2	1 (2)	0 (0)	1 (5)
Primary tumor location, No. (%)			
Extremity	23 (55)	11 (50)	12 (60)
Pelvis/Spine	4 (10)	3 (7)	1 (5)
Other	15 (36)	8 (36)	7 (35)
Histology, No. (%)			
Chondroblastic	13 (31)	5 (23)	8 (40)
Fibroblastic	1 (2)	1 (5)	0 (0)
Osteoblastic	8 (19)	6 (27)	2 (10)
Other	11 (26)	5 (23)	6 (30)
Unknown	9 (21)	5 (23)	4 (20)

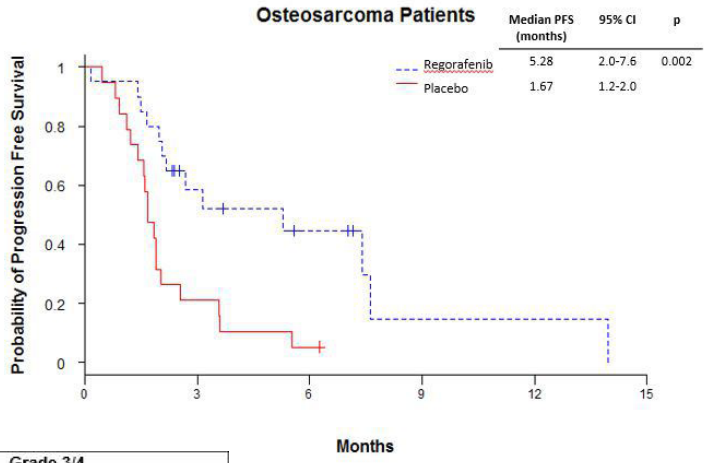

Figure 1. Kaplan Meier curves for progression free survival (PFS). Median PFS was 5.3 months (95% CI: 2.1-NR) for regorafenib and 1.7 months (95% CI: 1.2-2.6) for placebo (HR=3.25; 95% CI: 1.48-7.13; *p*=0.003).

Table 2. Treatment-emergent adverse events occurring in at least 5% of patients.

Adverse Event	Grade 1/2				Grade 3/4			
	Regorafenib (n=22)		Placebo (n=20)		Regorafenib (n=22)		Placebo (n=20)	
	No	%	No	%	No	%	No	%
General								
Chills	2	9%	0	0%	0	0%	0	0%
Fatigue	2	9%	2	10%	0	0%	0	0%
Fever	1	5%	1	5%	1	5%	1	5%
Myalgia	0	0%	0	0%	0	0%	2	10%
Pain	0	0%	0	0%	2	9%	0	0%
Weight loss	0	0%	0	0%	0	0%	2	10%
Gastrointestinal								
Abdominal pain	1	5%	0	0%	1	5%	0	0%
Constipation	0	0%	2	10%	0	0%	1	5%
Diarrhea	3	14%	0	0%	1	5%	0	0%
Mucositis	3	14%	0	0%	0	0%	0	0%
Nausea	5	23%	3	15%	0	0%	2	10%
Vomiting	3	14%	1	5%	0	0%	1	5%
Laboratory								
Anemia	0	0%	1	5%	0	0%	1	5%
Hypokalemia	0	0%	0	0%	0	0%	2	10%
Hypophosphatemia	0	0%	1	5%	2	9%	3	15%
Increased bilirubin	2	9%	0	0%	0	0%	0	0%
Increased lipase	0	0%	0	0%	0	0%	3	15%
Thrombocytopenia	0	0%	0	0%	2	9%	0	0%
Cardiovascular								
Hypertension	5	23%	4	20%	3	14%	1	5%
Skin								
Maculopapular rash	1	5%	1	5%	2	9%	1	5%
Palmar-plantar erythrodysesthesia	6	27%	0	0%	1	5%	0	0%
Pruritus	2	9%	0	0%	0	0%	2	10%

Paper 042 3042857

CABOZANTINIB IN PATIENTS WITH ADVANCED OSTEOSARCOMAS AND EWING SARCOMAS: A FRENCH SARCOMA GROUP (FSG)/ US NATIONAL CANCER INSTITUTE PHASE II COLLABORATIVE STUDY

Antoine Italiano[1]*; Nicolas Penel*[2]*; Emmanuelle Bompas*[3]*; Sophie Piperno-Neumann*[4]*; Marina Pulido*[1]*; Natacha Entz-Werle*[5]*; Axel Le Cesne*[6]*; Christine Chevreau*[7]*; Florence Duffaud*[8]*; Isabelle Ray-Coquard*[9]*; Maud Toulmonde*[1]*; Carine Bellera*[1]*; Jean-Yves Blay*[9]

[1]Institut Bergonié, Bordeaux, France; [2]Centre Oscar Lambret, Lille, France; [3]Institut Cancerologie de l'Ouest, Nantes, France; [4]Institut Curie, Paris, France; [5]CHU de Strasbourg, Strasbourg, France; [6]Institut Gustave Roussy, Villejuif, France; [7]Oncopole Toulouse, Toulouse, France; [8]APHM Marseille, Marseille, France; [9]Centre Leon Berard, Lyon, France

Objective: After standard multimodal therapy, the prognosis of relapsed and unresectable high-grade osteosarcoma and ewing sarcoma is dismal and unchanged over the last decades. There are no approved drugs in this setting. Pharmacologic inhibition of Met signaling and of aberrant angiogenesis has shown promising results in in several preclinical models of osteosarcoma and Ewing sarcomas. These are 2 multicentre single-arm 2-stage phase 2 trials assessing efficacy and safety of cabozantinib in patients (pts) with advanced osteosarcomas (OS) or Ewing sarcoma (ES).

Methods: Pts receive cabozantinib (oral route, adults: 60 mg, children: 40 mg/m2), daily until progressive disease (PD) or unacceptable toxicity. For osteosarcomas, the primary endpoint is a dual one based on 6-month objective response and non-progression. Assuming 25% 6-month non-PD (H0), 50% acceptable 6-month non-PD (H1); 5% objective response (H0), 20% objective response (H1); 5% type I error, 90% power, 41 assessable pts are necessary (21 in first stage + 20 in second stage). Based on the first 21 pts, if ≥ seven progressions or ≥ objective responses are observed, accrual will continue. For ewing sarcomas, the primary endpoint is objective response. Assuming 5% objective response (H0), 20% objective response (H1); 5% type I error, 90% power, 41 assessable pts are necessary (21 in first stage + 20 in second stage). After the first 21 pts, if ≥ objective responses are observed, accrual will continue. Accrual started in 03/2015 in 15 centers of the FSG.

Results: As of 06/2018, 88 patients (45 OS + 43 ES) have been included. 55.6% of patients had 3 or more previous lines of treatment. At the time of interim statistical analysis, 34 patients with OS and 23 patients with ES were eligible and evaluable for the first endpoint after central histological and radiological review. 18 OS pts (52.9%) had tumor shrinkage resulting in partial response in 6 cases (17.6%) and stable disease in 12 cases (35.3%). 12 patients (35.3%) were progression-free at 6 months. 16 ES (69.6%) had tumor shrinkage resulting in partial response in 5 cases (21.7%) and stable disease in 11 cases (47.8%). 7 (30.4%) patients were progression-free at 6 months. Cabozantinib reached the primary endpoint to justify continuing accrual for both strata. 19 patients are still on treatment.

Conclusion: Cabozantinib shows significant activity in patients with advanced OS and ES sarcomas. Final efficacy, safety and translational data will be presented at the meeting.

1:30 pm – 3:30 pm

– SESSION 8 –

Soft Tissue Sarcoma: Biology

Paper 043 3042288

WHOLE GENOME SEQUENCING OF 1,111 SARCOMA PROBANDS REVEALS POT-1 AS A SARCOMA PREDISPOSITION GENE

Mandy L. Ballinger[1]*; Mark Pinese*[1]*; Emma Rath*[1]*; Paul James*[2]*; Ajay Puri*[3]*; Nicolas Isambert*[4]*; Martin Tattersall*[5]*; Beatrice Seddon*[6]*; Ian Judson*[7]*; Winette van der Graaf*[7]*; Nicolas Penel*[8]*; Axel Lecesne*[9]*; Coonoor Chandrasekar*[10]*; Jean-Emmanuel Kurtz*[11]*; Joshua Schiffman*[12]*; R. Lor Randall*[12]*; Florence Duffaud*[13]*; Jin-Hee Ahn*[14]*; Rory Rickard*[15]*; Jean-Yves Blay*[16]*; Isabelle Ray-Coquard*[16]*; David M. Thomas*[1]

[1]Garvan Institute of Medical Research, Darlinghurst, New South Wales, Australia; [2]Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia; [3]Tata Memorial Hospital, Mumbai, India; [4]Centre Georges Francois Leclerc, Dijon, France; [5]University of Sydney, Sydney, New South Wales, Australia; [6]University College Hospital, London, United Kingdom; [7]The Royal Marsden NHS Foundation Trust, London, United Kingdom; [8]Centre Oscar Lambret, Lille, France; [9]Institut Gustav Roussy, Villejuif, France; [10]Royal Liverpool and Broadgreen University Hospital, Liverpool, United Kingdom; [11]Hopitaux Universitaires de Strasbourg, Strasbourg, France; [12]Huntsman Cancer Institute, Salt Lake City, UT, USA; [13]La Timone University Hospital, Marseille, France; [14]Asan Medical Centre, Seoul, Korea (the Republic of); [15]Derriford Hospital, Plymouth, United Kingdom; [16]Centre Leon Berard, Lyon, France

Objective: There is a strong genetic component to sarcomas and they are more common in hereditary cancer syndromes. The most recognised genetic drivers are germline mutations in the *TP53* gene (Li Fraumeni syndrome) but other risk genes include *NF1/2*, *Rb*, *SDH* genes and *BRCA2.* A polygenic contribution to sarcoma risk has also been recognised. We sought to understand further the genetic basis for sarcoma susceptibility.

Methods: The International Sarcoma Kindred Study (ISKS) is a prospective clinic based cohort study formed to investigate the heritable aspects of sarcoma. Whole genome sequencing of peripheral blood DNA from 1,111 ISKS probands was undertaken. A case:control design was applied using the Medical Genome Reference Bank to estimate the germline burden of common and rare pathogenic variation. Telomere content and length was assessed using qPCR and running terminal restriction fragments, respectively.

Results: Using the Cancer Gene Census list, preliminary results show 14% of probands carry pathogenic variants in high penetrance cancer genes. An additional 2% carried deleterious variants in medium penetrance cancer genes. The greatest enrichment in pathogenic variation was in *TP53* (OR 16.3, 95%CI 2.03-352.96, *P*=0.001), *NF1* (OR 13.0 95%CI 1.68-308.03, *P*=0.004), and *POT1* (OR 13.0, 1.68-308.03, *P*=0.004). POT1 (Protection of Telomeres 1) is a key component of the shelterin complex responsible for maintaining telomere integrity. Autosomal dominant mutations in *POT1* have been associated with familial melanoma, chronic lymphatic leukemia and glioma. A small case series reported an association with cardiac angiosarcoma. An enrichment of burden was observed across multiple genes in the shelterin complex including *TINF2, TERF2,* and *TPP1*. The ALT (alternate lengthening of telomeres) mechanism is a common characteristic of sarcomas associated with genomic instability. Interestingly, probands with mutations in the shelterin complex genes had significantly longer telomeres than age and gender matched controls (*P*=0.003).

Conclusion: Whole genome sequencing and the case:control design has the power to identify previously unrecognised contributors to pan-sarcoma risk.

Paper 044 3042786

SEQCOMPLEX UNRAVELLING OMICS LANDSCAPE AND TARGETING ONCOGENIC PATHWAYS IN UNDIFFERENTIATED PLEOMORPHIC SARCOMAS - AN INTEGRATED APPROACH

Maud Toulmonde[1]*; Damien Geneste*[1]*; Stephanie Verbeke*[1]*; Julien Adam*[2]*; Fabiola Cecchi*[3]*; Banafshe Larijani*[4]*; Francois Bertucci*[6]*; Florent Petitprez*[5]*; Audrey Laroche*[1]*; Carlo Lucchesi*[1]*; Antoine Italiano*[1]*; Todd Hembrough*[3]

[1]Institut Bergonié, Bordeaux, France; [2]Gustave Roussy, Villejuif, France; [3]Nantomics, Rockville, MD, USA; [4]Fastbase Solutions Ltd, Plentzia, Spain; [5]UMRS 1138 - Centre de Recherche des Cordeliers, Paris, France; [6]Institut Paoli Calmettes, Marseille, France

Objective: Undifferentiated Pleomorphic Sarcoma (UPS) are an heterogenous group of poorly differentiated tumors made up 'by default'. We hypothesized that there is a continuum between UPS and more differentiated sarcomas with complex

genomics, that there is a link between dedifferentiation state of UPS and immune infiltrate; that this relation relies on specific pathways activation and related genomics alterations; and that specific subgroups of UPS can be identified with potential therapeutic impact.

Objectives of this work are:
- To generate a comprehensive Omics landscape of true UPS
- To identify recurrently altered genes or pathways
- To better define and possibly subclassify UPS with an integrated genomic and immunophenotypic approach
- To identify and test potential targets for therapeutics approach on cell lines and patients (pts) tumor mouse pt derived xenografts (PDX)

Methods: We collected FFPE tumor blocks, frozen tumor and matched normal tissue samples of 28 pts with true primary UPS treated at Institut Bergonié, France.

Samples used in this study have been selected according to the following inclusion criteria:
- Histological review performed for each case by a soft tissue sarcomas (STS) referral Pathologist of the French Sarcoma Group (FSG),
- High grade evaluated according to the previously established FNCLCC system,
- No previous treatment done before sampling,
- Informed consent obtained for the analysis.

Institutional review board approval and pts consent have been obtained for this study. Experiments were performed in agreement with Bioethics Law No 2004-800 and the Ethics Charter from the National Institute of Cancer (INCa).
UPS cell lines and pts derived xenograft (PDX) were generated from pts samples and have been fully genomically characterized.

We performed Exome (ExonSeq) and RNA sequencing (RnaSeq) with Illumina TrueSeq protocol, paired-end 125x2 on a HiSeq 2500 platform (Illumina Inc. San Diego, CA, USA), proteomics profiling conducted by data-independent acquisition (DIA) mass spectrometry (Nantomics), as well as immune profiling by IHC for CD8, CD3, CD68, CD163, PDL1, IDO, and phosphoproteomics for Akt et Erk activation state using FRET Efficiency Technology (Fastbase Solutions).

Results: Overall, 25 pts had both ExonSEq and RnaSeq. Consensus Clustering identified 3 groups of pts, clusters A, B and C, with respectively 11, 10 and 4 pts. The top 30 upregulated genes in group A were gene involved in immune reaction. Using the enrichment in gene-set features of the Hallmark of Cancer, GO Molecular Function, GO Biological Processes, and Cybersort LM22 immune-cell signature, pts in group A consistently over-expressed genes significantly enriched in immune-related pathways, leading to call this group the “INFLAMMED group”. FGFR2 was one of the top gene upregulated in group B, called the “NON INFLAMMED” group. DKK1 and ARHGEF4 were among the most differentially expressed genes between groups. Using a gene expression signature related to betacatenine activation**,** we found a significant enrichement in betacatenine activation in the “NON INFLAMMED” group. Strikingly, copy numbers variations (CNV) were significantly more frequent in the “NON INFLAMMED” group. Main recurrent events were losses of genes belonging to genome integrity pathway such as PRB, P53, BRCAness, PTEN pathway, or immunity such as PDL1 loss.

Conclusion: This study is the first to assess a comprehensive genomic, transcriptomic, proteomic and immunophenotypic landscape of a series of true non pretreated primary UPS. We identified 2 main groups of UPS, of which one was strongly inflammed, potential best candidate for immunotherapy, and one with upregulation of FGFR2, leading to assess targeting this pathway *in vitro* and *in vivo* in dedicated models of UPS from this group. Full genomics, transcriptomics as well as proteomics and immunophenotypic data of the whole cohort will be presented at the meeting, together with preclinical results of FGFR2 targeting in the NON INFLAMMED group of UPS.

Paper 045 3010210

RATIONALES FOR TARGETING/CO-TARGETING LEIOMYOSARCOMA PATHWAYS: BIOLOGIC PROFILES IN 712 UTERINE OR SOFT-TISSUE LMS

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Objective: Leiomyosarcoma (LMS) is the most common soft tissue (ST) and uterine (UT) sarcoma. Nonetheless, there is no standard therapy for metastatic LMS and the role of various biomarkers in LMS diagnosis and grading is controversial. Genomic mutations dysregulating the p16/RB1, MDM2/TP53, and PI3K/mTOR pathways are recurrent aberrations in LMS, and subsets of LMS express estrogen and progesterone receptors (ER and PR). However, the frequencies and associations between these events are poorly understood. We characterized these key pathways in >700 ST and UT LMS, to better establish biologic rationales for therapeutic targeting.

Methods: Pathway features were evaluated in TMAs containing 712 LMS (Table 1) with 2 cores per case, prepared at MD Anderson Cancer Center (N=436) and Stanford University Medical Center (N=276). Validated IHC assays evaluated p16, RB1, TP53, PTEN, ER, and PR. Pathologic loss of expression or overexpression was assessed in relation to normal smooth muscle and benign leiomyoma controls. ER and PR were scored as negative (absence of staining), weak (1+ intensity in 1-100% of cells or 2+/3+ in <50% of cells), moderate (2+/3+ in ≥50% of cells) and strong (2+/3+ in ≥90% of cells). Presence and degree of nuclear atypia and cellularity were used for grading LMS (G1-3). Data sets were compared using the two-tailed Fisher's exact test.

Results: Key results are provided in Table 1. Alterations of the p16/RB1 axis were demonstrated in 95% of LMS, yet only 5% of LMS had simultaneous p16 inactivation with retained RB1, a profile predictive of response to CDK4/6-inhibition in other neoplasms. Aberrant TP53 was identified in 87% of LMS, which is noteworthy in view of new strategies to restore TP53, therapeutically. PTEN inactivation was demonstrated in 41% of LMS and was more frequent in ST than UT cases and in primary than metastatic/recurrent disease. Moderate/strong ER and/or PR expression was demonstrated in 34% of LMS and was more frequent in UT LMS (34% of which were high-grade) than ST LMS (17% of which were high-grade), and in metastatic/recurrent than primary disease. Concurrent PTEN and TP53 inactivation was demonstrated in 35% of LMS, whereas concurrent PTEN inactivation and ER and/or PR expression was demonstrated in 9% of LMS. Only 1% of LMS had both PTEN and p16 inactivation (with normal RB1), i.e. a profile providing biologic rationale for co-targeting of mTOR (or other PI3K-pathway targets) and CDK4/6.

Conclusion: These evaluations of 712 ST and UT LMS determine frequencies of events dysregulating key growth-promoting pathways, thereby better defining biologic rationales for therapeutic targeting and co-targeting of LMS oncogenic pathways. Dysregulation of the p16/RB1 axis occurs in most ST and UT LMS, but only 5% of cases have a biologic profile predictive of benefit from CDK4/6 inhibition. The data suggest that co-targeting the PI3K pathway and TP53 is relevant in 35% of LMS pts, and co-targeting PI3K and ER/PR relevant in 9% of pts, whereas co-targeting PI3K and CDK4/6 is less likely to be useful.

Table 1. Immunoprofiling results in soft tissue and uterine LMS.

	All cases	Soft tissue	Uterine	Primary	Recurrence[#]
Immunoprofiling	100% (N=712)	52% (N=358)	50% (N=354)	44% (N=312)	56% (N=400)
Inactivation					
p16	16%	13%*	19%*	18%	14%
RB1	89%	93%*	84%*	87%	90%
p16 (w/ retained RB1)	5%	4%	7%	7%	4%
TP53	87%	90%*	84%*	84%	89%
PTEN	41%	48%*	32%*	46%*	36%*
PTEN + TP53	35%	44%*	25%*	38%	33%
PTEN + p16 (w/ retained RB1)	1%	2%	0%	1%	1%
Moderate/strong expression					
ER/PR	34%	15%*	54%*	28%*	39%*
ER/PR (w/ PTEN inactivation)	9%	6%*	13%*	12%*	1%*

*P<0.05; [#]Includes local recurrences and distant metastases

Paper 046 3042897

CHROMATIN STATE TRANSITIONS ASSOCIATED WITH PRC2 FUNCTIONAL LOSS DRIVE A DE-DIFFERENTIATED PHENOTYPE IN MALIGNANT PERIPHERAL NERVE SHEATH TUMORS

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Objective: Malignant peripheral nerve sheath tumors (MPNSTs) are highly aggressive soft tissue sarcomas and more than 70% of cases are associated with mutations/deletions of SUZ12 and EED leading to functional inactivation of Polycomb Repressor Complex 2 (PRC2) and global loss of H3K27me3. This study was aimed at defining chromatin state transitions associated with global loss of H3K27me3 and its correlation to changes in expression patterns in MPNST that have not been explored before.

Methods: Comparative transcriptomic and epigenomic profiling of histone marks in PRC2 active and inactive MPNST cells was performed to determine functional chromatin state changes associated with global loss of H3K27me3 and to identify epigenetic changes at critical regulatory genes that drive MPNST pathogenesis.

Results: Transcriptomic analysis in MPNST patient samples with functionally inactive PRC2 identified a de-differentiated neural crest expression signature and activation of associated pathways. Epigenomic profiling in MPNST cell lines revealed significant changes in heterochromatin (H3K9me3), active enhancers (H3K27Ac) and transcriptional activation (H3K79me2) which regulated expression of critical genes of pathways driving MPNST progression due to loss of H3K27me3. Differentially enriched enhancers in PRC2 inactive MPNST lines were associated with genes regulating early nervous system development. Though new active enhancers were observed at some of the upregulated neural crest genes, expression of most of these genes was found to be driven by loss of bivalency from their promoters.

Conclusion: In this study we defined MPNST subtypes with distinct epigenetic signatures that were attributed to global loss of H3K27me3. Systematic analysis of the epigenomic changes in the context of PRC2 functional loss elucidated functionally significant transitions in chromatin states that imparted a de-differentiated and aggressive phenotype in MPNST and they could be targeted with novel epigenetic drug combinations.

Paper 047 3042069

TWIST BRIDGES P53 AND MDM2 AND REDUCES THE EFFICACY OF MDM2 INHIBITORS

Sara Piccinin[1]*; Elena Doriguzzi Breatta*[1]*; Sara Lombardi*[1]*; Mattia Lombardi*[1]*; Flavia Pivetta*[1]*; Michela Armellin*[1]*; Camillo Rosano*[2]*;* ***Roberta Maestro***[1]

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Objective: A significant fraction of primary soft tissue sarcomas (STS), especially simple karyotype STS, retains wild-type TP53. Nevertheless, the p53 response is attenuated in these tumors, indicating that p53 is inactivated through mechanisms alternative to TP53 mutation. We recently reported that the bHLH embryonic transcription factor Twist contributes to p53 inactivation in STS by directly binding p53 and impeding Ser392 phosphorylation, which results in increased p53 degradation. Here we investigated in better detail the Twist/p53 interplay in the pathogenesis of STS and its role in the response to p53/MDM2 inhibitors.

Methods: Co-Immunoprecipitation (Co-IP) and GST-pull down (GST-PD) experiments were used to investigate the interaction between Twist, p53 and MDM2. Docking simulations were done using SAM-T08 CNS and ClusPro 2.0 tools. Twist gain-of-function and loss-of-function cell models were generated and trypan blue exclusion and SRB assays were used to evaluate sensitivity to p53/MDM2 inhibitors (Nutlin-3a, SAR405838, RG 7112, AMG232).

Results: Co-PI and GST-PD experiments indicated that, besides binding p53, Twist binds directly also MDM2. Docking simulation and sequential co-PI supported the notion that Twist, p53 and MDM2 form a trimeric complex, with Twist bridging p53 and MDM2. Moreover, we found that the expression of Twist hampers the efficacy of p53/MDM2 inhibitors, as assessed in Twist gain-of-function and loss-of-function cell models.

Conclusion: Our study provides evidence that by binding to both p53 and MDM2 and bridging the two proteins, Twist favors

MDM2 mediated degradation of p53 and attenuates the efficacy of p53/MDM2 inhibitors. Thus, we consider that, besides the retention of wild-type TP53, the expression of Twist should also enter into the criteria of stratification for the treatment with MDM2 antagonists.

4:00 pm – 5:30 pm

– SESSION 9 –

Soft Tissue Sarcoma: Local Therapy

Paper 048 3042386

LONG-TERM COMPARISON OF LOCAL RECURRENCE AFTER CONVENTIONAL AND INTENSITY-MODULATED RADIATION THERAPY FOR PRIMARY SOFT TISSUE SARCOMAS OF THE EXTREMITY

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Objective: We previously reported that intensity-modulated radiation therapy (IMRT) was associated with significantly reduced local recurrence (LR) compared to conventional 3D conformal radiation therapy (3DCRT) in patients with primary soft tissue sarcoma (STS) of the extremity (Folkert MR, et al. *J Clin Oncol* 2014). The purpose of this study is to provide a long-term comparison of LR after 3DCRT and IMRT in patients with primary STS of the extremity treated with surgery and RT.

Methods: We retrospectively reviewed all patients with STS of the extremity who were treated with limb-sparing surgery and adjuvant RT between 1996 and 2015 at a single institution. A tumor was considered as upper extremity if it was at or distal to the shoulder and as lower extremity if it was at or distal to the groin. The chi-square test was used to compare groups for categorical variables. Cumulative incidence and Gray's test were used to analyze LR, with death without LR defined as a competing event for LR. Cox proportional hazards regression was used to estimate LR-free survival. Overall survival (OS) and distant metastatic disease-free survival (DFS) were estimated using the Kaplan-Meier method.

Results: There were 475 patients with a median age of 56 (range: 19-96) included in this analysis. Sixty-five percent of patients (n=310) were > 50 years of age. Seventy-one percent of cases (n=335) involved the lower extremity. There was a predominance of high risk features such as high grade (n=407, 86%), size > 10cm (n=202, 43%), deep tumors (n=443, 93%), and positive or close (within 1mm) margins (n=214, 45%). Twenty-three percent (n=111) of patients had chemotherapy as part of their treatment. Thirty-five percent of patients (n=165) received 3DCRT while 65% (n=310) received IMRT. RT was given pre-operatively to 104 patients (22%) and post-operatively to 371 patients (78%). The median preoperative RT dose was 50Gy and median post-operative RT dose was 63Gy.

Patients in the 3DCRT and IMRT groups were comparable in terms of location of tumor (p=0.33), size (p=0.46), depth (p=0.73), margin status (p=0.11), and histology, defined as undifferentiated pleomorphic sarcoma and myxofibrosarcoma *vs* other (p=0.77). There were more patients > 50 years of age in the IMRT cohort than in the 3DCRT cohort (68.4% *vs* 39.4%, p=0.050). The cohort receiving IMRT also had a significantly higher proportion of tumors with high grade (89.6% *vs* 78.8%, p=0.001).

With median follow-up time of 5.1 years for all patients and 6.1 years for surviving patients, the 5-year cumulative incidence of LR was 9.1% [95% CI: 6.6%, 12.0%] among all patients. Median time to LR was 19.3 months (range: 1.2 – 109.2 months). Median follow-up for patients treated with 3DCRT was 6.0 years and for patients treated with IMRT was 4.6 years. The five-year cumulative incidence of LR by treatment modality was 14.0% [95% CI: 9.1%, 20.0%] for patients receiving 3DCRT and 6.3% [95% CI: 3.8%, 9.5%] for patients receiving IMRT (p=0.006).

On univariable analysis, IMRT was associated with a significantly reduced risk of LR (HR 0.46, p=0.009). The other predictors of reduced risk of LR were age ≤ 50 years (HR 0.49, p=0.045) and tumor size ≤ 10cm (HR 0.46, p=0.010). Grade, depth, margin status, location of tumor, and sequencing of RT (preoperative *vs* post-operative) were not significantly associated with LR. On multivariable analysis, with all relevant variables, regardless of significance on univariable analysis, included in the model, the predictors of LR remained the same: IMRT (HR 0.43, p=0.005), age ≤ 50 years (HR 0.45, p=0.03), and tumor size ≤ 10cm (HR 0.49, p=0.02).

Five-year overall survival for all patients (n=475) was 74.8% [95% CI: 70.6%, 79.0%]. Distant metastatic disease-free survival was 67.1% [95% CI: 62.5%, 71.7%].

Conclusion: With long-term follow-up (median: 5.1 years), we continue to find on univariable and multivariable analysis that IMRT remains associated with significantly reduced LR compared with 3DCRT for primary STS of the extremity.

Paper 049 3028760

CAN WE CURE PATIENTS WITH ABDOMINAL DESMOPLASTIC SMALL ROUND CELL TUMOR? RESULTS OF A RETROSPECTIVE MULTICENTRIC STUDY ON 100 PATIENTS

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Objective: Desmoplastic Small Round Cell Tumor (DSRCT) is a rare peritoneal disease affecting children and young adults. Despite a very poor prognosis, long-term survivors have been reported. The Aim of the study is to identify in a nation-wide survey patients with a prolonged survival after DSRCT diagnosis and to identify factors associated with a cure.

Methods: All consecutive patients treated for DSRCT in 9 French expert centers between 1991 and 2018 were identified and retrospectively analyzed. Patients with a follow-up of less than 2 years were excluded from the analysis. Cure was defined as a disease-free survival of at least 5 years.

Results: 100 pts were identified (median age 25, 89% male). 27 had distant metastases at diagnosis. 80 pts underwent upfront chemotherapy and 51 pts were subsequently operated. 20 pts went directly to surgery. Surgery was macroscopically complete (CC0/1) in 50 pts. Intraperitoneal chemotherapy was associated to surgery in 17 pts. 54 pts had postoperative chemotherapy and 26 pts had postoperative whole abdomino-pelvic RT (WAP-RT). After a median follow-up of 124 months (range 23-311), the median overall survival (OS) was 25 months. 1- year, 3-year and 5-year OS rates were 90%, 35% and 4% respectively. 7 patients were considered cured after a median disease-free interval of 100 months (range 22-139). Predictive factor of cure were female sex (HR=4.46, p=0.005), median PCI<12 (HR=4.53, p=0.005), MD Anderson stage I (HR=3.97, p = 0.003), CC0/1 (HR=2.17, p = 0.05) and WAP-RT (HR=3.41; p=0.003). Neither Hyperthemic intraperitoneal chemotherapy (HIPEC) nor early postoperative intraperitoneal chemotherapy (EPIC) did increase the rate of cure.

Conclusion: Cure in DSRCT is possible in 7% of patients and is best achieved combining systemic chemotherapy, complete cytoreductive surgery and WAP-RT. Targeted treatments are urgently needed.

Paper 050 3027816

ENHANCED RECOVERY AFTER SURGERY (ERAS) IN PATIENTS UNDERGOING SURGERY FOR SOFT TISSUE SARCOMA (STS): EARLY RESULTS OF A PROSPECTIVE QUALITY IMPROVEMENT PROTOCOL

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Objective: Patients undergoing surgery for STS can have high morbidity rates, including wound complications, particularly after preoperative radiation therapy (RT). The ERAS program, in several surgical specialties, is associated with improved perioperative outcomes, including lower wound complication rates and shorter length of stay (LOS). We launched an ERAS program tailored for patients undergoing surgery for STS and report early outcomes.

Methods: ERAS was implemented at a single high volume sarcoma center in 2015 (preoperative oral hydration, goal-directed fluid therapy, non-narcotic analgesic adjuncts, early mobilization, early diet). All patients undergoing STS surgery with intent to treat with the ERAS protocol were compared in a case-match analysis with patients undergoing STS surgery without ERAS. The non-ERAS cohort was retrospectively case-matched with the prospectively collected ERAS cohort by site of surgery, surgeon, sarcoma histology and treatment with preoperative radiation therapy. The outcomes measured included wound complications (surgical site infections, wound dehiscence, and seroma formation), acute postoperative outcomes, discharge to a facility, and length of stay.

Results: The 234 STS ERAS cases performed by 3 surgical oncologists (July 2015 to March 2018) were matched with 237

STS non-ERAS cases performed by the same surgical oncologists (January 2012 to March 2018). Outcomes are shown in Table 1. Wound dehiscence rates were significantly lower in the ERAS cohort compared to the non-ERAS cohort (2 [0.9%] vs 31 [13.1%], p<0.001) and remained significant in the cohort of patients who received preoperative radiation (0 vs 11 [21.6%], p=0.004) and who underwent surgery for extremity STS (0 vs 6 [0.7%], p=0.04). Rate of postoperative obstruction (need for nasogastric tube) was significantly lower in the ERAS cohort (3 [1.3%] vs 17 [7.2%], p=0.003), and this difference was preserved in the cohort of patients who underwent surgery for retroperitoneal sarcoma (1 [2.8%] vs 10 [27.8%], p=0.009). Median LOS was significantly lower in the ERAS cohort (5 days [range 0-36] vs 6 days [range 0-67], p=0.003). Discharge to a facility was also significantly reduced in the ERAS cohort (13 [5.6%] vs 31 [13.1%], p=0.008).

Conclusion: Implementation of an ERAS program was associated with improved postoperative outcomes including reduced rates of wound complications (for all patients, extremity site, and use of preoperative RT), postoperative bowel obstructions, length of hospital stay, and discharge to a facility. Reduction of wound complication rates with ERAS after preoperative RT and in extremity STS patients has important implications in oncologic treatment as it offsets the most notable morbidity of neoadjuvant RT. Based on these results, an international protocol is planned.

Table 1. Outcomes for All Patients Undergoing Surgery for STS Stratified by ERAS Implementation (N=234 for ERAS, N=237 for Non-ERAS)

	ERAS (N[%])	Non-ERAS (N[%])	p-value
Return to the ED	8 [3.4%]	8 [3.4%]	P=1
Readmission	18 [7.7%]	23 [9.7%]	P=0.5
Bleeding	16 [6.8%]	30 [12.7%]	P=0.05
Surgical Site Infection	21 [9.0%]	28 [11.8%]	P=0.5
Wound Dehiscence	2 [0.9%]	31 [13.1%]	P<0.001
Seroma Formation	10 [4.3%]	13 [5.5%]	P=0.7
Ileus	19 [8.1%]	27 [11.4%]	P=0.3
Intraabdominal Fluid Collection	6 [2.6%]	3 [1.3%]	P=0.5
Obstruction	3 [1.3%]	17 [7.2%]	P=0.003
Initiation of TPN	8 [3.4%]	11 [4.6%]	P=0.7
Discharge to Facility	13 [5.6%]	31 [13.1%]	P=0.008

Paper 051 3042593

DEVELOPMENT OF A DYNAMIC PROGNOSTIC NOMOGRAM TO PREDICT OVERALL SURVIVAL DURING FOLLOW-UP IN PRIMARY EXTREMITY SOFT TISSUE SARCOMA PATIENTS TREATED WITH SURGERY

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Objective: Available prognostic nomograms for patients with primary extremity Soft Tissue Sarcoma (eSTS) assume that the effect of each covariate on overall survival (OS) is constant over time. Moreover, they do not factor the effect of postoperative events (local recurrence, LR, or distant metastasis, DM) on patient's outcome. Thus, they are designed to be used only right after surgery. The aim of the present study was to develop a prognostic nomogram that could predict patient prognosis at specific time-points during follow-up by using dynamic prediction.

Methods: Patients with primary eSTS surgically treated among three European and one North-American tertiary centers between 1994 and 2013 were included. Landmark (LM) analysis was performed by establishing a prediction windows at 5 years, LM time points T_{LM} at every third month between 0 and 3 years after surgery (starting date), creating a dataset at each T_{LM} including patients at risk at that time (left censored, with right censoring at T_{LM}+60), and stacking all the LM datasets into a unique super LM dataset, on which a multivariable Cox model was fitted. The initial model included patient's age, tumor size, FNCLCC grade, histological subtype, depth, surgical margins (R0 vs R1), chemotherapy (CT) and radiotherapy

(RT) administration, local relapse and DM occurrence; moreover, we included the first order interactions between the above covariates and T_{LM} in order to test for time-varying covariate effects. Numerical variables including T_{LM} were modeled using 3-knots restricted cubic splines. We applied a backward procedure based on the Akaike Information Criterion (AIC) for variable selection.

Results: 3752 patients were included in the analysis (median follow-up 79 months, interquartile range 44-119). Ten-year OS, crude cumulative incidence (CCI) of LR and CCI of DM were respectively 66.3% (64.3-68.2%), 8.2% (7.2-9.2%), and 28.2% (26.6-30.0%). After backward procedure, the final model (Fig 1, Tab 1) included patient's age, tumor size and its interaction with T_{LM}, grading and its interaction with T_{LM}, histology, LR and DM occurrence. The hazard ratio (HR) of a patient with G3 tumor compared to a patient with G1 tumor is 4.97 (95% confidence interval 3.45 – 7.14) immediately after surgery but decreases to 2.59 (1.80 – 3.73) one year after surgery, 1.59 (1.09 - 2.32) 2 years after surgery and 1.10 (0.72 - 1.69) 3 years after surgery. Similarly, the HR related to tumor size decreases from 3.11 (2.56 – 3.76) at surgery to 2.31 (1.92 – 2.78) after one year of follow-up, 1.89 (1.55,2.31) after 2 years and 1.67 (1.30,2.14) 3 years after surgery. At internal validation, the (bootstrap corrected) Harrell C statistic was 0.843.

Conclusion: A new nomogram is available to predict 5-year OS starting from 0 (surgery) to 3 years of follow-up in patients surgically treated for primary eSTS. The nomogram can help defining risk-based strategies for patient's FU, although a validation on independent series is needed.

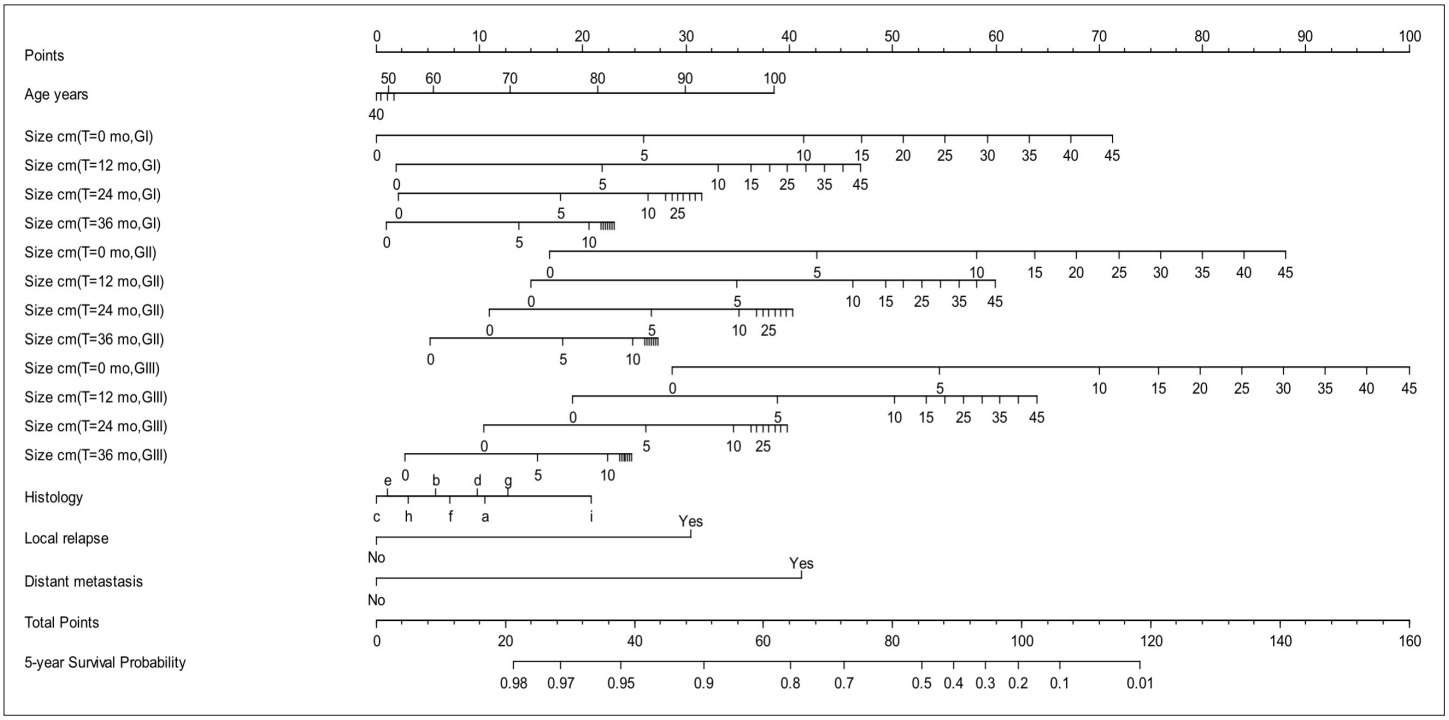

Figure 1: Nomogram for dynamic prediction of 5-year OS at up to 3 years of follow-up. For the covariates with a time-varying effect (tumor size and grading) T represents the time point at which OS prediction is made; we choose to represent T=0 (at surgery), and T=12, 24 and 36 months after surgery.

Histology legend: a: leiomyosarcoma (LMS); b: dedifferentiated (DD) /pleomorphic liposarcoma; c: myxoid liposarcoma; d: malignant peripheral nerve sheath tumor (MPNST); e: myxofibrosarcoma; f: other, g: synovial sarcoma; h: undifferentiated pleomorphic sarcoma (UPS); i: vascular sarcoma.

Multivariable Cox OS supermodel for landmark analysis

	OS		
	HR	95% CI	Wald p test
Time-independent covariates			
Age, years			<.0001
69 vs 42	1.79	(1.58,2.04)	
Local recurrence			<.0001
yes vs no	5.48	(4.16,7.22)	
Distant metastasis			<.0001
yes vs no	9.94	(8.46,11.69)	
Histological subtype			<.0001
LMS vs Myxoid lipo	1.80	(1.27,2.53)	
DD/plom lipo vs Myxoid lipo	1.37	(0.93,2.02)	
MPNST vs Myxoid lipo	1.73	(1.16,2.57)	
Myxofibro vs Myxoid lipo	1.06	(0.73,1.54)	
Synovial sarcoma vs Myxoid lipo	2.04	(1.43,2.89)	
UPS vs Myxoid lipo	1.19	(0.86,1.65)	
Vascular sarcoma vs Myxoid lipo	3.19	(1.84,5.53)	
Other vs Myxoid lipo	1.49	(1.07,2.06)	
Time-depedent covariates			
Size, cm (TLM, mo)			<.0001*
11 vs 4 (0)	3.11	(2.56,3.76)	
11 vs 4 (12)	2.31	(1.92,2.78)	
11 vs 4 (24)	1.89	(1.55,2.31)	
11 vs 4 (36)	1.67	(1.30,2.14)	
FNCLCC grade (TLM, mo)			<.0001*
III vs I (0)	4.97	(3.14,7.14)	
III vs I (12)	2.59	(1.80,3.73)	
III vs I (24)	1.59	(1.09,2.32)	
III vs I (36)	1.10	(0.72,1.69)	
* p value related to the covariate and its interaction with landmark time.			

Paper 052 3042509

THE IMPACT OF UNPLANNED EXCISIONS OF SOFT TISSUE SARCOMAS: A MULTI-INSTITUTIONAL PROPENSITY SCORE ANALYSIS FROM THE US-SARCOMA COLLABORATIVE

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Objective: Unplanned excisions of soft-tissue sarcomas (STS), defined as accidental, non-oncologic resections, have historically been associated with worse prognosis. This association has recently been challenged as patients who undergo unplanned excision (UE) with subsequent re-resection have comparable outcomes to those with planned excisions (PE). Thus, the aim of our study was to compare outcomes of patients who underwent UE to those who underwent PE of STS in a modern, multi-institutional cohort of patients.

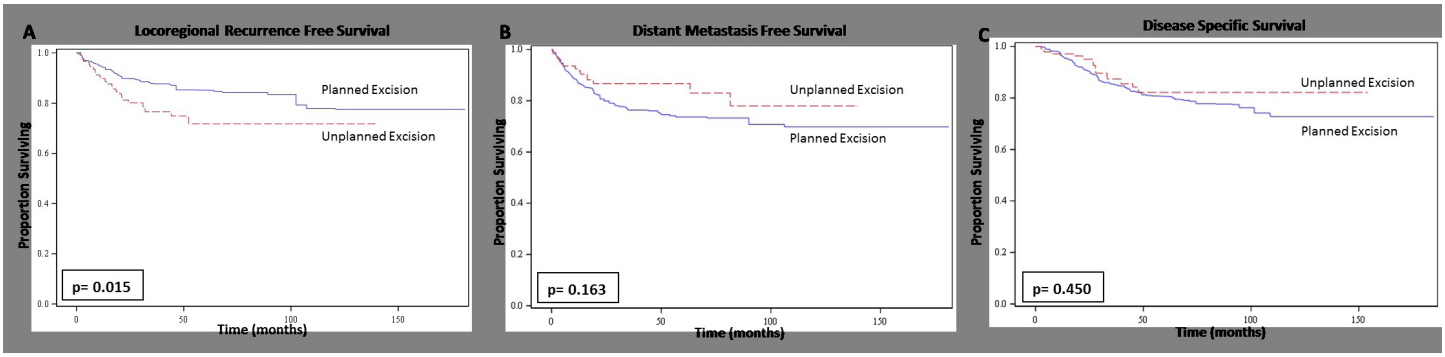
Methods: A retrospective review was performed of the 7-institution US Sarcoma Collaborative (USSC) database. All patients with primary truncal/extremity STS who underwent curative-intent resection between 2000-2016 were included. Patients were identified as either having an UE or a PE. A propensity score weighting analysis (PSWA) was performed to balance the baseline covariates of gender, age, ASA class, tumor size, location, tumor depth, final resection status, presence of

necrosis, and receipt of radiotherapy, and such balance was further achieved within subgroups by tumor grade. Primary endpoints were locoregional recurrence free survival (LR-RFS), distant metastasis free survival (DMFS), and disease-specific survival (DSS).

Results: Of the 4153 patients within the USSC database, 1596 patients underwent resection of a truncal/extremity STS. Median age was 58 years and 54% were male. Eighty-two percent (n=1315) of patients underwent a PE, while 18% (n=281) underwent an UE. Patients who underwent UE generally had more favorable prognostic characteristics compared to PE including younger age (56yo vs. 59yo, p=0.016), smaller tumor size (3cm vs. 9cm, p<0.001), and less tumor necrosis (21% vs. 54%, p<0.001), though there was no difference in tumor grade between groups (high grade 74% vs 71%, p=0.337). Unmatched, multivariable analysis of the entire cohort revealed that PE was associated with worse DMFS (HR 1.95, p=0.009) and worse DSS (HR 1.78, p=0.039) compared to UE, even when considering tumor size, tumor depth, tumor location, tumor grade, tumor necrosis, and final resection status. PE and UE did not have an association with LR-RFS (HR 0.74, p=0.143).

On PSWA, there is no significant advantage of PE over UE on LR-RFS (HR 0.62, p=0.172), DMFS (HR 1.55, p=0.208), or DSS (HR 1.43, p=0.350). When stratified by grade, PSWA of patients with high-grade tumors who underwent UE had worse LR-RFS compared to those who underwent PE (1-year LR-RFS 90% vs 94%, p=0.0152), however there was no difference in DMFS or DSS in these patients (Figure 1). Additionally, on PSWA, there was no difference in LR-RFS, DMFS, or DSS between UE and PE among patients with low-grade tumors.

Conclusion: Unplanned excision of STS with subsequent re-resection is not associated with worse prognosis compared to planned excisions, though unplanned excision appears to be associated with earlier locoregional recurrences in patients with high-grade tumors. This emphasizes the need for multidisciplinary management of such tumors for consideration of multimodality therapy.



Kaplan-Meier analysis of the propensity weighted cohort of patients with high-grade tumors who underwent unplanned and planned excisions of soft tissue sarcomas. Patients with high grade tumors who underwent an unplanned excision had worse locoregional recurrence free survival compared to those who underwent a planned excision (a), though there was no difference in distant metastasis free survival or disease specific survival between groups (b and c).

Poster 001 3027672

MULTICENTER, OPEN-LABEL PHASE II STUDY OF DAILY ORAL REGORAFENIB FOR CHEMOTHERAPY-REFRACTORY, METASTATIC AND LOCALLY ADVANCED ANGIOSARCOMA

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Poster 002 3042315

PITFALLS IN ANGIOSARCOMA DIAGNOSIS: LESSONS LEARNED FROM CENTRAL REVIEW OF 657 DUTCH CASES

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Poster 003 3042833

LOCALIZED RADIATION-ASSOCIATED ANGIOSARCOMA OF THE BREAST: A MONO-INSTITUTIONAL CASE SERIES

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Poster 004 3000082

TRAMETINIB INDUCES RESPONSE IN REFRACTORY HRAS G13D-MUTATED ANGIOSARCOMA OF SCALP

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Poster 005 3037976

THE ANGIOSARCOMA PROJECT: GENERATING THE GENOMIC LANDSCAPE OF A RARE SARCOMA THROUGH A NATIONWIDE PATIENT-DRIVEN INITIATIVE

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Poster 006 3042503

A RETROSPECTIVE REVIEW OF PATIENTS WITH ANGIOSARCOMA TREATED IN BRITISH COLUMBIA

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Poster 007 3042537

DETECTION OF ENDOGLIN-EXPRESSING CTCS IN PATIENTS ENROLLED IN AN ADAPTIVE ENRICHMENT PHASE 3 TRIAL OF TRC105 AND PAZOPANIB VERSUS PAZOPANIB ALONE IN PATIENTS WITH ADVANCED ANGIOSARCOMA (TAPPAS)

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Poster 008 3042562

NEOADJUVANT CHEMOTHERAPY ASSOCIATED WITH ENHANCED LOCAL CONTROL IN RADIATION-INDUCED ANGIOSARCOMA OF BREAST AND CHEST

Audrey Michot[1]*; Marie Karanian*[2]*; Maryck Lae*[11]*; Romuald Wernert*[3]*; Marie-Pierre Sunyach*[4]*; Dimitri Tzanis*[5]*; Jean-Marie Guilloit*[6]*; Maria Rios*[7]*; Antoine Giraud*[8]*; François Le Loarer*[9]*; Jean-Yves Blay*[10]*; Eberhard Stoeckle*[1]

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Poster 009 3015887

ASSOCIATION OF BETA-BLOCKER USE WITH CLINICAL OUTCOMES IN PATIENTS WITH ADVANCED ANGIOSARCOMA

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Poster 010 3016619

ACTIVITY AND SAFETY OF CRIZOTINIB IN PATIENTS WITH ADVANCED, METASTATIC ALVEOLAR SOFT PART SARCOMA (ASPS) WITH REARRANGEMENT OF TFE[3]EUROPEAN ORGANIZATION FOR RESEARCH AND TREATMENT OF CANCER (EORTC) PHASE 2 TRIAL 90101 "CREATE"

Patrick Schöffski[1]*; Agnieszka Wozniak*[2]*; Bernd Kasper*[4]*; Steinar Aamdal*[3]*; Michael Leahy*[6]*; Piotr Rutkowski*[7]*; Sebastian Bauer*[12]*; Hans Gelderblom*[8]*; Antoine Italiano*[5]*; Lars Lindner*[9]*; Ivo Hennig*[15]*; Sandra Strauss*[10]*; Branko Zakotnik*[14]*; Alan Anthoney*[13]*; Silvia Stacchiotti*[11]

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Poster 011 3042589

TREATMENT PATTERNS OF ALVEOLAR SOFT PART SARCOMA PATIENTS AND RESPONSE TO MULTIPLE EXPERIMENTAL THERAPIES

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Poster 012 3042597

CLINICAL CHARACTERISTICS OF ALVEOLAR SOFT PART SARCOMA PATIENTS WITH BRAIN METASTASIS

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Poster 013 3019420

EXPANDING THE HISTONE MUTATION LANDSCAPE IN SARCOMA

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Poster 014 3042534

DEVELOPMENT OF A PLASMA MICRORNA BIOMARKER FOR PEDIATRIC OSTEOSARCOMA

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Poster 015 3042930

SHIFTING THE PARADIGM IN PRECLINICAL CANCER MODELING: A MOUSE-DOG-HUMAN PERSONALIZED MEDICINE PIPELINE TO IDENTIFY NOVEL THERAPEUTICS FOR OSTEOSARCOMA

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Poster 016 3025705

XENOSARC: PATIENT-DERIVED XENOGRAFT (PDX) MODELS OF SOFT TISSUE SARCOMA (STS) – AND UPDATE ON A PRECLINICAL PLATFORM FOR EARLY DRUG TESTING

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Poster 017 3029268

BMP-2 SIGNALLING INFLUENCES TUMOUR BIOLOGY IN PRE-CLINICAL MODELS OF OSTEOSARCOMA

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Poster 018 3036616

PHENOTYPIC CHARACTERIZATION OF IGFR2R KNOCKOUT IN HUMAN OSTEOSARCOMA CELLS

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Poster 019 3041727

THE ODC1/POLYAMINES/C-MYC AXIS PROMOTES OSTEOSARCOMA TUMORGENESIS BY REGULATING GLUTAMINOLYSIS

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Poster 020 3042199

THE TYPE OF NR4A3 FUSION PARTNER DICTATES AN AXON GUIDANCE SWITCH IN EXTRASKELETAL MYXOID CHONDROSARCOMAS

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Poster 021 3042292

THE MECHANISMS OF ZOLEDRONIC ACID-INDUCED AUTOPHAGY ON OSTEOSARCOMA CELLS

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Poster 022 3042653

***ATRX* MUTATIONS INCREASE TUMORIGENICITY IN OSTEOSARCOMA**

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Poster 023 3042613

DOXORUBICIN, GEMCITABINE, IFOSFAMIDE, AND THE EZH2 INHIBITOR EPZ-011989 IN EPITHELIOID SARCOMA: A COMPARISON OF DIFFERENT REGIMENS IN A PATIENT-DERIVED XENOGRAFT

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Poster 024 3042633

REACTIVATION OF WILD TYPE P53 BY MDM2 INHIBITION IN SYNOVIAL SARCOMAS

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Poster 025 3026307

MACHINE LEARNING ANALYSIS OF GENE EXPRESSION DATA REVEALS NOVEL DIAGNOSTIC AND PROGNOSTIC BIOMARKERS AND IDENTIFIES THERAPEUTIC TARGETS FOR SOFT TISSUE SARCOMAS

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Poster 026 3042679

THE DEVELOPMENT AND CHARACTERTIZATION OF A HUMANIZED XENOGRAFT MURINE MODEL FOR OSTEOSARCOMA

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Poster 027 3042837

COMBINATION OF CISPLATIN AND HIV PROTEASE INHIBTOR NELFINAVIR SHOWS SYNERGISTIC EFFECTS AGAINST THE GROWTH OF HUMAN OSTEOSARCOMA CELLS

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Poster 028 3042736

PROGNOSTIC IMPACT OF THE FGFR EXPRESSION IN LIPOSARCOMA ROLE OF FGFR AND MDM2 DUAL TARGETING

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Poster 029 3042825

DISCOVERY SCREEN OF SMALL MOLECULE INHIBITORS OF THE PAX3-FOXO1 FUSION PROTEIN NOMINATES THERAPEUTIC COMBINATION STRATEGIES

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Poster 030 3042839

HIGH-THROUGHPUT DRUG SCREENING OF PATIENT-DERIVED SARCOMA TUMOR ORGANOIDS FOR PERSONALIZED THERAPY

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Poster 031 3042840

TARGETING ACTIVATING TRANSCRIPTION FACTOR 6 ALPHA (ATF6 A): A NOVEL APPROACH FOR THE TREATMENT OF PEDIATRIC OSTEOSARCOMA

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Poster 032 3042902

ELUCIDATING THE ROLE OF THE EPHRIN TYPE-A RECEPTOR (EPHA2) AS THERAPEUTIC TARGET IN OSTEOSARCOMA USING PATIENT-DERIVED TUMOR XENOGRAFTS

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Poster 033 3042984

PATIENT-DERIVED SARCOMA MODELS - FIRST RESULTS FROM THE SARQMA STUDY

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CLEAR CELL SARCOMA OF THE KIDNEY SHOWS ELEVATED LEVELS OF THE ONCOMETABOLITE AND EPIGENETIC MODIFIER L-2-HYDROXYGLUTARATE

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ANTI-TUMOR EFFECTS OF TAS-115 ON MURINE OSTEOSARCOMA CELL LINE(LM8) WITH HIGH METASTATIC POTENTIAL TO THE LUNG

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MESENCHYMAL STROMAL CELLS ENHANCE METASTASIS FORMATION IN OSTEOSARCOMA

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TNIK IS A NOVEL MOLECULAR TARGET FOR OSTEOSARCOMA TREATMENT AND CONTROLS OSTEOSARCOMA CELL FATE

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IRE1α-XBP1 INHIBITORS EXERTS ANTITUMOR ACTIVITY IN OSTEOSARCOMAS

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ESTABLISHMENT OF PATIENT-DERIVED XENOGRAFT MODELS OF MUSCULOSKELETAL SARCOMA SERIALLY EVALUATED WITH COMPREHENSIVE GENE EXPRESSION PROFILING

Michiyuki Hakozaki[1]*; Yuu Dobashi*[2]*; Hitoshi Yamada*[1]*; Takahiro Tajino*[3]*; Yoichi Kaneuchi*[1]*; Junichi Imai*[2]*; Kiyoaki Katahira*[2]*; Shin-ichi Konno*[1]*; Shinya Watanabe*[2]

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IMAGING THE INTERACTION OF OSTEOSARCOMA CELLS WITH HOST STROMAL CELLS AND TUMOR SCAFFOLD COLLAGEN IN THE TUMOR MICROENVIRONMENT

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ACIDIC MICROENVIRONMENTS IN SOFT-TISSUE SARCOMA PROMOTES FOXM1 EXPRESSION AND TUMORIGENESIS

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CYTOTOXIC AND ANTI-METASTATIC EFFECTS OF MYCOPHENOLATE MOFETIL IN OSTEOSARCOMA: DRUG REPURPOSING FROM PROTEOMIC DATA

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COMPLEX AUTOCRINE AND PARACRINE INTERACTIONS IN A SERIES OF SINGLE-BACKGROUND MURINE FIBROSARCOMA CELL LINES

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CXCR4 INHIBITORS AS CHEMOSENSITIZER IN BONE MARROW-DERIVED MESENCHYMAL STEM CELL-MEDIATED OSTEOSARCOMA AND SYNOVIAL SARCOMA CELL APOPTOSIS AND MIGRATION

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THE PHOSPHATASE PTPRG CONTROLS FGFR1 ACTIVITY AND INFLUENCES SENSITIVITY TO FGFR KINASE INHIBITORS

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EUTHYROID HYPOTHYROXINEMIA [EH] MODULATED BY EXOGENOUS L -TRIIODOTHYRONINE MAY EXTEND SURVIVAL IN ADVANCED SARCOMA-AN UPDATED FOLLOW-UP

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NOVEL BIOINFORMATICS APPROACH FOR SARCOMA PROTEOGENOMICS; MUTATED NUCLEOTIDES AND AMINO-ACIDS GENERATOR (MUNAGE)

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EFFECT OF ANLOTINIB, A NOVEL SMALL MOLECULAR TYROSINE KINASE INHIBITOR, ON GROWTH, METASTASIS AND ANGIOGENESIS IN OSTEOSARCOMA

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EFFECT OF CHEMOTHERAPY ON CANCER STEM CELLS AND TUMOR-ASSOCIATED MACROPHAGES IN A PROSPECTIVE STUDY OF PREOPERATIVE CHEMOTHERAPY IN SOFT TISSUE SARCOMA

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DRUG SENSITIVITY TESTING ON PATIENT-DERIVED SARCOMA CELLS PREDICTS PATIENT RESPONSE TO TREATMENT AND IDENTIFIES C-SARC INHIBITORS AS ACTIVE DRUGS FOR TRANSLOCATION SARCOMAS

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THE EFFECT OF BUPIVACAINE AND LIDOCAINE ON OSTEOSARCOMA CELLS

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THE PROTEIN EXPRESSION OF NF1; P16INK4A, PTEN AND THEIR INVOLVED SIGNAL PATHWAY FATORS IN UNDIFFERENTIAED PLEOMORPHIC SARCOMA

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TWO NOVEL HUMAN MYXOFIBROSARCOMA CELL LINES REPRESENT A CELLULAR MODEL FOR TUMOR HETEROGENEITY

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APOPTOTIC INDUCTION AND G1 CELL CYCLE ARREST OF MULTIDRUG RESISTANT SARCOMA CELL LINES BY THE HISTONE DEACETYLASE INHIBITORS VERINOSTAT AND PANOBINOSTAT

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Poster 055 3042709

THERAPEUTIC VULNERABILITIES IN UNDIFFERENTIATED SARCOMAS

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SCREENING OF SYNERGISTIC REAGENT WITH PAZOPANIB AGAINST OSTEOSARCOMA USING COMPOUND LIBRARY.

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Poster 057 3042757

TARGETTING EPIDERMAL GROWTH FACTOR RECEPTORS AND UROKINASE-TYPE PLASMINOGEN ACTIVATOR RECEPTORS FOR SARCOMA THERAPY

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IMPROVING ONCOLYTIC VIROTHERAPY USING VANADIUM-BASED COMPOUNDS IN SARCOMAS

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SOMATIC TUMOR PASSENGER EVENTS ACT AS A FLIGHT RECORDER "BLACK BOX" TO PINPOINT THE CHROMATIN STATE OF THE TUMOR CELL OF ORIGIN

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CANONICAL AND RECIPROCAL FUSION GENE EXPRESSION IN TRANSLOCATION ASSOCIATED SOFT TISSUE SARCOMA TUMORS IS ASSOCIATED WITH DISTINCT MOLECULAR SIGNATURES

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IDENTIFICATION OF SPLICING FACTOR-3B1 AS A PUTATIVE REGULATOR OF OSTEOSARCOMA METASTASIS

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IONIZING RADIATION CAUSES SARCOMAS THROUGH MECHANISMS INDEPENDENT OF INCREASING MUTATIONAL LOAD

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PRECLINICAL MODELING OF RESISTANT DISEASE USING AUTOPSY SAMPLES FROM PEDIATRIC PATIENTS WITH SOLID TUMORS

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TARGETING STRESS GRANULES: A NOVEL APPROACH TO BLOCK SARCOMA METASTASIS

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Poster 065 2992803

INNATE IMMUNITY TOLL LIKE RECEPTORS TLR1/2; TLR6 AND MUCIN MUC5B ARE BINDING INTERACTION PARTNERS WITH ANTIPROLIFERATIVE PEPTIDE PRP-1 IN HUMAN CHONDROSARCOMA

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INHIBITION OF EMBRYONIC STEM CELL MARKERS EXPRESSION BY PRP-1 LEADS TO ELIMINATION OF CANCER STEM CELL POPULATION IN HUMAN CHONDROSARCOMA

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TUMOR SUPPRESSOR GENE MUTATION IN THE HEDGEHOG PATHWAY DEFINES A NEW SUBSET OF PLEXIFORM FIBROMYXOMA

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THERAPEUTIC EFFECT OF SCLEROSTIN ON OSTEOSARCOMA

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MACROPHAGES FACILITATE OCCURRENCE AND DEVELOPMENT OF HUMAN OSTEOSARCOMA CELLS MEDIATED BY NF-KB

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CYCLIN-DEPENDENT PROTEIN KINAE 9 (CDK9) IS A NOVEL PROGNOSTIC MARKER AND THERAPEUTIC TARGET IN OSTEOSARCOMA

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METHYLATION-SILENCING OF MULTIPLE TUMOR-SUPPRESSOR AND OSTEO/CHONDROGENESIS RELATED GENES IN OSTEOSARCOMA

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IL-6 MEDIATED SELECTIVE TOXICITY FOR TUMOR-INITIATING CELLS FUNCTIONS TO PREVENT OSTEOSARCOMA METASTASIS

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IDENTIFICATION OF INFLAMMATORY FACTORS AND THE NOTCH PATHWAY AS THERAPEUTIC TARGETS FOR SARCOMA-ASSOCIATED CACHEXIA

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ANTIPROLIFERATIVE EFFECT OF BUPIVACAINE ON PATIENT-DERIVED SARCOMA CELLS

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THE EFFECT OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS ON OSTEOSARCOMA CELLS

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THE ATR INHIBITOR M4344 INDUCES TUMOR REGRESSION IN A PATIENT-DERIVED XENOGRAFT MODEL OF ALTERNATIVE LENGTHENING OF TELOMERS (ALT)- POSITIVE OSTEOSARCOMA.

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ROLE OF HSF1 IN OSTEOSARCOMA INITIATION AND DEVELOPMENT

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ERIBULIN SHOWS HIGH EFFICACY ON HIGLY CHEMOTHERAPY-RESISTANT OSTEOSARCOMA IN PATIENT-DERIVED ORTHOTOPIC XENOGRAFT MOUSE MODEL

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DD LIPO CELL LINES AND PDX TO EXPLORE THE ACTIVITY OF ANTICANCER DRUGS AND COMBINATIONS

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CIRCULATING TUMOR CELL DETECTION FOR HEMANGIOSARCOMA DIAGNOSIS IN DOGS

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INCIDENCE OF CARDIOMYOPATHY WITH TRABECTEDIN USE IN SOFT TISSUE SARCOMAS

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A PHASE 1B/2 STUDY OF VORINOSTAT IN COMBINATION WITH GEMCITABINE AND DOCETAXEL IN ADVANCED SOFT TISSUE SARCOMAS (STS)

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EVALUATION OF LENVATINIB, EVEROLIMUS OR THE COMBINATION IN PEDIATRIC SARCOMA MODELS

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RADIOTHERAPY (RT) COMBINED WITH TRABECTEDINE FOR LOCALLY ADVANCED OR METASTATIC, SOFT TISSUE SARCOMA (STS): AN UPDATE OF A SINGLE INSTITUTION EXPERIENCE

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LEUCOENCEPHALOPATHY IS A COMMON COMPLICATION IN PATIENTS TREATED WITH HIGH DOSE METHOTREXTATE

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TARGETING MICROENVIRONMENT AND CELLULAR IMMUNITY IN SARCOMAS WITH WEEKLY TRABECTEDIN COMBINED WITH METRONOMIC CYCLOPHOSPHAMIDE (TARMIC)

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THE IMPACT OF CHEMOTHERAPY ON PRIMARY BONE TUMORS OF THE VERTEBRAL COLUMN: A NATIONAL CANCER DATABASE REVIEW

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NEOADJUVANT CHEMOTHERAPY IN LOCALLY ADVANCED SOFT-TISSUE SARCOMA: THE GUSTAVE ROUSSY EXPERIENCE

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REAL-WORLD TREATMENT PATTERNS AMONG ADVANCED SOFT TISSUE SARCOMA PATIENTS RECEIVING SYSTEMIC THERAPY IN A COMMUNITY ONCOLOGY SETTING IN THE UNITED STATES

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A RETROSPECTIVE STUDY TO ASSESS THE INCIDENCE OF EARLY AND LATE CARDIOTOXICITY EVALUATED BY MUGA IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC SARCOMA TREATED WITH DOXORUBICIN

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NEOADJUVANT CHEMORADIOTHERAPY IN ADVANCED SOFT TISSUE SARCOMA (ASTS)

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OLARATUMAB PLUS DOXORUBICIN FOLLOWED BY OLARATUMAB MONOTHERAPY FOR THE TREATMENT OF PATIENTS WITH ADVANCED/METASTATIC SOFT TISSUE SARCOMA: REAL-WORLD UTILIZATION AND OUTCOMES IN THE UNITED STATES

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PHASE IB STUDY OF DECITABINE IN COMBINTATION WITH GEMCITABINE IN TREATMENT OF REFRACTORY ADVANCED SOFT TISSUE OR BONE SARCOMAS

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CHARACTERISTICS AND TREATMENT PATTERNS WITH ADVANCED SOFT TISSUE SARCOMA IN KOREA

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TRABECTEDIN-INDUCED MONOCYTES REDUCTION: A POTENTIAL SURROGATE PROGNOSTIC FACTOR?

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CLINICAL OUTCOME OF ERIBULIN IN PATIENTS WITH ADVANCED SOFT TISSUE SARCOMA: A COHORT STUDY INCLUDING NON-L-SARCOMAS

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PAZOPANIB NEOADJUVANT TRIAL IN SOFT TISSUE SARCOMAS: A REPORT OF MAJOR WOUND COMPLICATIONS DURING DOSE-FINDING PHASE ON ARST 1321

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USE OF CARDIOPROTECTIVE DEXRAZOXANE AND MYELOTOXICITY IN ANTHRACYCLINE-TREATED SOFT-TISSUE SARCOMA PATIENTS

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COMBINATION OF ERIBULIN PLUS GEMCITABINE IN L-SARCOMAS

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PREDICTIVE ROLE OF HMG PROTEINS FOR RESPONSE TO TRABECTEDIN IN PATIENTS WITH ADVANCED SOFT TISSUE SARCOMA (STS): A SPANISH GROUP FOR RESEARCH ON SARCOMAS (GEIS-38 STUDY)

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REAL-WORLD EXPERIENCES WITH PAZOPANIB TREATMENT FOR PATIENTS WITH ADVANCED SOFT TISSUE AND BONE SARCOMA IN NORTHERN CALIFORNIA

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NEUTROPHIL-TO-LYMPHOCYTE RATIO AFTER PAZOPANIB TREATMENT PREDICTS RESPONSE IN PATIENTS WITH ADVANCED SOFT TISSUE SARCOMA

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THE SIGNIFICANT EFFECTS OF PAZOPANIB ON ADVANCED SOFT TISSUE SARCOMA: A RETROSPECTIVE ANALYSIS IN CHINA

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SHOULD NEOADJUVANT CHEMOTHERAPY BECOME STANDARD TREATMENT FOR HIGH-RISK SOFT TISSUE SARCOMAS? A SINGLE CENTRE RETROSPECTIVE ANALYSIS.

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GEMCITABINE AND DOCETAXEL AS TREATMENT OPTION FOR ADVANCED ANGIOSARCOMA

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TROFOSFAMID AND ETOPOSID – AN EFFECTIVE PALLIATIVE CHEMOTHERAPY FOR RECURRENT MENINGEAL SARCOMA

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TEMOZOLOMOMID MONOTHERAPY AS AN OPTION IN LOCALLY ADVENCED AND METASTATIC SOLITARY FIBROUS TUMOR: A GUSTAVE ROUSSY SERIES

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HEPATOTOXICITY AS A PREDICTIVE FACTOR FOR SOFT TISSUE SARCOMA TREATED WITH TRABECTEDIN

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THE RESULTS OF TREATMENT WITH TRABECTEDIN FOR ADVANCED SOFT TISSUE SARCOMAS: A JAPANESE SINGLE-CENTER EXPERIENCE

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SAFETY AND EFFICACY OF OLARATUMAB ADDED TO DOXORUBICIN-BASED COMBINATION CHEMOTHERAPY IN THE TREATMENT OF ADVANCED SOFT-TISSUE SARCOMA (STS).

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PREDICTING SURVIVAL IN LOCALIZED CHONDROSARCOMA

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PARP INHIBITORS; A NOVEL THERAPEUTIC STRATEGY FOR CHONDROSARCOMA?

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CLINICAL UTILITY OF 2-HG AS A BIOMARKER IN IDH MUTATED CHONDROSARCOMA

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IMMUNE LANDSCAPE OF HIGH GRADE CHONDROSARCOMAS: IDENTIFICATION OF KEY PLAYERS CREATING AN IMMUNOSUPPRESSIVE TUMOR ENVIRONMENT

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CLEAR CELL CHONDROSARCOMA: CLINICAL CHARACTERISTICS AND TREATMENT OUTCOMES IN 19 PATIENTS

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IMPACT OF NODAL INVOLVEMENT ON DISEASE SPECIFIC SURVIVAL IN CHONDROSARCOMA: ANALYSIS OF THE SURVEILLANCE, EPIDEMIOLOGY, AND END RESULTS (SEER) DATABASE (2004 – 2015)

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CLEAR CELL CHONDROSARCOMA: REPORT OF 7 CASES AND METAANALYSIS OF LITERATURE

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PROGNOSTIC FACTORS FOR SURVIVAL IN DEDIFFERENTIATED CHONDROSARCOMA

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DRUG REPURPOSING AS A SOURCE OF INNOVATIVE THERAPIES IN CHONDROSARCOMA

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CISPLATIN IN ADVANCED CHORDOMA: A RETROSPECTIVE CASE-SERIES ANALYSIS

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WHAT IS THE RISK OF MORTALITY FOLLOWING LOCAL RECURRENCE OF A SURGICALLY TREATED CHORDOMA OF THE SACRUM?

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FACTORS ASSOCIATED WITH 5-YEAR SURVIVAL IN CHORDOMAS: A NATIONAL CANCER DATABASE STUDY

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CIRCULATING TUMOR DNA IS DETECTABLE IN TRANSLOCATION POSITIVE RHABDOMYOSARCOMA: A REPORT FROM THE CHILDREN'S ONCOLOGY GROUP (COG)

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RELATIVE FUSION GENE LEVEL IN CIRCULATING CELL-FREE DNA SERVES AS A PROGNOSTIC BIOMARKER IN EWING SARCOMA

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PILOT STUDY EVALUATING THE CONCORDANCE OF CIRCULATING TUMOR DNA ALTERATIONS WITH TUMOR-BASED SEQUENCING IN SOFT TISSUE SARCOMA

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CIRCSARC; NON-INVASIVE MONITORING OF SARCOMAS PATIENTS BY CIRCULATING TUMOUR DNA IN PLASMA

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ULTRA-SENSITIVE DETECTION OF TRANSLOCATIONS IN THE CELL-FREE DNA OF PEDIATRIC SARCOMA PATIENTS

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NONINVASIVE MOLECULAR PROFILING AND RESPONSE MONITORING BY CELL-FREE DNA ANALYSIS IN OSTEOSARCOMA

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RNA-SEQUENCING OF TUMOR-EDUCATED PLATELETS, A NOVEL BIOMARKER FOR BLOOD BASED SARCOMA DIAGNOSTICS

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TREATMENT MONITORING IN PATIENTS WITH PEDIATRIC SARCOMAS USING CIRCULATING TUMOR DNA ANALYSIS: A FEASIBILITY STUDY

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DESMOID TUMORS: A SINGLE INSTITUTION EXPERIENCE.

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YOUNG PATIENTS WITH DESMOID FIBROMATOSIS HAVE HIGH RATES OF LOCAL RECURRENCE: IS IT TIME TO RETHINK TREATMENT STRATEGIES IN THIS SUBSET?

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FAP-RELATED DESMOID TUMORS TREATED WITH LOW-DOSE CHEMOTHERAPY: RESULTS FROM A MULTICENTRE RETROSPECTIVE ANALYSIS

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SIGNIFICANT RISK FACTORS OF LOCAL RECURRENCE AFTER SURGERY IN EXTRA-PERITONEAL DESMOID-TYPE FIBROMATOSIS: A MULTICENTER STUDY IN JAPAN

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EFFECTS OF MATRIX STIFFNESS ON CULTURED CELLS OF DESMOID-TYPE FIBROMATOSIS

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MUTATION STRATIFICATION OF DESMOID-TYPE FIBROMATOSIS USING A RADIOGENOMICS APPROACH – PRELIMINARY RESULTS

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ACTIVITY OF SORAFENIB IN A DIVERSE POPULATION OF PATIENTS WITH DESMOID TUMORS INCLUDING POOR PERFORMANCE STATUS.

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A CLINICAL COMPARISON OF FAMILIAL (APC MUTATED) VS SPORADIC (CTNNB1 MUTATED) DESMOID TUMORS

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WNT TARGET GENES ARE NOT DIFFERENTIALLY EXPRESSED IN DESMOID TUMORS BEARING DIFFERENT ACTIVATING BETA-CATENIN MUTATIONS

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DESMOID TUMOURS TREATED WITH ORAL VINORELBINE. A RETROSPECTIVE ANALYSIS OF 14 PATIENTS

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TEMOZOLOMIDE COMBINED WITH PARP INHIBITOR OLAPARIB SHOWS SYNERGISTIC EFFFECTS IN DESMOPLASTIC SMALL ROUND CELL TUMOR CELLS

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PHASE 2 WEEKLY ORAL ONC201 IN DESMOPLASTIC SMALL ROUND CELL TUMOR (DSRCT) AND CLEAR CELL SARCOMA

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IMPROVED 3 AND 5 YEAR SURVIVAL WITH MULTIMODALITY TREATMENT OF DESMOPLASTIC SMALL ROUND CELL TUMOR

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RECURRENT FGFR4 AND ARID1A SOMATIC ALTERATIONS ARE DETECTED IN DESMOPLASTIC SMALL ROUND CELL TUMORS (DSRCT)

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PRECLINICAL EFFICACY OF ANDROGEN RECEPTOR-BASED ANTI-SENSE THERAPY FOR THE TREATMENT OF DESMOPLASTIC SMALL ROUND CELL TUMOR

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IMPACT OF WHOLE ABDOMINOPELVIC RADIOTHERAPY AND INTRAPERITONEAL RADIOIMMUNOTHERAPY AFTER COMPLETE RESECTION ON SURVIVAL IN PATIENTS WITH DESMOPLASTIC SMALL ROUND CELL TUMOR

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ADVANCED EPITHELIOID HAEMANGIOENDOTHELIOMA: FEVER, PAIN AND PLEURAL EFFUSION PREDICT A WORSE OUTCOME

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THE PROGNOSTIC SIGNIFICANCE OF SURGICAL TREATMENT FOR EXCESSIVE ELDERLY PATIENTS WITH SOFT TISSUE SARCOMA

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CLINICAL OUTCOMES AND COSTS FOLLOWING UNPLANNED EXCISIONS OF SOFT TISSUE SARCOMS IN THE ELDERLY: DOES PREOPERATIVE PLANNING CHANGE OUTCOMES?

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EXTREMITY SOFT TISSUE SARCOMA IN THE ELDERLY: ARE WE OVERTREATING OR UNDERTREATING THIS VULNERABLE PATIENT POPULATION?

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INFLUENCE OF AGE AND SUBTYPE IN OUTCOME OF OPERABLE LIPOSARCOMA

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WORSE SURVIVAL IN OLDER ADULTS WITH RHABDOMYOSARCOMA: RESULTS OF A LARGE SINGLE INSTITUTIONAL COHORT

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PROGNOSIS OF ELDERLY PRIMARY OSTESARCOMA PATIENTS

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POSTOPERATIVE COMPLICATIONS, CLINICAL AND FUNCTIONAL OUTCOME OF ELDERLY PATIENTS WITH PRIMARY HIGH GRADE MALIGNANT BONE AND SOFT TISSUE TUMOR

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THE ADDITION OF CYCLES OF IRINOTECAN/TEMOZOLOMIDE TO CYCLES OF VINCRISTINE, DOXORUBICIN, CYCLOPHOSPHAMIDE (VDC) AND CYCLES OF IFOSFAMIDE, ETOPOSIDE (IE) FOR THE TREATMENT OF EWING SARCOMA (ES).

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INVESTIGATING THE ROLE OF LSD2 IN EWING SARCOMA

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PROGNOSTIC VALUE OF TUMOR VOLUME IN PATIENTS WITH LOCALIZED EWING SARCOMA TREATED WITH INTERVAL-COMPRESSED CHEMOTHERAPY: A REPORT FROM CHILDREN'S ONCOLOGY GROUP STUDY AEWS0031

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PATTERN OF TRANSLOCATION TESTING IN PATIENTS ENROLLING TO A COOPERATIVE GROUP TRIAL FOR NEWLY DIAGNOSED METASTATIC EWING SARCOMA: A REPORT FROM THE CHILDREN'S ONCOLOGY GROUP (COG)

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EXPERIENCE IN DIFFERENTIAL DIAGNOSIS OF EWING SARCOMA AND EWING-LIKE SARCOMA BY TARGETED RNA-SEQ

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ROLE OF P21-ACTIVATED KINASES IN DEVELOPMENT AND PROGRESSION OF EWING SARCOMA

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ACTIVATION OF SPECIFIC KINASE PATHWAYS ARE REQUIRED FOR CD99 INHIBITION MEDIATED EWING SARCOMA CYTOTOXICITY

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FUNCTIONAL STUDIES REVEAL DYNAMIC ROLE OF FLI IN EWS/FLI-DRIVEN EWING SARCOMA

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INTEGRIN-MEDIATED SIGNALING AS A NOVEL THERAPEUTIC TARGET IN METASTATIC EWING SARCOMA

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A RATIONAL COMBINATION THERAPY APPROACH WITH RADIATION THERAPY IN EWING SARCOMA

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THE ROLE OF HIGH DOSE CHEMOTHERAPY IN REFRACTORY AND RECURRENT EWING SARCOMA: REPORT OF A SINGLE CENTRE EXPERIENCE

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EWINGS SARCOMA IN ADULTS - IS SOFT TISSUE EWINGS DIFFERENT FROM BONY EWINGS?

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POTENTIAL EWS-FLI1- FOXM1- BUB1B AXIS CONTRIBUTES TO MITOTIC CELL CYCLE CONTROL IN EWING SARCOMA

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CORRELATION BETWEEN PATHOLOGICAL, RADIOLOGICAL AND METABOLIC RESPONSE AFTER NEOADJUVANT CHEMOTHERAPY IN LOCALIZED EWING SARCOMA

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INITIAL REPORTS OF LOCAL CONTROL MODALITIES IN EURO EWING 2012: AN INTERNATIONAL RANDOMISED CONTROLLED TRIAL OF CHEMOTHERAPY FOR NEWLY DIAGNOSED EWING SARCOMAS (ES)

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EXPRESSION OF SLFN11 AND MGMT IN ARCHIVAL TUMOR TISSUE AS POSSIBLE BIOMARKERS OF RESPONSE TO TEMOZOLOMIDE AND IRINOTECAN IN RELAPSED EWING SARCOMA PATIENTS

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IGF-1R/MTOR TARGETED THERAPY FOR EWING SARCOMA: A META-ANALYSIS OF FIVE IGF-1R-RELATED TRIALS MATCHED TO PROTEOMIC AND RADIOLOGIC PREDICTIVE BIOMARKERS.

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PRECLINICAL EFFICACY OF TARGETING EWSR1 IN EWING SARCOMA AND DESMOPLASTIC SMALL ROUND CELL TUMORS

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HOW DO WE ACHIEVE THE GREATER COLLABORATION NEEDED TO IMPROVE OUTCOMES FROM EWING SARCOMA: THE EXPERIENCE OF THE EURO EWING CONSORTIUM

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EWS-FLI1 EXPRESSION LEVEL MODULATES T-CELL MEDIATED TUMOR APOPTOSIS IN EWING SARCOMA

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THE ROLE OF DENOSUMAB IN JOINT PRESERVATION FOR PATIENTS WITH GIANT CELL TUMOUR OF BONE: NOT A MAGIC BULLET?

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EPIGENETIC COMPOUND SCREEN REVEALS HISTONE DEACETYLASE INHIBITORS TO EFFECTIVELY TARGET THE NEOPLASTIC CELLS IN GIANT CELL TUMOR OF BONE

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GIANT CELL TUMOUR OF DISTAL RADIUS: RESULTS OF WIDE EXCISION AND AUTOGENOUS NONVASCULARIZED FIBULA GRAFT RECONSTRUCTION

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DISCOVERY AND CHARACTERIZATION OF RECURRENT, TARGETABLE ALK FUSIONS IN LEIOMYOSARCOMA

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GENOME INFORMED THERAPY FOR OSTEOSARCOMA

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DISTINCT EVOLUTIONARY TRAJECTORIES UNDERLIE GENOMIC HETEROGENEITY AND COMPLEXITY IN UNDIFFERENTIATED SARCOMAS

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COMPREHENSIVE GENOMIC PROFILING OF SYNOVIAL SARCOMAS IDENTIFIES GENOMICALLY DEFINED SUBGROUPS WITH CHARACTERISTIC ALTERATION PATTERNS

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THE FUSION LANDSCAPE AND ACTIONABLE ALTERATIONS OF SARCOMA REVEALED BY "REAL WORLD" GENOMIC SEQUENCING

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BRINGING A PERSONALIZED MEDICINE PIPELINE TO THE CLINIC: A CROSS-SPECIES APPROACH REVEALS NEW THERAPIES AND NEW CHALLENGES

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UTILITY OF FOUNDATIONONE HEME PROFILING IN SARCOMA: INSTITUTIONAL EXPERIENCE AND CLINICAL OUTCOMES

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METASTATIC INITMAL SARCOMA CASE WITH NTRK3 GENE REARRANGEMENT TREATED WITH ENTRECTINIB

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EXTENDED CONTICAGIST ANALYSIS ADDS TO THE AMENDED PROGNOSTICATION IN GIST BASED ON TUMOR KIT/PDGFRA GENOTYPE STATUS

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ONCOLOGICAL OUTCOME AFTER DIAGNOSTIC BIOPSIES IN GASTROINTESTINAL STROMAL TUMOURS

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PAEDIATRIC, ADOLESCENT, WILD TYPE, SYNDROMIC GASTROINTESTINAL STROMAL TUMOURS (PAWS-GIST) UNITED KINGDOM (UK) NATIONAL CLINIC: A JOINT PATIENTS/CARERS/SPECIALISTS INITIATIVE

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THE RELATIONSHIP BETWEEN POSITIVE RESECTION MARGINS, TUMOUR RUPTURE AND PROGNOSIS IN GASTROINTESTINAL STROMAL TUMOUR. A POPULATION-BASED ANALYSIS

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AN INTEGRATED RNA AND MICRORNA PROFILING OF THE MALIGNANT EVOLUTION OF MINIGIST TO GIST

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NOVEL DIAGNOSTIC APPROACH FOR GASTROINTESTINAL STROMAL TUMOR USING AN ANTI-KIT DNA APTAMER

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PLOCABULIN, A TUBULIN INHIBITOR, HAS ANTITUMOUR ACTIVITY IN PATIENT-DERIVED XENOGRAFT (PDX) MODELS OF GASTROINTESTINAL STROMAL TUMOUR (GIST)

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MORE FREQUENT OCCURRENCE OF UNUSUAL CENTRAL NERVOUS SYSTEM METASTASES IN GIST PATIENTS

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NEW PROTOCOL FOR IMAGE GUIDED SURGERY OF GASTROINTESTINAL STROMAL TUMOUR

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PRIMARY SARCOMA OF THE VULVA AND VAGINA: OUTCOMES AFTER DEFINITIVE THERAPY

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INTEGRATED MOLECULAR ANALYSIS OF UNDIFFERENTIATED UTERINE SARCOMAS REVEALS CLINICALLY RELEVANT SUBTYPES

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TREATMENT OF RECURRENT AND METASTATIC UTERINE ADENOSARCOMAS

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EFFICACY OF TRABECTEDIN IN METASTATIC UTERINE LEIOMYOSARCOMA: A RETROSPECTIVE MULTICENTER STUDY OF THE SPANISH OVARIAN CANCER RESEARCH GROUP (GEICO)

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PROGNOSTIC FACTORS IN ENDOMETRIAL STROMAL SARCOMA (ESS): A SUBGROUP ANALYSIS OF THE GEIS 26 STUDY (SPANISH GROUP FOR RESEARCH ON SARCOMAS)

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UPFRONT ISOLATED LIMB PERFUSION (ILP) IN UNTREATED PATIENTS WITH UNRESECTABLE NON-METASTATIC PRIMARY SOFT-TISSUE SARCOMAS (STS) OF THE LIMB: A RETROSPECTIVE SERIES ON 41 PATIENTS

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SURVEILLANCE CHEST COMPUTED TOMOGRAPH (CT) IMAGING DURING CHEMOTHERAPY IN PEDIATRIC SARCOMA PATIENTS: IS THE RADIATION RISK JUSTIFIED?

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ADVANCED IMAGING IS A COST-EFFECTIVE SURVEILLANCE STRATEGY FOLLOWING SOFT TISSUE SARCOMA RESECTION

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RADIATION EXPOSURE IN PEDIATRIC SARCOMA PATIENTS RECEIVING INITIAL CHEMOTHERAPY

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ACCURACY OF FDG-POSITRON EMISSION TOMOGRAPHY (PET) SCAN IN DESMOPLASTIC SMALL ROUND CELL TUMOR

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COMPLIANCE OF RADIOLOGICAL FOLLOW-UP FOLLOWING RESECTION OF PRIMARY INTRAABDOMINAL SOFT TISSUE SARCOMA WITH ESMO/ESNWG GUIDELINES: A 10-YEAR AUDIT OF PRACTICE FROM A UK QUATERNARY REFERRAL CENTRE

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DIFFERENTIATING WELL-DIFFERENTIATED LIPOSARCOMAS FROM LIPOMAS USING A RADIOMICS APPROACH – PRELIMINARY RESULTS

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SIGNAL INTENSITY OF MRI COULD PEDICT THE EFFICACY OF MELOXICAM TREATMENT IN PATIENTS WITH DESMOID-TYPE FIBROMATOSIS

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THE UTILITY OF FLUORINE-18-FDG PET/MRI FOR DIAGNOSING BONE AND SOFT TISSUE MALIGNANCIES SECONDARY TO PREEXISTING BENIGN CONDITIONS

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THE UTILITY OF PET/CT VERSUS BONE SCAN FOR DIAGNOSIS AND MONITORING OF PEDIATRIC SARCOMA PATIENTS

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COMBINING ONCOLYTIC VIROTHERAPY AND PD-1 INHIBITION IN AN ANIMAL MODEL OF ISOLATED LIMB PERFUSION TO IMPROVE LOCAL AND DISTANT DISEASE CONTROL IN ADVANCED EXTREMITY SOFT TISSUE SARCOMA

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NEOADJUVANT THERAPY INDUCES A POTENT INFLAMMATORY AND CORRESPONDING REGULATORY RESPONSE WITHIN THE SARCOMA IMMUNE MICROENVIRONMENT

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PD-1 BLOCKADE COMBINED WITH ONCOLYTIC HERPES HSV1716 VIROIMMUNOTHERAPY ENHANCES SURVIVAL IN AN IMMUNOGENIC MURINE OSTEOSARCOMA MODEL

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DECREASED T CELL INFILTRATION IN UNDIFFERENTIATED PLEOMORPHIC SARCOMA (UPS)—MEDIATED BY WNT, TGF-β AND MEX3B—PREDICTS POOR SURVIVAL

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THE IMMUNE MICROENVIRONMENT IN LEIOMYOSARCOMA, DEDIFFERENTIATED LIPOSARCOMA AND UNDIFFERENTIATED PLEOMORPHIC SARCOMA

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KRAS/P53 MEDIATED MURINE MODEL OF RHABDOMYOSARCOMA HAS AN IMMUNE INERT MICROENVIRONMENT AND IS AN IDEAL MODEL TO TEST NOVEL IMMUNOTHERAPIES.

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HOST IMMUNE RESPONSE IN UNDIFFERENTIATED PLEOMORPHIC SARCOMA - A 10-YEAR RETROSPECTIVE ANALYSIS

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TUMOR INFILTRATING LYMPHOCYTES MAY PREDICT FOR DISTANT METASTASIS IN SOFT TISSUE SARCOMAS TREATED WITH PREOPERATIVE RADIATION THERAPY

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IMMUNE PROFILING OF INTRATUMORAL TERTIARY LYMPHOID STRUCTURES IN DEDIFFERENTIATED LIPOSARCOMA

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COMPREHENSIVE GENOMIC PROFILING IDENTIFIES A POTENTIAL IMMUNOTHERAPEUTIC OPPORTUNITY IN GASTROINTESTINAL STROMAL TUMORS

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INTERLEUKIN-13 IN THE SARCOMA MICROENVIRONMENT PROMOTES EXPRESSION OF THE INTERLEUKIN-13 RECEPTOR ALPHA-2

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IMMUNOMODULATORY ROLE OF PAZOPANIB IN ADVANCED SOFT-TISSUE SARCOMAS

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SOX2/OCT4-HIGH SUBGROUP OF RELAPSED AND METASTATIC OSTEOSARCOMA HAS HIGH PD-L1

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INDUCTION OF ANTI-TUMOR IMMUNITY AND EFFECTS ON SURVIVAL OF NEOADJUVANT ONCOLYTIC VIROTHERAPY IN DOGS WITH OSTEOSARCOMA: AN UPDATE OF THE VIGOR CLINICAL TRIAL

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RESPONSE TO SUBSEQUENT THERAPY IN NY-ESO-1 POSITIVE SOFT TISSUE SARCOMA PATIENTS TREATED WITH CMB305 THERAPY

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IMMUNE RESPONSE, SAFETY, AND OVERALL SURVIVAL OF NY-ESO-1+ SOFT TISSUE SARCOMA PATIENTS TREATED WITH CMB305 THERAPY

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MACROPHAGES DOMINATE THE IMMUNE LANDSCAPE ACROSS MOST SARCOMA SUBTYPES

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SOLUBLE PD-L1 IN PATIENTS WITH SOFT TISSUE TUMORS

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PROGNOSTIC ROLE OF NEUTROPHIL-TO-LYMPHOCYTE RATIO (NLR) IN PATIENTS WITH SARCOMA TREATED WITH IMMUNOTHERAPY

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DISULFIRAM INDUCES IMMUNOGENIC CELL DEATH AND ENHANCES ANTI-PD-1-MEDIATED TUMOR SUPPRESSION IN OSTEOSARCOMA

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CHARACTERIZING THE IMMUNE LANDSCAPE IN ALVEOLAR SOFT PART SARCOMA

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EXPRESSION OF PROGRAMMED DEATH LIGAND 1 (PD-L1) AND EFFECT OF IMMUNOTHERAPY IN MALIGNANT SOFT TISSUED SARCOMA

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THE SAINT: INITIAL RESULTS OF A PHASE 1/2 STUDY OF SAFETY/EFFICACY USING SAFE AMOUNTS OF IPILIMUMAB, NIVOLUMAB AND TRABECTEDIN AS FIRST LINE TREATMENT OF ADVANCED SOFT TISSUE SARCOMA

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ACTIVITY OF TREMELIMUMAB AND DURVALUMAB IN ADVANCED SARCOMAS: PRELIMINARY RESULTS OF A SIGNAL-SEEKING PHASE 2 TRIAL

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ACTIVITY OF SINGLE-AGENT PD-1 INHIBITOR (PD-1I) THERAPY IN ADVANCED SARCOMA: A SINGLE-CENTER RETROSPECTIVE ANALYSIS

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INTERFERON GAMMA MAKES "COLD" SYNOVIAL SARCOMA AND MYXOID/ROUND CELL LIPOSARCOMA "HOT": RESULTS OF A PHASE 0 TRIAL

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SARCOMA MOUSE MODEL FOR COMBINED ONCOLYTIC VIRUS AND IMMUNE CHECKPOINT INHIBITOR THERAPY

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EFFICACY OF CHECKPOINT INHIBITORS IN PATIENTS WITH METASTATIC SOFT TISSUE SARCOMAS

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TUMOR SLICE CULTURE REPRESENTS A UNIQUE MODEL IN WHICH TO INTERROGATE THE IMMUNE RESPONSE TO HUMAN SOFT TISSUE SARCOMA

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EXPANSION AND CHARACTERIZATION OF TUMOR-INFILTRATING LYMPHOCYTES IN SOFT TISSUE SARCOMA

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KAPOSI'S SARCOMA IN THE ERA OF HAART: A SINGLE INSTITUTIONAL RETROSPECTIVE REVIEW

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KAPOSI SARCOMA, A SINGLE CENTER EXPERIENCE

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THE MEF2-CLASS IIA HDAC AXIS IN LEIOMYOSARCOMAS; PROLIFERATIVE OPTIONS AND POSSIBLE THERAPEUTIC TARGETS

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PEDIATRIC LIPOSARCOMA: A REPORT FROM THE TEXAS CHILDREN'S RARE TUMOR REGISTRY

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INTEGRATED WHOLE EXOME AND RNA SEQUENCING FOR DEDIFFERENTIATED LIPOSARCOMA

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SURGICAL AND CLINICAL OUTCOMES OF ATYPICAL LIPOMATOUS TUMOR OF THE TRUNK AND EXTREMITY

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CLINICOPATHOLOGIC CHARACTERISTICS AND CLINICAL OUTCOMES OF LIPOSARCOMA: A RETROSPECTIVE ANALYSIS OF SINGLE CENTER EXPERIENCE FOR 25 YEARS

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WATCHFUL WAITING IN PATIENTS WITH WELL-DIFFERENTIATED LIPOSARCOMA IN THE EXTREMITY

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TRANSIENT INTERFERON SUPPRESSION RENDERS NERVE SHEATH SARCOMAS SUSCEPTIBLE TO VIRO-IMMUNOTHERAPY

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STING ACTIVITY PREDICTS RESISTANCE TO ONCOLYTIC VIROTHERAPY IN MALIGNANT PERIPHERAL NERVE SHEATH TUMORS

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S-100 EXPRESSION AS A POSSIBLE PROGNOSTIC FACTOR FOR MALIGNANT PERIPHERAL NERVE SHEATH TUMOR

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STAGING AND SURVEILLANCE OF MYXOIDLIPOSARCOMA: IS CT SCAN ENOUGH?

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DEVELOPMENT OF A MODEL TO PREDICT OVERALL SURVIVAL OF MYXOID LIPOSARCOMA PATIENTS

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TIME TRENDS AND PROGNOSTIC FACTORS FOR OVERALL SURVIVAL IN MYXOID LIPOSARCOMA: 901 CASES WITH A MEDIAN FOLLOW-UP OF 8 YEARS

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SHORT TAU INVERSION RECOVERY MAGNETIC RESONANCE IMAGING FOR STAGING AND SCREENING IN MYXOID LIPOSARCOMA

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MANAGEMENT OF MYXOID LIPOSARCOMA: A SURVEY OF THE MEMBERS OF THE CONNECTIVE TISSUE ONCOLOGY SOCIETY

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ONCOLOGICAL OUTOMES OF MYXOID LIPOSARCOMA IN EXTREMITIES AND TRUNK AFTER WIDE EXCISION AND ADJUVANT TREATMENT

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OVERCOMING TRABECTEDIN RESISTANCE OF MYXOID LIPOSARCOMA BY COMBINING IT WITH PPARγ AGONISTS

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A COMPARISON OF ONCOLOGICAL AND SURGICAL OUTCOMES IN ENDOPROSTHETIC RECONSTRUCTION VERSUS ROTATIONPLASTY FOR PEDIATRIC LOWER EXTREMITY BONE SARCOMAS

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PRESS FIT VS. CEMENTED FEMORAL STEMS IN ARTHROPLASTY FOR ONCOLOGIC INDICATIONS

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THE IMPACT OF FACILITY VOLUME ON SURVIVAL IN PATIENTS WITH PRIMARY BONE TUMORS OF THE VERTEBRAL COLUMN

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POSTIVE MARGIN STATUS IS PROGNOSTIC OF POORER SURVIVAL IN PRIMARY BONE TUMORS OF THE SPINE: A NATIONAL CANCER DATABASE STUDY

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EPIDEMIOLOGIC AND SURVIVAL TRENDS IN PRIMARY MALIGNANT OSSEOUS TUMORS OF THE SPINE: A NATIONAL CANCER DATABASE STUDY

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PIN OR REPLACE: AN ALGORITHM FOR THE MANAGEMENT OF NON-PATHOLOGIC FEMORAL NECK FRACTURES IN CANCER PATIENTS

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SOFT TISSUE SARCOMAS OF THE ANKLE AND FOOT: CLINICAL OUTCOME AND PROGNOSTIC FACTORS

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EFFECT OF BODY MASS INDEX (BMI) ON OUTCOMES OF PATIENTS WITH BONE TUMORS WHO UNDERGO ENDOPROSTHETIC JOINT RECONSTRUCTION

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COMPUTER-ASSISTED NAVIGATION FOR SURGERY OF ILIOSACRAL BONE SARCOMAS: WHAT IS THE EVIDENCE?

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FUNCTION AFTER DISTRACTION OSTEOGENESIS FONR BONE RECONSTRUCTION OF OSSEOUS TUMORS IN THE UPPER AND LOWER EXTREMITY

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USE OF MAGNETIC GROWING INTRAMEDULLARY NAILS IN COMPRESSION DURING INTERCALARY ALLOGRAFT RECONSTRUCTION

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LONG TERM (>15 YEARS) OUTCOME OF CUSTOM CROSS-PIN FIXATION OF TUMOR ENDOPROSTHESES STEMS

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OPTIMIZING THE USE OF INDOCYANINE GREEN FOR OSTEOSARCOMA TUMOR DETECTION USING A XENOGRAFT MURINE MODEL

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TARGETED MUSCLE REINNERVATION: A STRATEGY TO PREVENT NEUROMAS AND PHANTOM LIMB PAIN IN ONCOLOGIC AMPUTEES

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USE OF FLAP RECONSTRUCTION AFTER RADICAL SURGERY FOR TRUNCAL AND EXTREMITY SARCOMAS

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MIDTERM FOLLOW-UP OF A CUSTOM NON-FLUTED DIAPHYSEAL PRESS-FIT TUMOR PROSTHESIS SYSTEM

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DUAL MOBILITY COMPONENTS CEMENTED INTO AN ACETABULAR RECONSTRUCTIVE CAGE FOR LARGE OSSEOUS DEFECTS IN THE SETTING OF PERIACETABULAR METASTATIC DISEASE

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LONG TERM OUTCOMES OF TOTAL HUMERAL REPLACEMENT FOR PRIMARY BONE TUMORS IN 18 PATIENTS

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CHARACTERIZATION OF A BONE BIOREPOSITORY: COMPARISON OF SARCOMAS AND BONE METASTASES FROM BREAST, PROSTATE, RENAL, LUNG CANCERS, AND MYELOMA

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AN INVESTIGATION OF BONE REGENERATION BY USING BONE SUBSTITUTE MATERIALS AFTER BONE TUMOR CURETTAGE

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FUNCTIONAL OUTCOME AND COMPLICATIONS OF EXTERNAL HEMIPELVECTOMY IN THE SEVEN PATIENTS UNDERWENT FOR MALIGNANT BONE AND SOFT TISSUE TUMORS

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RELATIVE PERCENTAGE OF CIRCULATING ACTIVATED EFFECTOR NKT CELLS FOLLOWING FIRST CYCLE OF CHEMOTHERAPY CORRELATES WITH HISTOLOGIC NECROSIS IN OSTEOSARCOMA PATIENTS

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IDENTIFYING JUDICIOUS APPLICATIONS FOR SPONTANEOUS BONE CANCER OF DOGS AS A MODEL FOR PEDIATRIC OSTEOSARCOMA

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MODULATION OF MRNA TRANSLATION REGULATION IN HIGHLY METASTATIC OSTEOSARCOMA CELLS INHIBITS LUNG METASTASIS PROGRESSION

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FACTORS ASSOCIATED WITH LIFE IN ADULTS WITH LOCALIZED OSTEOSARCOMA

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HIGH GRADE INTRAMEDULLARY OSTEOSARCOMA: DOES HISTOLOGIC SUBTYPE AFFECT OUTCOME?

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THE CLINICAL OUTCOME OF THE OSTEOARTICULAR EXTRACORPOREAL IRRADIATED AUTOGRAFT FOR BONE SARCOMA

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OSTEOBLASTOMA-LIKE OSTEOSARCOMA: IS GRADING USEFUL?

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CXCR4 AS POTENTIAL MARKER IN OSTEOSARCOMA

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ONCOLOGIC OUTCOME IN PATIENTS WITH OSTEOSARCOMA OF THE EXTREMITIES AND PATHOLOGIC FRACTURES: DIFFERENCES IN MICRO RNA PROFILE

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CSF-1R IS A POTENTIAL PREDICTIVE BIOMARKER OF THE THERAPEUTIC RESPONSE OF OSTEOSARCOMA IN THE GSF-GETO OS2006 STUDY

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DO POSTOPERATIVE INFECTIONS INFLUENCE THE SURVIVAL OF OSTEOSARCOMA PATIENTS? RESULTS OF A MULTICENTER TRIAL

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MYC AMPLIFICATION IN OSTEOSARCOMA PATIENTS IS A BIOMARKER FOR POOR OUTCOME AND VERY RAPID DISEASE PROGRESSION

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A PHASE II STUDY OF PAZOPANIB WITH ORAL TOPOTECAN IN PATIENTS WITH METASTATIC OSTEOSARCOMA

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MULTI-ARM TRIAL IN LOCALIZED OSTEOSARCOMA: MOVING FROM A DREAM TO REALITY

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ANGIOPOIETIN LIKE 2: A POTENTIAL NOVEL BIOMARKER FOR PATIENTS WITH OSTEOSARCOMA

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EVALUATION OF THE EFFICACY AND TOXICITY OF HIGH DOSE OF THIOTEPA (HDT) AS ADJUVANT TREATMENT TO STANDARD CHEMOTHERAPY (SCT) IN RELAPSED OSTEOSARCOMA: FINAL RESULTS OF THE MULTI-CENTRIC RANDOMIZED PHASE II TRIAL OSIITTP

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EFFICACY AND SAFETY OF CHEMOTHERAPY IN RELAPSED OSTEOSARCOMA

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UTILIZING A NOVEL FORMULATION OF NICLOSAMIDE TO TREAT CANINE METASTATIC OSTEOSARCOMA

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COMBINED RADIATION THERAPY AND SURGERY PROVIDE EXCELLENT LOCAL CONTROL FOR PATIENTS WITH EXTRASKELETAL OSTEOSARCOMA

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CLINICAL OUTCOME OF PERIOSTEAL OSTEOSARCOMA: A SINGLE INSTITUTIONAL STUDY

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THE EFFECT OF RADIOTHERAPY COMBINED WITH IRON OXIDE-BASED NANOVEHICLE AND PHOTOSENSITIZER IN OSTEOSARCOMA

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OSTEOFIBROUS DYSPLASIA LIKE ADAMANTINOMA IS NOT ADAMANTINOMA

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REFERRAL PATTERNS OF SOFT TISSUE SARCOMAS TO A TERTIARY SARCOMA CENTER OVER A 20 YEAR PERIOD

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THE INFLUENCE OF HEALTH INSURANCE STATUS ON OUTCOMES IN SOFT TISSUE SARCOMA

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CLINICOPATHOLOGIC FEATURES,TREATMENT UTILIZATION TRENDS AND OUTCOMES OF PRIMARY BREAST SARCOMA :A POPULATION BASED ANALYSIS

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INDETERMINATE PULMONARY NODULES AT DIAGNOSIS IN PEDIATRIC RHABODMYOSARCOMA: ARE WE UNDERTREATING PATIENTS? A REPORT FROM THE EUROPEAN PAEDIATRIC SOFT-TISSUE SARCOMA STUDY GROUP-RMS-2005 STUDY

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THE USE OF HEALTHCARE SERVICES TWO YEARS BEFORE DIAGNOSIS IN DANISH SARCOMA PATIENTS, 2000-2013

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THE ASSOCIATION BETWEEN SOCIOECONOMIC POSITION AND TUMOUR SIZE, GRADE, STAGE, AND MORTALITY IN DANISH SARCOMA PATIENTS – A NATIONAL, OBSERVATIONAL STUDY FROM 2000 TO 2013

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NODAL INVOLVEMENT AND SURVIVAL IN SYNOVIAL, CLEAR CELL, ANGIO, RHABDO AND EPITHELIOID SARCOMA

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SARCOMA TREATENT IN ONTARIO: A POPULATION-BASED STUDY

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THE ROUTE TO DIAGNOSIS (RTD) OF SARCOMA PATIENTS: A QUALITATIVE STUDY IN THE NETHERLANDS (NL) AND THE UNITED KINGDOM (UK)

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OUTCOUME DATA OF ADVANCED SOFT TISSUE SARCOMA PATIENTS FROM A TERTIARY REFERRAL CENTER: NOT SO BAD AS OFTEN REPORTED?

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A CLINICOPATHOLOGIC EXAMINATION OF MYXOFIBROSARCOMA. RATES OF LOCAL RECURRENCE, METASTASES AND PATIENT SURVIVAL FROM A SINGLE INSTITUTION

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METASTASECTOMY IN SOFT TISSUE SARCOMA IS ASSOCIATED WITH A POST-METASTASIS SURVIVAL BENEFIT. RESULTS FROM A BI-CENTRE STUDY INCLUDING 135 PATIENTS.

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SOFT TISSUE SARCOMA OF THE EXTREMITY: ASSOCIATION BETWEEN TREATMENT DELAY, TUMOR FEATURES AND SURVIVAL

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DESCRIPTIVE ANALYSIS OF LONG-TERM SURVIVORS AMONG PATIENTS WITH METASTATIC SOFT TISSUE SARCOMA

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THE CLINICAL CHARACTERISTICS AND OUTCOMES OF PRIMARY BREAST SARCOMA: RETROSPECTIVE STUDY OVER 20 YEARS FROM A SINGLE, TERTIARY CENTER

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TWENTY-EIGHT-YEAR EXPERIENCE OF SOFT-TISSUE AND BONE SARCOMAS AT A TERTIARY CARE HOSPITAL IN KOREA

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MULTIMODAL TREATMENT IN PATIENTS (PTS) WITH ADVANCED/METASTATIC SOFT TISSUE SARCOMA (A/M STS): IMPROVMENT IN OVERALL SURVIVAL (OS) IS MAINLY ASSOCIATED WITH COMBINATION OF CHEMO-THERAPY (RX) AND SURGERY (SX).

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PROGNOSTIC SIGNIFICANCE OF SARCOPENIA IN PATIENTS WITH SOFT TISSUE SARCOMA

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REAL-WORLD TREATMENT PATTERNS AND OUTCOMES FOR PATIENTS WITH ADVANCED SOFT TISSUE SARCOMA RECEIVING SYSTEMIC THERAPY IN BRAZIL

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NETWORK META-ANALYSIS OF RANDOMIZED TRIALS FOR SECOND OR LATER-LINE TREATMENTS OF METASTATIC LIPOSARCOMA

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DESCRIPTIVE EPIDEMIOLOGY AND CLINICAL OUTCOMES OF SOFT TISSUE SARCOMAS IN ADOLESCENT AND YOUNG ADULT PATIENTS IN JAPAN

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PATTERNS OF CARE OF ADVANCED SOFT TISSUE SARCOMAS (STS) NON-GIST IN FOUR EUROPEAN COUNTRIES (EU4)

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A MATCHED COHORT STUDY OF ADJUVANT RADIO-CHEMOTHERAPY VERSUS RADIOTHERAPY ALONE IN SOFT TISSUE SARCOMA PATIENTS

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RISK STRATIFICATION OF SOFT TISSUE SARCOMA FOR PREDICTION OF LOCAL RECURRENCE

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CLINICAL IMPLEMENTATION OF A NANOSTRING-BASED PANSARCOMA FUSION ASSAY

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VIRTUAL BIOBANKING FOR RETROPERITONEAL SARCOMA – A TARPSWG INITIATIVE

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IDENTIFICATION OF RECURRENT FUSIONS WITHIN SUCCINATE DEHYDROGENASE A (SDHA) IN WELL DIFFERENTIATED RETROPERITONEAL LIPOSARCOMA

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SENSITIVITY OF DIFFERENT BIOPSY METHODS IN SOFT TISSUE AND BONE SARCOMAS: CORE NEEDLE VS. INCISIONAL BIOPSY

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UTILITY OF CORE NEEDLE BIOPSY IN RETROPERITONEAL LIPOSARCOMA: A FIFTEEN YEAR REVIEW

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WHAT IS THE DIAGNOSTIC ACCURACY OF BIOPSIES OF SOFT TISSUE SARCOMAS?

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DIAGNOSTIC ACCURACY OF PERCUTANEOUS BIOPSY IN RETROPERITONEAL SARCOMA

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MDM2 AMPLIFICATION AND FUSION GENE _SS18-SSX_ IN A POORLY DIFFERENTIATED SARCOMA: A RARE BUT PUZZLING CONJUNCTION

Florence Pedeutour[1]*; Ilaria Di Mauro*[1]*; Lénaïg Mescam-Mancini*[2]*; Bruno Chetaille*[2]*; Marick Lae*[5]*; Gaelle Pierron*[6]*; Dominique Ranchere-Vince*[3]*; Berengere Dadone-Montaudie*[1]*; Thibault Fabas*[1]*; Jean-François Michiels*[4]
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DESMOID FIBROMATOSIS THROUGH THE PATIENTS' EYES: TIMES TO CHANGE THE FOCUS AND ORGANISATION OF CARE?

Olga Husson[1]*; Eugenie Younger*[2]*; Alison Dunlop*[2]*; Lucy Dean*[2]*; Dirk Strauss*[2]*; Charlotte Benson*[2]*; Andy Hayes*[2]*; Aisha Miah*[2]*; Winan J. van Houdt*[3]*; Shane Zaidi*[2]*; Myles J. Smith*[2]*; John Williams*[2]*; Robin Jones*[2]*; Winette van der Graaf*[1]
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IS ANYBODY LISTENING? CLINICIAN UNDER-RECOGNITION OF SYMPTOM SEVERITY IN RETROPERITONEAL SARCOMA PATIENTS: A COMPARISON OF PHYSICIAN ASSESSMENTS AND PATIENT SELF-REPORTED OUTCOMES

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EXPERIENCES OF PATIENTS WITH BONE CANCER: THE ROLE OF ILLNESS AND DEVELOPMENT TRAJECTORIES, HEALTHCARE PROFESSIONALS, SOCIAL SUPPORT AND COPING STRATEGIES

Ana Martins[7]*; Lesley Storey*[2]*; Mary Wells*[3]*; Lorna A. Fern*[4]*; Lindsey Bennister*[5]*; Craig Gerrand*[1]*; Maria Onasanya*[6]*; Julie Woodford*[1]*; Rachael Windsor*[7]*; Jeremy Whelan*[7]*; Rachel Taylor*[7]
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PERCEPTIONS OF CLINICAL TRIAL ENROLLMENT AND MOLECULAR PROFILING IN PATIENTS WITH BONE AND SOFT TISSUE SARCOMA

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PATIENT-REPORTED FUNCTIONAL OUTCOMES IN A COHORT OF HAND AND FOOT SARCOMA SURVIVORS TREATED WITH LIMB SPARING SURGERY AND RADIATION THERAPY

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A SCANDINAVIAN POINT OF VIEW -CARING FOR PATIENTS WITH SARCOMA ACROSS BOUNDARIES

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DEPRESSION AND ANXIETY AMONG NEWLY DIAGNOSED SARCOMA PATIENTS

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RELAX: AN IMMERSION VIRTUAL REALITY RELAXATION INTERVENTION FOR QUALITY OF LIFE IMPROVEMENT IN CANCER PATIENTS

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CAREER AND FINANCIAL SITUATION OF PATIENTS DIAGNOSED WITH SOFT TISSUE SARCOMAS

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PREFERENCES FOR END-OF-LIFE DISCUSSIONS AND CARE AMONG PATIENTS WITH ADVANCED OR RECURRENT SARCOMA

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A NOVEL APPROACH FOR ASSESSING FUNCTIONAL BURDEN OF SOFT TISSUE SARCOMA SURGERY: DIGITAL PHENOTYPING AND RECOVERY AFTER RESECTION OF RETROPERITONEAL AND ABDOMINAL SOFT TISSUE TUMORS

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DEFINITIVE HIGH DOSE PROTON THERAPY FOR UNRESECTED OSTEOSARCOMAS OF THE SPINE AND PELVIS: A VIABLE ALTERNATIVE?

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RADIOTHERAPY FOR EXTREMITY SOFT TISSUE SARCOMA: THE ROLE OF A NORMAL SOFT TISSUE STRIP IN VMAT PLANNING

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FEMUR FRACTURE IN PRIMARY SOFT-TISSUE SARCOMA OF THE THIGH AND GROIN TREATED WITH INTENSITY-MODULATED RADIATION THERAPY: OBSERVED VS EXPECTED RISK

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HISTOPATHOLOGIC RESPONSE TO NEOADJUVANT RADIATION THERAPY DOES NOT PREDICT ONCOLOGIC OUTCOME IN PATIENTS WITH SOFT TISSUE SARCOMA OF THE TRUNK AND EXTREMITY

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ACUTE POST-OPERATIVE WOUND COMPLICATIONS FOLLOWING PRE-OPERATIVE PROTON BEAM IRRADIATION FOR SOFT TISSUE SARCOMAS

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PROTON-BASED HIGH-DOSE PRE-OPERATIVE RADIATION IS ASSOCIATED WITH HIGHER LOCAL CONTROL THAN LOW-DOSE PRE-OPERATIVE RADIATION WITH EQUIVALENT RATE OF WOUND COMPLICATION IN SACROCOCCYGEAL CHORDOMAS

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URETERAL STRICTURE AND RADIATION DOSE CONSTRAINT IN THE TREATMENT OF RETROPERITONEAL SARCOMA

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LONG TERM OUTCOMES AND TOXICITIES FROM A PHASE II TRIAL OF FOCAL CONFORMAL RADIATION THERAPY (RT) FOR CHILDREN WITH RHABDOMYOSARCOMA (RMS)

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ACHIEVING HIGH RATES OF LOCAL CONTROL AND FAVORABLE TOXICITY USING STEREOTACTIC BODY RADIOTHERAPY FOR SARCOMA PULMONARY METASTASES: A MULTI-INSTITUTIONAL EXPERIENCE

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TIME DEPENDENT DYNAMICS OF WOUND COMPLICATIONS AFTER PREOPERATIVE RADIOTHERAPY IN EXTREMITY SOFT TISSUE SARCOMAS

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EFFICACY OF ADJUVANT RADIOTHERAPY IN NON-EXTREMITY SOFT TISSUE SARCOMA WITH MODERATE CHEMOSENSITIVITY

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IMPACT OF RADIATION DOSE AND METHOD OF DELIVERY ON SURVIVAL IN CHORDOMAS

Brian L. Dial[1]; *David Kerr*[1]; *Alexander L. Lazarides*[1]; *Anthony Catanzano*[1]; *Whitney Lane*[2]; *Dan Blazer III*[2]; *Brian Brigman*[1]; *William Eward*[1]; *Melissa Erickson*[1]; *Sergio Mendoza*[1]

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EARLY ANALYSIS OF PROSPECTIVE PHASE II CLINICAL TRIAL ON PREOPERATIVE HYPOFRACTIONATED RADIOTHERAPY (RT) COMBINED WITH CHEMOTHERAPY IN PRIMARY MARGINALLY RESECTABLE HIGH GRADE SOFT TISSUE SARCOMAS (STS) OF EXTREMITIES OR TRUNK WALL

Piotr Rutkowski[1]; *Mateusz Spalek*[2]; *Aneta Borkowska*[2]; *Michal Wagrodzki*[3]; *Andrzej Cieszanowski*[4]; *Patricia Castaneda-Wysocka*[4]; *Tomasz Switaj*[1]; *Slawomir Falkowski*[1]; *Monika Dudzisz-Sledz*[1]; *Anna M. Czarnecka*[1]; *Edyta Dabrowska-Szewczyk*[2]; *Hanna Kosela-Paterczyk*[1]

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PATTERNS OF PRACTICE SURVEY: RADIOTHERAPY FOR EXTREMITY SOFT TISSUE SARCOMA

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EFFECT OF RADIOTHERAPY ON MRI MEASURES OF TUMOR INVASIVENESS AND OUTCOMES IN PATIENTS WITH SOFT TISSUE SARCOMA TREATED WITH PREOPERATIVE RADIOTHERAPY AND SURGICAL EXCISION

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PHASE 1 TRIAL OF PREOPERATIVE IMAGE GUIDED INTENSITY MODULATED PHOTON RADIATION THERAPY (IMRT) WITH SIMULTANEOUSLY INTEGRATED BOOST TO THE HIGH-RISK MARGIN FOR RETROPERITONEAL SARCOMAS

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NOVEL THERAPY WITH 103PD-DIRECTIONAL BRACHYTHERAPY DEVICE FOR RECURRENT SOFT TISSUE SARCOMAS: SAFETY AND EARLY POSTOPERATIVE OUTCOMES

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TOMOTHERAPY IMRT IN MANAGEMENT OF EXTREMITY SOFT TISSUE SARCOMAS - 8 YEARS' EXPERIENCE, NORTHERN CENTRE FOR CANCER CARE, FREEMAN HOSPITAL

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COMPLETION RATE AND TOXICITY OF HYPO-FRACTIONATED RADIOTHERAPY FOR RETROPERITONEAL AND PELVIC SOFT TISSUE SARCOMAS

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EFFICACY AND SAFETY OF STEREOTACTIC BODY RADIATION THERAPY SBRT WITH CONCURRENT TRABECTEDIN IN METASTATIC SOFT-TISSUE SARCOMA PATIENTS. A SINGLE INSTITUTION EXPERIENCE

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OPTIMIZING TREATMENT DECISIONS FOR PATIENTS WITH EXTREMITY SOFT TISSUE SARCOMA (STS): INDIVIDUAL IDENTIFICATION OF RESPONDERS TO AJDUVANT RADIOTHERAPY (AXRT).

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ANGIOSARCOMA OF THE SCALP AND FACE TREATED WITH HIGH-DOSE-RATE SURFACE APPLICATOR (HDR SA) BRACHYTHERAPY

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PREDICTORS OF LYMPH NODE INVOLVEMENT AND BENEFIT OF REGIONAL RADIOTHERAPY IN SOFT TISSUE SARCOMA

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PENCIL BEAM SCANNING PROTON RADIOTHERAPY REDUCES DOSE TO THE PLANNED SURGICAL SKIN FLAP AND UNINVOLVED BONE IN PREOPERATIVE RADIOTHERAPY FOR SOFT TISSUE SARCOMAS OF THE LOWER EXTREMITY

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PRELIMINARY DATA OF PROSPECTIVE PHASE II CLINICAL TRIAL WITH PREOPERATIVE HYPOFRACTIONATED RADIOTHERAPY (RT) IN PATIENTS WITH LOCALIZED MYXOID LIPOSARCOMAS

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ADVANCED RADIATION TECHNIQUES TO PRESERVE FERTILITY IN FEMALE PATIENTS RECEIVING PELVIC RADIOTHERAPY FOR SOFT TISSUE TUMORS

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IS SURVEILLANCE IMAGING IN PAEDIATRIC PATIENTS TREATED FOR LOCALIZED RHABDOMYOSARCOMA USEFUL? THE EUROPEAN EXPERIENCE

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MANAGEMENT OF PEDIATRIC PERITONEAL RHABDOMYOSARCOMATOSIS WITH CYTOREDUCTIVE SURGERY (CRS), HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY (HIPEC) AND WHOLE ABDOMINAL RADIOTHERAPY (WART)

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EMBRYONAL AND ALVEOLAR RHABDOMYOSARCOMAS IN ADULTS: A SINGLE INSTITUTION RETROSPECTIVE ANALYSIS

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DISEASE OUTCOME IN PATIENTS WITH INTERMEDIATE- AND HIGH- RISK RHABDOMYOSARCOMA BASED ON CHEMOTHERAPY REGIMEN: A SINGLE CENTER RETROSPECTIVE ANALYSIS

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RHABDOMYOSARCOMA IN ADULTS: A SEER POPULATION-BASED STUDY OF 1942 PATIENTS

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VAC REGIMEN TO RHABDOMYOSARCOMA: THE DIFFERENCES OF RESPONSE ANS PROGNOSES IN PATIENTS OF AYA AND OLDER AGES

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OPTIONAL PET SCAN UPSTAGING FOR CASES OF PEDIATRIC RHABDOMYOSARCOMA

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LIPOSARCOMA-SPECIFIC RADIATION THERAPY FOR RETROPERITONEAL SARCOMA - A REPORT FROM TARPSWG

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MALNUTRITION AND PERIOPERATIVE NUTRITIONAL SUPPORT IN RETROPERITONEAL SARCOMA (RPS) PATIENTS. RESULTS FROM A PROSPECTIVE FEASIBILITY STUDY

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POST-OPERATIVE RADIOTHERAPY IMPROVES OVERALL SURVIVAL IN MARGIN-POSITIVE RETROPERITONEAL SARCOMAS

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MEASURING THE IMPACT OF COMPLICATIONS AFTER SURGERY FOR RETROPERITONEAL SARCOMA (RPS): IS COMPREHENSIVE COMPLICATION INDEX (CCI) BETTER THAN CLAVIEN-DINDO CLASSIFICATION (CDC)?

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MANAGEMENT AND OUTCOME OF INTERMEDIATE-HIGH GRADE RETROPERITONEAL SARCOMAS: A SINGLE INSTITUTION STUDY

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MANAGEMENT OF LOCOREGIONAL RECURRENCE AFTER RADICAL RESECTION OF A PRIMARY NON-METASTATIC RETROPERITONEAL SOFT TISSUE SARCOMA: RESULTS OF A RETROSPECTIVE SERIES IN A TERTIARY CARE CENTER

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OUTCOME AND QUALITY OF LIFE AFTER RESECTION FOR RETROPERITONEAL SARCOMA

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NO BENEFIT OF PREOPERATIVE CHEMOTHERAPY FOR PRIMARY RETROPERITONEAL SARCOMAS: RESULTS FROM A SINGLE CENTER PROPENSITY MATCHED ANALYSIS

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EVALUATION OF TREATMENT RESPONSE TO PREOPERATIVE THERAPY IN RETROPERITONEAL LEIOMYOSARCOMA

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ROLE OF NUTRITIONAL STATUS IN THE EARLY POSTOPERATIVE PROGNOSIS OF PATIENTS OPERATED FOR RETROPERITONEAL LIPOSARCOMA (RLS): A SINGLE CENTER EXPERIENCE

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WHY WERE NON-METASTATIC PRIMARY RETROPERITONEAL SARCOMAS NOT RESECTED?

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WHY PRIMARY RETROPERITONEAL SARCOMA (PRPS) PATIENTS (PTS) UNDERGOING TREATMENT AT STRASS INSTITUTIONS DID NOT ENROLL IN STRASS: THE STREXIT STUDY FROM EORTC STBSG AND TARPSWG

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SHOULD LOCALIZED RETROPERITONEAL SARCOMAS BE TREATED IN REFERENCE CENTERS?: RESULTS OF A SINGLE INSTITUTION

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PREDICTIVE FACTORS FOR COMPLICATIONS AFTER SURGICAL TREATMENT FOR SCHWANNOMAS OF THE EXTREMITIES

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CLINICOPATHOLOGICAL AND RADIOLOGIC FEATURES OF GASTRIC SCHWANNOMA

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SOLITARY FIBROUS TUMOR - A SINGLE INSTITUTION RETROSPECTIVE STUDY

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HIGH-GRADE UNDIFFERENTIATED SMALL ROUND CELL SARCOMA (USRCS): A CLINICAL-PATHOLOGICAL STUDY BY THE ITALIAN SARCOMA GROUP (ISG)

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DESIGNING A RATIONAL FOLLOW-UP SCHEDULE FOR SOFT TISSUE SARCOMA

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RADIATION-ASSOCIATED SARCOMA AFTER BREAST CANCER IN FINLAND DURING 1953-2014: A STRONG INCREASE OF ANGIOSARCOMA

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MULTIDISCIPLINARY TUMOR BOARD RECOMMENDATIONS FOR SARCOMA PATIENTS WITH OLIGOMETASTATIC DISEASE

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ULCERATING SOFT TISSUE SARCOMAS

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THE PROGNOSTIC VALUE OF INTERLEUKIN-6 IN PATIENTS WITH SOFT TISSUE SARCOMA

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TRABECTEDIN IN 473 PATIENTS WITH ADVANCED SOFT TISSUE SARCOMA (STS): AN ITALIAN SARCOMA GROUP (ISG), OBSERVATIONAL, MULTICENTER, RETROSPECTIVE STUDY

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"FASCIA-INFILTRATING SARCOMA": A CATEGORIE OF HIGH RISK OF RECURRENCE AND POOR OUTCOME

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ESOPHAGEAL GASTROINTESTINAL STROMAL TUMOR VERSUS LEIOMYOSARCOMA: NATIONAL CANCER DATABASE COMPARATIVE STUDY

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PRIMARY SARCOMA OF LUNG (PSL). A RETROSPECTIVE SERIES.

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SCLEROSING EPITHELIOD FIBROSARCOMA OF SOFT TISSUE AND BONE: REPORT OF 12 CASES.

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PREDICTORS OF VENOUS THROMBOEMBOLISM IN PATIENTS WITH PRIMARY SOFT TISSUE SARCOMA

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DYNAMIC PREDICTION FOR PATIENTS WITH HIGH-GRADE EXTREMITY SOFT TISSUE SARCOMA - PERSONALIZED SARCOMA CARE (PERSARC DYNAMIC)

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SPONTANEOUS REGRESSION OF SOFT TISSUE SARCOMA

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SOFT TISSUE SARCOMA OF THE EXTREMITY: THE IMPACT OF TREATMENT AT MULTIPLE FACILITIES

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TREATMENT AND FOLLOW-UP OF 5 PATIENTS WITH INFANTILE MYOFIBROMATIS - A SINGLE CENTER EXPERIENCE

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INTIMAL SARCOMA: A CLINICOPATHOLOGIC AND IMMUNOHISTOCHEMICAL EXPRESSION IN SEVEN CASES IN THE NATIONAL CANCER INSTITUTE.

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MORBIDITY, QUALITY OF LIFE AND PAIN IN RETROPERITONEAL SARCOMA (RPS). RESULTS FROM A PROSPECTIVE STUDY

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LOCALIZED MYXOFIBROSARCOMAS: ROLE OF SURGICAL MARGINS AND (NEO)ADJUVANT RADIOTHERAPY

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MANAGEMENT AFTER UNPLANNED EXCISION IN ADULT EXTREMITY AND SUPERFICIAL TRUNK SOFT TISSUE SARCOMA: ABSTENTION OF SYSTEMATIC RE EXCISION DOES NOT AFFECT OVERALL SURVIVAL, NOR AMPUTATION RATE

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INCREASED SURVIVAL AFTER SURGICAL MANAGEMENT OF HIGH-GRADE AND DEEP-SEATED SOFT TISSUE SARCOMA IN HIGH-VOLUME HOSPITALS: A NATIONWIDE STUDY

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CHARACTERISTICS OF THE UNPLANNED RESECTION OF A SOFT-TISSUE SARCOMA

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OUTCOMES OF SOFT TISSUE SARCOMA RESECTED WITH CLOSE OR POSITIVE MARGINS ON PRIMARY SURGERY

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CLINICAL OUTCOME IN PATIENTS WITH SOFT TISSUE SARCOMA WHO RECEIVED ADDITIONAL EXCISION AFTER UNPLANNED EXCISION: REPORT FROM THE BONE AND SOFT TISSUE TUMOR REGISTRY IN JAPAN

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ASSESSMENT OF THE TIME TO TREATMENT INITIATION = 0 COHORT IN SOFT TISSUE SARCOMA PATIENTS AT A TERTIARY CANCER CENTER: ARE WE DEFINING THIS CORRECTLY?

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PROGNOSTIC RELEVANCE OF SYSTEMIC INFLAMMATORY MARKERS IN SOFT-TISSUE SARCOMA PATIENTS TREATED WITH CURATIVE RESECTION

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PREDICTORS OF LYMPH NODE EVALUATION AND MANAGEMENT OF POSITIVE LYMPH NODES IN TRUNCAL/ EXTREMITY SOFT TISSUE SARCOMA PATIENTS: THE WHO, THE WHEN AND THE DIFFERENCE IT MAKES

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NUTRITIONAL PREDICTORS OF WOUND COMPLICATIONS IN PATIENTS WITH SOFT TISSUE SARCOMAS OF THE LOWER EXTREMITIES

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PRIMARY VERSUS STAGED SOFT TISSUE RECONSTRUCTION HAVE SIMILAR WOUND AND ONCOLOGIC OUTCOMES AFTER SOFT TISSUE SARCOMA EXCISION

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SURGICAL ADJUVANT THERAPY USING ACRIDINE ORANGE AFTER INTRA-LESIONAL OR MARGINAL RESECTION IN PATIENTS WITH HIGH-GRADE SOFT TISSUE SARCOMA. A PILOT STUDY.

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LONG-TERM OUTCOME IN PATIENTS WITH COMPLICATED NON-METASTATIC RETROPERITONEAL SOFT TISSUE SARCOMAS REQUIRING UNPLANNED EMERGENCY SURGERY

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BENEFIT OF SURGICAL TREATMENT FOR PULMONARY METASTASIS IN SOFT TISSUE SARCOMA PATIENTS

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ALGORITHMS FOR THE SURGICAL MANAGEMENT OF SOFT TISSUE TUMOURS OF THE ABDOMINAL WALL: RETROSPECTIVE SINGLE CENTRE STUDY ON 120 PATIENTS

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FLUORESCENCE-GUIDED LYMPH VESSEL SEALING TO PREVENT LYMPHOCELE AFTER SARCOMA RESECTION

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TUMOR NECROSIS FOLLOWING NEOADJUVANT CHEMOTHERAPY FOR SYNOVIAL SARCOMA: A REPORT FROM CHILDREN'S ONCOLOGY GROUP STUDY ARST0332

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COMBINATION PREOPERAIVE CHEMOTHERAPY AND SURGERY FOR LOCALIZED SYNOVIAL SARCOMA: RETROSPECTIVE ANALYSIS OF 117 PATIENTS AT A SINGLE INSTITUTE FOR 26 YEARS.

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PAZOPANIB IN ADVANCED SYNOVIAL SARCOMA: THE GUSTAVE ROUSSY EXPERIENCE

Marine Sroussi[1]*; Sixtine De Percin*[1]*; Miruna Grecea*[1]*; Marc-Antoine Benderra*[1]*; Maud Velev*[1]*; Sarra Akla*[1]*; Naima Lezghed*[1]*; Sarah N. Dumont*[1]*; Cécile Le Péchoux*[2]*; Charles Honoré*[3]*; Leila Haddag*[4]*; Matthieu Faron*[3]*; Philippe Terrier*[5]*; Olivier Mir*[1]*; Axel Le Cesne*[1]

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SYNERGISM OF P53 ACTIVATORS WITH BCL-2 INHIBITORS IN SYNOVIAL SARCOMA

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SURVIVAL PREDICTION MODEL OF SYNOVIAL SARCOMA USING ARTIFICIAL NEURAL NETWORKS WITH THE SEER DATABASE

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DOES CSF1 OVER-EXPRESSION OR REARRANGEMENT INFLUENCE BIOLOGICAL BEHAVIOUR IN TENOSYNOVIAL GIANT CELL TUMOURS OF THE KNEE?

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Poster 442 3042843

SURGERY IN TENOSYNOVIAL GIANT CELL TUMORS IMPROVES PATIENT REPORTED QUALITY OF LIFE AND JOINT FUNCTION

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CHEMOTHERAPY IN THE TREATMENT OF UNDIFFERENTIATED HIGH GRADE PLEOMORPHIC SARCOMA (UPS) OF BONE

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Poster 444 3042645

HIGH-RISK UNDIFFERENTIATED PLEOMORPHIC SARCOMA (UPS) TREATED WITH PERIOPERATIVE CHEMOTHERAPY: A SECONDARY ANALYSIS OF A ISG-GEIS RANDOMISED CLINICAL TRIAL (RCT) COMPARING 3 VERSUS 5 CHEMOTHERAPY CYCLES FOR HIGH-RISK SOFT TISSUE SARCOMA (STS)

Sandro Pasquali[1]*; Chiara Colombo*[1]*; Sara Pizzamiglio*[1]*; Paolo Verderio*[1]*; Dario Callegaro*[1]*; Silvia Stacchiotti*[1]*; Javier Martín-Broto*[2]*; Antonio Lopez-Pousasup*[3]*; Stefano Ferrari*[4]*; Andres Povedasup*[5]*; Antonino De Paoli*[6]*; Vittorio Quagliuolosup*[7]*; Josefina Cruz*[8]*; Alessandro Comandone*[9]*; Tiziana Venesio*[10]*; Rita De Sanctissup*[7]*; Elena Palassini*[1]*; Antonio Llomboart-Bosch*[11]*; Angelo P. Dei Tos*[12]*; Paolo Casali*[1]*; Piero Picci*[4]*; Alessandro Gronchi*[1]
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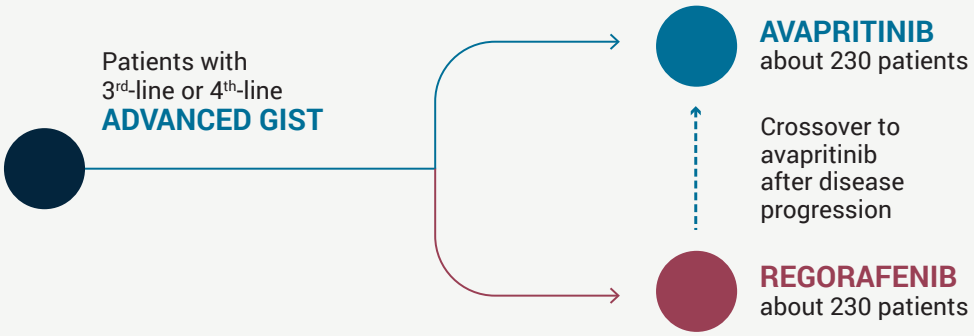
Avapritinib clinical trial in gastrointestinal stromal tumors (GIST)

About the trial[1]

VOYAGER (NCT03465722) is a global, open-label, randomized phase 3 study of avapritinib vs regorafenib **in patients with locally advanced unresectable or metastatic GIST.**

VOYAGER trial design[1]



Select inclusion criteria[1]

- Must be at least 18 years of age
- Must have histologically confirmed unresectable or metastatic GIST
- Must have disease progression after imatinib and 1 or 2 other tyrosine kinase inhibitors
- Must have Eastern Cooperative Oncology Group Performance Status of 0 or 1
- Must not have taken regorafenib

Primary end point[1]

- Progression-free survival using modified Response Evaluation Criteria In Solid Tumors (mRECIST)

Avapritinib mechanism of action

Avapritinib is a potent and selective type 1 kinase inhibitor that binds to the active kinase conformation, directly preventing ATP from binding and thus interrupting subsequent disease signaling.[2] In GIST, primary and secondary activation-loop mutations in KIT contribute to disease resistance to type 2 kinase inhibitors, such as imatinib.[3,4] Avapritinib shows broad inhibitory activity against oncogenic KIT/PDGFRA mutants, including activity against activation-loop mutants, which approved therapies do not inhibit.[2,4]

The VOYAGER trial is now enrolling patients at clinical sites globally.

References: 1. (VOYAGER) study of avapritinib vs regorafenib in patients with locally advanced unresectable or metastatic GIST. ClinicalTrials.gov website. https://clinicaltrials.gov/ct2/show/NCT03465722?term=NCT03465722&rank=1. Published March 14, 2018. Updated August 23, 2018. Accessed September 4, 2018. **2.** Evans EK, Gardino AK, Kim JL, et al. A precision therapy against cancers driven by *KIT/PDGFRA* mutations. *Sci Transl Med.* 2017;9(414):eaao1690. **3.** Spitaleri G, Biffi R, Barberis M, et al. Inactivity of imatinib in gastrointestinal stromal tumors (GISTs) harboring a *KIT* activation-loop domain mutation (exon 17 mutation pN822K).*Onco Targets Ther.* 2015;8:1997-2003. **4.** Gajiwala KS, Wu JC, Christensen J, et al. KIT kinase mutants show unique mechanisms of drug resistance to imatinib and sunitinib in gastrointestinal stromal tumor patients. *Proc Natl Acad Sci.* 2009;106(5):1542-1547.

For more information, please contact us at VOYAGER@blueprintmedicines.com or +1 617 714 6707.
You can also learn more about the VOYAGER trial at www.voyagertrial.com or www.clinicaltrials.gov.

Poster 001 3027672

MULTICENTER, OPEN-LABEL PHASE II STUDY OF DAILY ORAL REGORAFENIB FOR CHEMOTHERAPY-REFRACTORY, METASTATIC AND LOCALLY ADVANCED ANGIOSARCOMA

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Objective: Angiosarcoma has a particularly poor prognosis with 5 year overall survival rates of approximately 30-40%. Treatment of locally advanced and metastatic angiosarcoma is inadequate. Data strongly suggest concurrent, potent inhibition of VEGFR and Tie2 represents an attractive therapeutic strategy in angiosarcoma. Regorafenib displays potent VEGFR and Tie2 receptor inhibition and also possesses activity against additional potential targets in angiosarcoma including PDGFRs, RAF, KIT and FGFR.

Methods: A multicenter phase II study of regorafenib in patients with locally advanced or metastatic angiosarcoma was conducted through the Midwest Sarcoma Trials Partnership. Adequate performance status, organ function, measurable disease (RECIST 1.1) and 1-4 prior therapies were required. Regorafenib 160 mg PO daily was given in 28 day cylces (21 days on, 7 days off) until disease progression (PD) or unacceptable toxicity. The primary endpoint was progression-free survival (PFS), assessed at 16 weeks. Secondary endpoints include overall response rate (ORR), clinical benefit rate (CBR), OS, and safety and tolerability. A Simon 2-stage design was used.

Results: A total of 18 pts were enrolled at 5 sites, 14 are evaluable for response. Median age was 55.6 (range 21-82); 61% were female; 72% metastatic disease. PFS at 4 months is 46% with a median PFS and OS of 2.7 and 15 months, median follow-up 7.9 months (0.4-23). 1 confirmed CR and PR, 5 SD and 7 PD were observed. ORR and CBR are 14 and 50%, respectively. Common grade 3-4 adverse events were as expected.

Conclusion: Regorafenib was well tolerated in this study of pretreated patients with angiosarcomas. Median PFS and PFS at 4 months are promising. Regorafenib will continue to be explored in this two-stage optimal Simon design, for a total of 31 patients.

Poster 002 3042315

PITFALLS IN ANGIOSARCOMA DIAGNOSIS: LESSONS LEARNED FROM CENTRAL REVIEW OF 657 DUTCH CASES

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Objective: Angiosarcoma (AS) is a rare sarcoma originating from endothelial cells. In addition, AS morphology is quite heterogeneous and raises difficulties differentiating AS from for instance epithelioid hemangioendothelioma (EHE), Kaposi sarcoma or other vascular tumors. Immunohistochemical stainings offer increasing support to make the right diagnosis. As part of a large angiosarcoma project, we performed central review of a large cohort of AS cases from the Netherlands and aimed to gain insight in the histological diagnosis and its pitfalls.

Methods: We carried out a nationwide search for AS and EHE diagnosed between 1989 and early 2015 in the Netherlands by PALGA (Dutch nationwide network and registry of histo- and cytopathology). We included EHE because we estimated to find some angiosarcomas in this cohort. Based on pathology report summaries, we selected FFPE samples and complete pathology reports to collect for revision. Of the available cases, H&E slides and, if present, additional stainings were reviewed by an expert sarcoma pathologist (UF) and researcher (MW). Additional stainings (CD31, ERG, CAMTA1, TFE3, HHV8) were carried out on selected cases as deemed necessary by the pathologist. The definitive diagnosis after revision was noted. Statistical analyses were performed with IBM SPSS Statistics, version 22.0.0.1, using Pearson Chi square test.

Results: Our search yielded 3162 pathology report summaries of 1095 AS and EHE cases. Based on these reports, 1368 samples were requested at the pathology labs of origin. We received 769 samples of 657 AS and EHE cases. Additional stainings were performed on 155 samples. Based on pathology reports, 560 cases were initially diagnosed as certain AS of which 468 (84%)

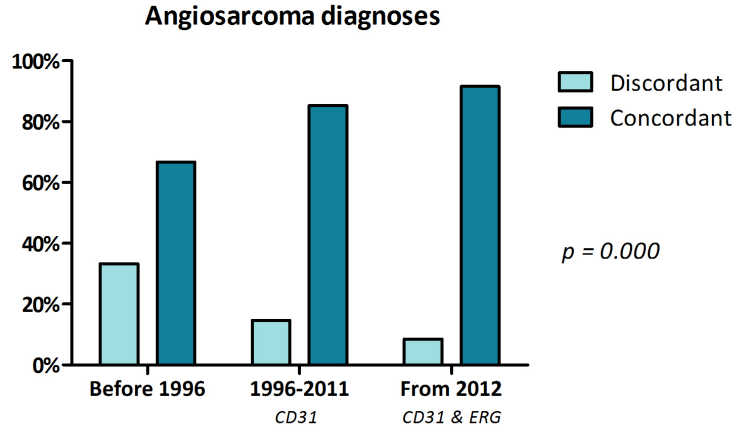
were confirmed by our central review (Table 1). Of the 92 cases that were reported as AS but could not be confirmed, 69 remained uncertain but were definitely not AS. The definite diagnoses of these 69 cases are yet to be determined. In 23 cases the diagnosis was altered into EHE (n=11), Kaposi sarcoma (n=5), AFX (atypical fibroxanthoma, n=2) and into myxofibrosarcoma, irradiation sarcoma, pseudomyogenic hemangioendothelioma, sclerosing epithelioid fibrosarcoma and solitary fibrous tumor (1 each). Use of CD31 in AS diagnosis was first reported in 1995, ERG in AS diagnosis in 2011. The number of discordant diagnoses in our database significantly decreased over time, with a discordance rate of 33.3% before the introduction of CD31, 14.7% between 1996 en 2011, and only 8.5% after the introduction of ERG in 2011 (p=0.000, Figure 1).

Conclusion: Overall, 16% of reported angiosarcomas could not be confirmed. This may be partly due to the initial lack of proper immunohistochemical markers, as we demonstrated a significant decrease in discordant diagnoses after the introduction of CD31 and ERG. CAMTA1 and TFE3 can further prove useful to detect EHEs. Skin lesions can resemble Kaposi sarcoma, to be confirmed with HHV8. Based on our findings, in doubtful cases of vascular tumors we recommend to seek advice or revision from an expert sarcoma pathologist.

Table 1 Reported and definite diagnoses

	REVIEW Diagnosis AS n (%)	REVIEW Diagnosis EHE n (%)	REVIEW Diagnosis other vascular tumor n (%)	REVIEW Diagnosis other, non-vascular n (%)	REVIEW Uncertain diagnosis (not AS) n (%)	Total n
Reported AS	468 (84)	11 (2)	6 (1)	6 (1)	69 (12)	560
Reported EHE	1 (2)	34 (77)	1 (2)	0 (0)	8 (18)	44
Reported vascular tumor	1 (14)	0 (0)	4 (57)	1 (14)	1 (14)	7
Reported other diagnosis	2 (29)	0 (0)	0 (0)	0 (0)	5 (71)	7
Uncertain diagnosis AS/EHE	8 (20)	2 (5)	2 (5)	2 (5)	25 (64)	39
Total	480 (73)	47 (7)	13 (2)	9 (1)	108 (16)	657

Figure 1 ***Diagnoses related to introduction of CD31 and ERG***



Poster 003 3042833

LOCALIZED RADIATION-ASSOCIATED ANGIOSARCOMA OF THE BREAST: A MONO-INSTITUTIONAL CASE SERIES

Elena Palassini[1]*; Silvia Stacchiotti*[1]*; Claudia Sangalli*[1]*; Alessandro Gronchi*[1]*; Carlo Morosi*[1]*; Paola Collini*[1]*; Salvatore Provenzano*[1]*; Rossella Bertulli*[1]*; Giacomo Giulio Baldi*[1]*; Marta Barisella*[1]*; Massimiliano Gennaro*[1]*; Paolo Casali*[1]
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Objective: Radiation-associated angiosarcoma (RAAS) of the breast is characterized by a poor outcome, with a 5-year overall survival (OS) rate around 50% in historical series. Herein we report on a series of consecutive patients with localized RAAS of the breast treated at a single institution.

Methods: We retrospectively reviewed all cases of localized, primary or locally recurrent, RAAS of the breast, amenable to complete surgery, treated at our institution from January 2007. Pathologic diagnosis was reviewed. Data on pathological and clinical aspects as well as on treatment were collected. Disease-free survival (DFS) and OS were calculated from start of neoadjuvant chemotherapy (for those patients who received it) or surgery. Patients at with a follow-up shorter than 6 months were excluded from this analysis.

Results: Twenty-seven female patients were retrospectively identified. Previous radiotherapy was delivered for breast carcinoma in 25 patients (93%), for hematological malignancies in 2 (7%). The median latency period following radiotherapy was 7.3 years (range 3.8-25.2). Median age was 70 years (range: 27-87). Twenty-five patients (93%) had primary disease and 2 (7%) had locally recurrent disease. Eleven patients (41%) had a single lesion (median size 4 cm, range 1-10) and 16 (59%) had a locoregional multifocal disease. All patients but one (who progressed during neoadjuvant treatment) were treated with surgery: 3 (11%) were treated with surgery alone and 23 (85%) with multimodality treatment (11 = neo- and/or adjuvant chemotherapy + neo- or adjuvant radiotherapy + surgery; 12 = neo- and/or adjuvant chemotherapy + surgery). Of 24/27 patients (89%) treated with neo- and/or adjuvant chemotherapy, 15 (56%) received chemotherapy in a neoadjuvant setting, 3 (11%) in an adjuvant setting and 6 (22%) both in a neoadjuvant and adjuvant setting. Median numbers of cycles was 5 (range 3-10). 23/27 patients (85%) received gemcitabine-based chemotherapy (8 = gemcitabine monotherapy; 12 = gemcitabine + docetaxel; 3 = gemcitabine monotherapy followed by paclitaxel), 3/27 (11%) anthracycline (2 = monotherapy; 1 = anthracycline + ifosfamide), 3/27 (11%) high-dose prolonged infusion ifosfamide (all concurrently with radiotherapy). Of 11/27 patients (41%) who received neoadjuvant or adjuvant radiotherapy, 4 (15%) received radiotherapy preoperatively (in combination with chemotherapy) and 7 (26%) after surgery. With a median FU of 43.8 months (range: 3.1-125), 10 patients progressed/relapsed (1 progression during neoadjuvant chemotherapy, 7 local recurrences and 2 distant metastases). Of 7 local recurrences, 6 occurred in patients who did not received radiotherapy. Median DFS was 73.8 months (CI 95% 16.8-nr). Six patients died (two because of local control failure). Median OS was not reached, with 1-year, 2-year and 5-year OS rate being 95%, 80% and 70%.

Conclusion: With the limitation of a small retrospective analysis, this series of localized breast RASS shows a better outcome compared to others. Of interest, most patients in this series received a multimodality approach. An effort to validate prospectively the role of chemotherapy and radiotherapy in this rare subgroup of sarcoma patients is needed.

Poster 004 3000082

TRAMETINIB INDUCES RESPONSE IN REFRACTORY HRAS G13D-MUTATED ANGIOSARCOMA OF SCALP

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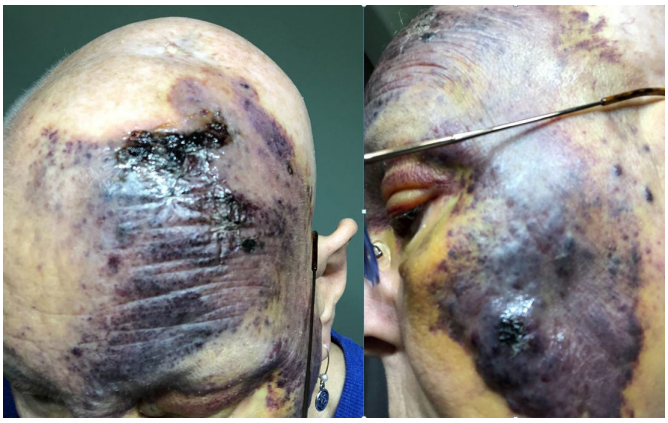
Objective: To report a case of refractory, HRAS-mutated angiosarcoma responding to MEK inhibition with trametinib

Methods: Our patient was diagnosed with angiosarcoma behind her left ear in Oct 2016. She underwent repeated wide local excisions of the scalp due to subsequent positive margins, requiring thigh flap for coverage in Nov 2016. Cervical sentinel lymph node sampling was negative twice. She started adjuvant paclitaxel 80mg/m2 IV weekly 3 of 4 weeks in Dec 2016. After a few cycles, she had locally recurrent disease, so neoadjuvant radiation was added to a weekly dose of 30mg/m2 paclitaxel IV during radiation. She finished this combined therapy Fri 6/16/17 (20Fxs, 62.5Gy). Restaging scans still showed no signs of metastatic disease, so she went for wide local excision on 7/27, 8/10 and 8/30/17, all proving to have positive margins. Surgery on 9/12/17 looked to have finally cleared the margins adequately, but a repeat CT done 9/19/17 showed a new metastatic segment 2 hepatic lesion. On 9/25/17, due to large defect in scalp, she underwent a split-thickness skin grafting measuring 49 sq cm to the scalp and neck. Because of the potential complications with the healing graft, she was not a candidate for chemo or anti-VEGF therapy then, so she underwent microwave ablation of this liver lesion on 10/2/17. By Nov 2017, she had at least two new small nodules in lungs on CT, and a pink nodule with “rash” developing on L forehead area. She tolerated 3 cycles of palliative doxorubicin 60mg IV q3weeks, but restaging CT then showed new left 10th rib metastasis, worsening cavitary lesions in lungs, stable ablated liver lesion. She was switched to sorafenib 200mg BID, but her angiosarcoma continued to spread across her L side of face quickly over three weeks (image 1). She had new areas of nodularity noted at different areas throughout her face/scalp. Foundation One testing showed a solitary HRAS G13D alteration; no other alterations were detected. On the basis of clinical benefit seen in patients with other HRAS-mutated tumor types treated with trametinib, we decided to try off-label trametinib 2mg PO daily starting early March 2018.

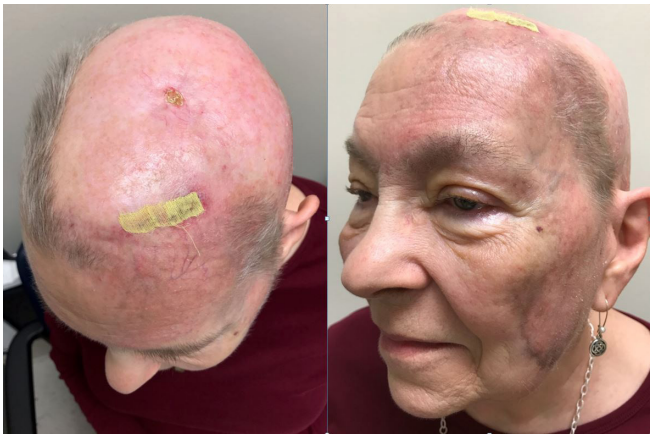
Results: After ten weeks (image 2), there has been a marked improvement both via exam and imaging. CT scan mid-May

2018 matched her response in the face, with near complete resolution of several small pulmonary nodules, with increased sclerosis of the metastatic lesion involving the left 10th rib and decrease in size of the ablated hepatic segment 4B lesion. She was able to celebrate her 50th wedding anniversary in mid June, and continues to show no signs of relapse.

Conclusion: Murali et al reported HRAS activating mutations in 4 of 34 angiosarcoma cases studied. (Murali et al. "Targeted massively parallel sequencing of angiosarcomas reveals frequent activation of the mitogen activated protein kinase pathway". Oncotarget. 2015 Nov 3; 6(34): 36041–36052.) Here we report the first case of angiosarcoma responding to MEK inhibition. We show a quick impressive response in a refractory case of angiosarcoma using standard 2mg trametinib orally daily.



Angiosarcoma overtaking patient's face, immediately prior to starting trametinib
[Patient has given us permission to use her face with discussing this case]



After 10 weeks of trametinib, near complete resolution of angiosarcoma involving face.

Poster 005 3037976

THE ANGIOSARCOMA PROJECT: GENERATING THE GENOMIC LANDSCAPE OF A RARE SARCOMA THROUGH A NATIONWIDE PATIENT-DRIVEN INITIATIVE

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Objective: Angiosarcoma (AS) is a rare soft tissue sarcoma, with an incidence of 300 cases/yr and a 5-year disease-specific survival of 30%. The low incidence has impeded large-scale research efforts that may lead to improved clinical outcomes. To address this, we launched a patient-partnered nationwide study, which seeks to empower patients to accelerate research by sharing their samples and clinical information remotely.

Methods: With patients and advocacy groups, we developed a website to allow AS patients to participate across the US and Canada. Patients can access the study online (ASCproject.org). Enrolled patients are mailed saliva and blood draw kits. The study team obtains medical records and stored FFPE tumor samples. Medical records are abstracted. All FFPE samples are examined by an expert pathologist to confirm a diagnosis of angiosarcoma. Whole Exome Sequencing (WES) is performed on tumor and saliva samples. Transcriptome analysis is performed on tumor samples. Ultra-low pass whole genome sequencing (ULP-WGS) is performed on cell free DNA (cfDNA) obtained from blood samples, and WES when tumor-derived cfDNA is sufficiently high. The resulting clinically annotated genomic database is shared widely to identify genomic drivers and mechanisms of response and resistance to therapies. Study updates are shared with patients regularly.

Results: Through social media, we launched The Angiosarcoma Project on March 13, 2017. A total of 315 patients have registered to date. The average age of patients is 56 yr (range 22-89). Primary locations of AS were primary breast 70 (24%), breast with prior radiation 58 (20%), head/face/neck/scalp 63 (21%), bone/limb 27 (9%), abdominal 8 (3%), heart 10 (3%), lung 2 (1%), liver 4 (1%), lymph 1 (0.5%), multiple locations 31 (11%), and other locations 14 (5%). 142 (48%) reported being disease free at the time of enrollment. To date, 153 saliva kits, 167 medical records, 43 blood samples, and 84 tissue samples have been received. WES was performed on FFPE/saliva matched pairs with a goal mean target coverage of 150x for tumors. ULP-WGS was performed on cfDNA to determine tumor fraction. Of 10 cfDNA samples sequenced, 4 samples met criteria to perform WES. Transcriptome sequencing was performed on 9 FFPE samples. Sequence data processing and analysis are complete on 22 samples and in progress for subsequent samples. We sought to characterize previously described genes known to be altered in angiosarcoma (e.g., *TP53, NF1, KDR, BRCA2, MET, ARID1A, POT1, BRCA1, ASXL1, KDM6A, BRAF, SETD2, PTPRB, NRAS*). Recurrent alterations in *KDR* were detected in 32% (7/22) of analyzed samples, comprising 4 missense mutations and 3 amplifications. Alterations were seen in at least one sample in all other genes selected for this initial analysis. Tumor mutational burden (TMB) and mutational signature activities were quantified for each sample. Each of three cutaneous samples exhibited a high TMB (>150 mutations) and dominant UV Light (COSMIC Signature 7) signature activity.

Conclusion: A patient-partnered approach enabled rapid identification and enrollment of over 300 patients with AS, an exceedingly rare cancer, in 15 months. We were able to obtain tumor, blood, saliva samples to perform genomic analyses, which were then merged with detailed clinical information. Patient-reported, clinical, and genomic data generated from the first 12 patients and 14 samples are available on cbioportal.org. Additional data will be released in six-month intervals. The early results, which show high TMB and a UV signature, could provide rationale for clinical interventions using checkpoint inhibitors for cutaneous angiosarcoma. Analyses of additional samples are under way to further characterize mutational signatures in cutaneous angiosarcomas and implications for patient care. This study serves as proof of principle that patient-partnered genomics efforts can democratize cancer research for exceedingly rare cancers, which to date have been understudied.

Poster 006 3042503

A RETROSPECTIVE REVIEW OF PATIENTS WITH ANGIOSARCOMA TREATED IN BRITISH COLUMBIA

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Objective: Angiosarcoma represents 2% of soft-tissue sarcomas and has limited large cohort data with an estimated 5 year survival of 12% for unresectable or metastatic disease. We evaluate the real world outcomes of patients with angiosarcoma treated in our provincial institution.

Methods: A retrospective chart review of patients across British Columbia was undertaken from the Sarcoma Outcomes Unit at BC Cancer from January 1, 1969 to September 19, 2017, inclusive. Cox proportional hazard models were used to calculate hazard ratios (HR) for overall survival (OS) and progression free survival (PFS).

Results: 145 patients with angiosarcoma were identified, of which 68 were metastatic or unresectable at presentation. 38/145 patients received chemotherapy of which 15/38 received a taxane. 1/38 patient received chemotherapy in the neoadjuvant setting. 80/145 had surgery and 70/145 had radiation during their treatment. 38/145 had prior radiation for an unrelated cancer. Angiosarcoma arose within a prior radiotherapy volume in 28/36 patients with sufficient radiotherapy data available (23/28 adjuvant breast, 3/28 head and neck/skin, 1/28 prostate). 4/145 patients had chronic lymphedema. Resectable disease (HR 0.22, $p<0.01$), first treatment with surgery (HR 0.08, $p<0.01$), radiation (HR 0.19, $p<0.01$) or chemotherapy (HR 0.22, $p<0.01$) were statistically significant predictors of improved OS. Upfront surgery resulted in improved OS (HR 0.36, $p<0.01$) and PFS (HR 0.48, $p<0.01$). OS was positively impacted by extent of surgery R0 versus R1 (HR 0.26, $p<0.01$) and R0 verus R2 (HR 0.08, $p<0.01$) resection.

Conclusion: Patients able to undergo upfront surgery had improved PFS and OS. The extent of surgery is an important predictor of OS. Patients did better with any treatment than best supportive care alone. Multidisciplinary care is critical for the survival of patients diagnosed with angiosarcoma.

Poster 007 3042537

DETECTION OF ENDOGLIN-EXPRESSING CTCS IN PATIENTS ENROLLED IN AN ADAPTIVE ENRICHMENT PHASE 3 TRIAL OF TRC105 AND PAZOPANIB VERSUS PAZOPANIB ALONE IN PATIENTS WITH ADVANCED ANGIOSARCOMA (TAPPAS)

Ravi Vinod[2]*; Andrew Brohl*[3]*; Robin Jones*[4]*; Sant P. Chawla*[5]*; Kristen Ganjoo*[14]*; Steven Attia*[10]*; Atrayee Basu-Mallick*[9]*; Darren Davis*[6]*; Mario Cervantes*[6]*; Wen Liu*[6]*; Lilian Liu*[1]*; Charles Theuer*[1]*; Steven Robinson*[11]*; Nicolas Penel*[12]*; Silvia Stacchiotti*[13]*; William D. Tap*[7]*; Robert Maki*[8]

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Objective: Endoglin (CD105) is an essential angiogenic receptor expressed on Angiosarcoma (AS) tumor cells and vessels that is upregulated following hypoxia and promotes resistance to VEGF inhibition. TRC105, an endoglin antibody, combined with pazopanib (P) achieved durable complete responses in AS patients, with encouraging median PFS of 7.8 months in chemotherapy-refractory and P-naïve patients enrolled in a Phase 1/2 trial. The objective of this report is to quantify endoglin expressing circulating tumor cells (CTCs) using ApoStream® dielectrophoresis field flow assist from the whole blood of AS patients enrolled in the ongoing Phase 3 TAPPAS trial.

Methods: AS CTCs were enriched by ApoStream® from samples drawn prior to treatment, with either TRC105/P or single agent P, at C1D1 and 6 weeks following initiation of study treatment, at C3D1. CTCs that expressed endoglin and DAPI (nucleus) by immunofluorescence that used a non-competing endoglin antibody were quantified. endoglin+/DAPI+ CTCs were further characterized as atypical cells using Diff-Kwik staining.

Results: Paired samples (taken at C1D1 and C3D1) from 25 patients were analyzed. Endoglin+ CTCs were detected in all samples at baseline (C1D1 mean = 127/ml; median = 1.75/ml; range 0.13 – 1128/ml) and 6 weeks following treatment with TRC105/P or P (C3D1 mean = 13.1/ml; median = 1.63/ml; range 0.13 – 90.1/ml).). Endoglin+ CTCs decreased between C1D1 and C3D1 in 14 patients (6 of which decreased > 10-fold) and increased in 11 patients (6 of which increased > 10-fold). Diff-Kwik staining confirmed the enriched CTCs had atypical morphology containing hemosiderin deposits and large irregularly shaped nuclei in all cases.

Conclusion: ApoStream® technology isolated endoglin+ CTCs from the whole blood of AS patients. Significant changes in endoglin+ CTCs were observed following treatment with TRC105/P and/or single agent P. Baseline endoglin+ CTC and the response of endoglin+ CTC to treatment will be correlated with outcome.

Poster 008 3042562

NEOADJUVANT CHEMOTHERAPY ASSOCIATED WITH ENHANCED LOCAL CONTROL IN RADIATION-INDUCED ANGIOSARCOMA OF BREAST AND CHEST

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Objective: Radiation-induced/associated angiosarcoma (RAAS) frequently recur locally and distantly. Identified prognostic factors are rare, and despite their dismal prognosis, treatment is limited to surgery in RAAS. We wondered whether we could identify new prognostic factors in patients with breast/chest (b/c)RAAS and whether we could observe outcome differences according treatment: upfront surgery (S) vs. neoadjuvant chemotherapy (NAC).

Methods: We consulted Conticabase, searching for RAAS patients treated in French centers. We retained resectable, M0 b/cRAAS and divided the group into cohorts S and NAC. Survival outcomes for the whole group and the two cohorts were determined. Cox regression prognostic analysis was performed for overall survival (OS), local recurrence-free survival (LRFS) and metastases-free survival (MFS).

Results: At 5.5 years follow-up, 5-y OS, MFS and LRFS of 180 patients with b/cRAAS were 50%, 68% and 36%, respectively. Comparing S (n=141) to NAC (n= 39), patient and tumor characteristics were well balanced. 5-y OS and MFS were not different between cohorts. In contrast 5-y LRFS were 30% vs. 53%, respectively (logrank p = 0.03). Age, size and depth independently predicted OS. Grade 3 predicted MFS. Age, grade and treatment sequence (S vs. NAC: HR 2.22, 95% CI 1.26-3.04) independently predicted LRFS.

Conclusion: Prognosis of localized b/cRAAS seems better than expected. However, 2/3 will recur locally, a major risk in RAAS that is sustained by multifocal growth. Neoadjuvant chemotherapy is associated with a significant better local control and should be evaluated for b/cRAAS.

Poster 009 3015887

ASSOCIATION OF BETA-BLOCKER USE WITH CLINICAL OUTCOMES IN PATIENTS WITH ADVANCED ANGIOSARCOMA

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Objective: Angiosarcomas (AS) are uncommon malignant neoplasms with aggressive clinical behavior and limited treatment options. Patients with metastatic disease have a dismal prognosis and new therapeutic options are needed. AS cells express beta-1 and beta-2 adrenergic receptors and undergo apoptosis when exposed to propranolol *in vitro*. However, clinical data supporting beta-blockers (BB) in the treatment of AS is limited, thus, we undertook a retrospective study in order to explore this hypothesis. The main objective of this study was to investigate the clinical outcomes of patients receiving BB for other clinical indications concurrently with systemic therapies for the treatment of advanced AS. Specifically, we sought to compare progression-free survival (PFS), overall survival (OS), and response rates (RR) for patients taking and not taking BB while receiving treatment for advanced AS. We also aimed to describe the clinical characteristics and treatment courses of these patients.

Methods: AS patients with advanced (unresectable or metastatic) disease treated at our institution between January 1, 2008, and August 31, 2017, were identified. Dates of diagnosis, treatment, progression of disease, and last follow-up were abstracted. Presence or lack of response to each line of treatment and other factors that may have played a role in treatment outcomes, such as concomitant use of inhaled beta-agonists, antineoplastic agents administered, prior surgery or radiation, and performance status were noted. PFS, OS, and RR were calculated and compared between patients taking and not taking BB. For the PFS analysis, patients were censored if they remained on treatment at the conclusion of the study or if they were removed from first-line treatment for non-progression. Additional patient and treatment characteristics were reviewed to assess for further variables that may have impacted response rates and survival data.

Results: We identified 23 AS patients who received systemic treatment for advanced disease (Figure 1). Of these, 7 patients were taking BB during treatment. 5 out of 7 patients taking BB had a clinical response or stable disease with first-line systemic treatment for advanced AS vs. 7 out of 16 patients not taking BB (OR 3.21, 95% CI 0.47-21.8, p = 0.37, Table 1). AS patients taking BB trended toward a longer median PFS (224 vs. 82 days, log-rank: p = 0.12, Table 2 and Figure 2) and OS (588 vs. 156 days, log-rank: p = 0.36, Table 2 and Figure 3). Baseline performance status and exposure to prior (non-palliative) treatments was similar between the two groups. The mean age of patients taking BB was 69 years vs. 54 years for patients not taking BB. Most patients in both groups received taxane-based treatment as the first line of therapy. Treatment responses or stable disease were seen in patients taking metoprolol, atenolol, and carvedilol. A higher proportion of patients taking BB had primary cutaneous tumors than visceral or radiation-induced tumors, but this did not correlate with likelihood of response to first-line treatment. Interestingly, all 4 patients taking inhaled beta-agonists had treatment responses or stable disease.

Conclusion: The results of this study show a trend toward higher RR to first-line treatment and increased PFS and OS among patients with advanced AS taking BB compared with patients not taking BB. There are no other clear differences in baseline characteristics of patients in the two groups that would account for these differences in response rates and survival. Patients taking BB may have better response and survival rates due to a synergistic effect of beta-adrenergic blockade with chemotherapy agents in inducing apoptosis of angiosarcoma cells, which is supported by previously published investigations. While our results do not reach statistical significance due to the small number of patients included in the study, they lend support for further retrospective and prospective studies to assess the role of BB in treatment of AS.

Table 1: Response Rates

	All Patients Taking Beta Blockers (n = 7)	All Patients Not Taking Beta Blockers (n = 16)	Odds Ratio (95% CI)	P-value
Number of Patients (%) with Treatment Response	4 (57.1)	5 (31.3)	2.93 (0.47, 18.33)	0.36
Number of Patients (%) with Stable Disease	1 (14.3)	2 (12.5)	1.17 (0.09, 15.46)	
Number of Patients (%) with Treatment Response or Stable Disease	5 (71.4)	7 (43.8)	3.21 (0.47, 21.80)	0.37
Number of Patients (%) with Progressive Disease	2 (28.6)	9 (56.3)		

Comparison of numbers and percentages of patients with partial responses and stable disease with first-line treatment of advanced angiosarcoma while taking or not taking beta-blockers. Fisher's exact test was used to compare response rates between the two groups of patients.

Table 2: Progression-Free and Overall Survival

	Patients Taking Beta-Blockers	Patients Not Taking Beta-Blockers	P-value
Median Progression-Free Survival from Treatment Start (Days)	224	82	0.12
Median Overall Survival from Treatment Start (Days)	588	156	0.36

Progression-free and overall survival for patients taking beta-blockers and not taking beta-blockers while undergoing treatment for advanced angiosarcoma. The Kaplan-Meier method was used to estimate the median for the survival curves. The log-rank test was used to compare survival between the two groups of patients.

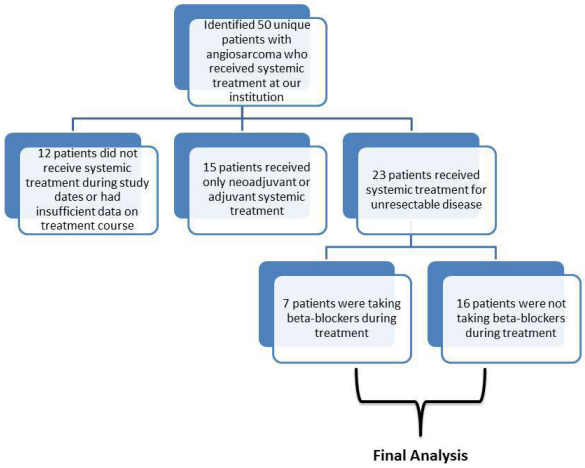

Figure 1: Flow chart depiction of the process of patient analysis for this retrospective study.

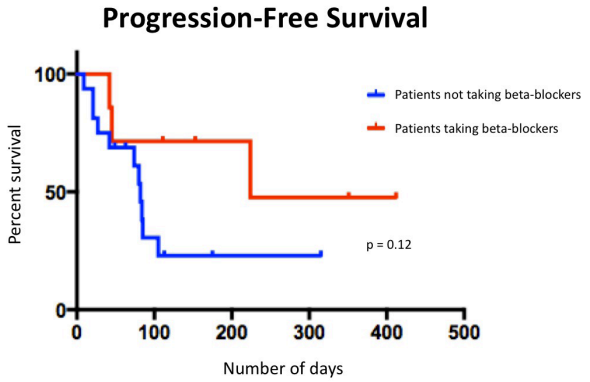

Figure 2: A Kaplan-Meier curve comparing progression-free survival of patients taking beta-blockers during treatment for advanced angiosarcoma vs. patients not taking beta-blockers.

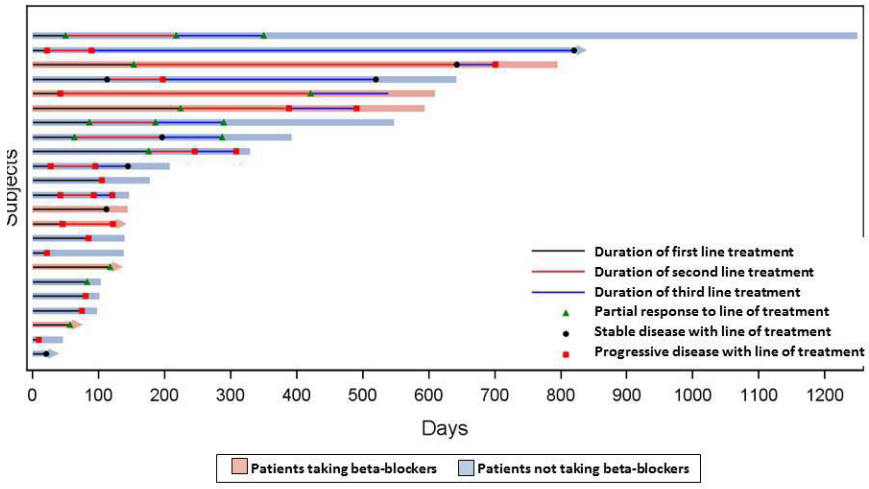

Figure 3: A swimmer's plot depicting the treatment courses for each patient analyzed in this study. Duration and best responses for the first three lines of treatment for each patient are depicted. The length of each bar indicates overall survival time and may include additional lines of treatment beyond the third line. Arrows at the ends of some bars indicate ongoing treatment at the end of the study.

Poster 010 3016619

ACTIVITY AND SAFETY OF CRIZOTINIB IN PATIENTS WITH ADVANCED, METASTATIC ALVEOLAR SOFT PART SARCOMA (ASPS) WITH REARRANGEMENT OF TFE[3]EUROPEAN ORGANIZATION FOR RESEARCH AND TREATMENT OF CANCER (EORTC) PHASE 2 TRIAL 90101 "CREATE"

Patrick Schöffski[1]*; Agnieszka Wozniak*[2]*; Bernd Kasper*[4]*; Steinar Aamdal*[3]*; Michael Leahy*[6]*; Piotr Rutkowski*[7]*; Sebastian Bauer*[12]*; Hans Gelderblom*[8]*; Antoine Italiano*[5]*; Lars Lindner*[9]*; Ivo Hennig*[15]*; Sandra Strauss*[10]*; Branko Zakotnik*[14]*; Alan Anthoney*[13]*; Silvia Stacchiotti*[11]

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Objective: ASPS is an orphan malignancy associated with a rearrangement of transcription factor E3 (*TFE3*), leading to abnormal *MET* gene expression. We prospectively assessed the efficacy and safety of the MET/ALK/ROS1 tyrosine kinase inhibitor crizotinib in patients with advanced or metastatic ASPS (trial NCT01524926).

Methods: Eligible patients with reference pathology-confirmed ASPS received oral crizotinib 250 mg twice daily. By central assessment of *TFE3* rearrangement (fluorescence *in situ* hybridization using custom bacterial artificial chromosome RP11-344N17 and RP11-552J9 probes flanking the *TFE3/Xp11.2* gene), patients were attributed to *MET*+ or *MET*- sub-cohorts. Primary endpoint was the objective response rate (ORR; RECIST 1.1) according to local investigator. Secondary endpoints included duration of response (DOR), disease control rate (DCR), progression-free survival (PFS), progression-free rate (PFR), overall survival rate (OSR), overall survival (OS) and safety.

Results: Among 53 consenting patients with centrally confirmed diagnosis of ASPS, 48 were treated and 45 were evaluable for the primary endpoint. Among 40 *MET*+ patients, one achieved a confirmed partial response (PR) that lasted 215 days, and 35 had stable disease (SD) as best response (ORR: 2.5%, 95%CI: 0.6-80.6%). Further efficacy endpoints in *MET*+ cases were a DCR of 90.0% (95%CI: 76.3-97.2%), a 1-year PFR of 37.5% (95%CI: 22.9-52.1%) and 1-year OSR of 97.4% (95%CI: 82.8-99.6%). Among 4 *MET*- patients, one achieved a PR that lasted 801 days and 3 had SD (ORR: 25.0%, 95%CI: 0.6-80.6%) for a DCR of 100% (95%CI: 39.8-100.0%). The 1-year PFR in *MET*- cases was 50% (95%CI: 5.8-84.5%) and the 1-year OSR was 75% (95%CI: 12.8-96.1%). One patient with unknown *MET* status due to technical failure achieved SD but progressed after 17 3 week treatment cycles. Shrinkage of target lesions was seen in 17 patients, both in *MET*+ and *MET*- cases. The most common crizotinib-related adverse events were nausea (34/48 [70.8%]), vomiting (22/48 [45.8%]), blurred vision (22/48 [45.8%]), diarrhea (20/48 [41.7%]) and fatigue (19/48 [39.6%]).

Conclusion: According to EORTC efficacy criteria for soft tissue sarcoma, our study results suggest that crizotinib has activity in *TFE3* rearranged ASPS *MET*+ patients. While objective RECIST responses were infrequent, we observed tumor shrinkage in a significant proportion of patients, excellent DCR and good survival rates. The long follow-up in this study allows us to present mature and reliable PFS and OS estimates as an important reference for future research in patients with advanced, metastatic ASPS.

Poster 011 3042589

TREATMENT PATTERNS OF ALVEOLAR SOFT PART SARCOMA PATIENTS AND RESPONSE TO MULTIPLE EXPERIMENTAL THERAPIES

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Objective: Alveolar soft part sarcoma (ASPS) is a tumor of uncertain mesenchymal origin that is often characterized by a relatively indolent clinical course but late metastasis. The fusion of der(17)t(X;17) (p11;q25) creates the characteristic ASPSCR1-TFE3 fusion, resulting in significant nuclear overexpression of transcription factor 3. Interest in the biologic characteristics of this rare cancer has recently been kindled by sporadic reports of its responsiveness to immune checkpoint blockade. We reviewed charts of patients with ASPS to further evaluate responses to experimental therapies including checkpoint inhibitors.

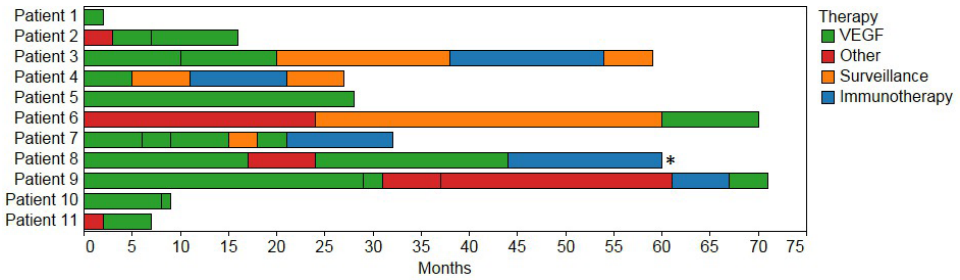
Methods: We conducted a retrospective review of ASPS patients treated on clinical trials in our phase 1 clinic between 2009 and 2017. Demographic information was collected, including diagnosis, age, sex, date of first dose on trial, date of progression, best response by RECIST criteria, and if applicable, date of death and clinical NGS profiles performed in a CLIA environment.

Results: Among 11 patients with ASPS, the median age was 21 years (range, 14-37 years); patients were predominantly female (F:M, 8:3). Five patients (45%) died, with overall survival durations of 10, 12, 15, 58, and 70 months. Three patients (27%) were lost to follow-up, with times of 3, 6, and 19 years. The three patients who were still being followed up had been diagnosed 10, 11, and 12 years previously. Among all patients, the most common primary tumor site was the lower extremities (n=7; 64%). The metastatic sites were almost exclusively the brain (n=5; 45%) and lungs (n=11; 100%). One patient had liver metastasis. Among the 7 patients who underwent NGS testing, only 2 mutations were detected: *CDKN2A* mutation (n=1) and *HGF* amplification (n=1). Within the GENIE database another 12 patients were identified and only 4 had any identifiable fusions (Table 1). Ten (91%) patients were enrolled on at least 1 trial that included VEGF inhibitor-based therapy, pazopanib (N=3), vandetanib+everolimus (n=4), and bevacizumab (n=3). The best response achieved was stable disease in 9 patients on a VEGF inhibitor for a median of 12 months duration. Four patients (40%) were treated with checkpoint immunotherapy targeting the PD-1/PD-L1 axis. Three patients experienced a partial response, and 1 had stable disease as the best response, resulting in an overall response rate to immunotherapy of 75%.

Conclusion: ASPS patients derive clinical benefit from VEGF-based agents. In light of the frequently indolent and variable course of ASPS, stable disease is a difficult endpoint to interpret. In contrast, immune checkpoint blockade yields clear partial responses. A combination of VEGF and immune checkpoint inhibitors should be explored in these patients.

Mutations in ASPS patient identified by AACR project Genie

Patient 1	ATRX BCORL1 PMS1 PTEN RB1 TP53
Patient 2	CBL
Patient 3	KMT2D
Patient 4	IRS2



Relative progression free survival of each ASPS patient on sequential therapies

Poster 012 3042597

CLINICAL CHARACTERISTICS OF ALVEOLAR SOFT PART SARCOMA PATIENTS WITH BRAIN METASTASIS

Tonita Bates[1]*; Akash Mitra*[2]*; John A. Livingston*[1]*; Alexander J. Lazar*[3]*; Andrew J. Bishop*[4]*; B. Ashleigh Guadagnolo*[4]*; Ravin Ratan*[1]*; Vinod Ravi*[1]*; Neeta Somaiah*[1]*; Maria A. Zarzour*[1]*; Daniela A. Camacopa*[1]*; Dejka M. Araujo*[1]*; Robert Benjamin*[1]*; Shreyaskumar Patel*[1]*; Anthony P. Conley*[1]

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Objective: Alveolar soft part sarcoma (ASPS) is a rare translocation-driven soft tissue neoplasm of uncertain origin that commonly affects adolescents and young adults. A unique aspect of this disease is the ability to metastasize to the brain. Little is known regarding the characteristics of ASPS patients with brain metastasis and their outcomes. We sought to define the clinical features, treatment modalities, and outcomes for ASPS patients with brain metastasis.

Methods: From our sarcoma database, 94 ASPS patients treated at our institution were identified between the time period of 2000 to 2017. Descriptive statistics and several analytical tests, including Log rank test, Schoenfeld residuals test, and Cox proportional hazard models, were performed to evaluate several survival metrics. All statistical analyses were performed using SAS 9.3 for Windows and R-based software.

Results: 18 of 94 (19%) patients were noted to have brain metastasis. Median age at diagnosis was 27.5 yrs (range 17-55). 10 (56%) were male. All but 1 patient had metastatic disease prior to brain metastasis, but only 7 had concurrent brain metastasis at diagnosis. 15 (83%) had their primary tumor in an extremity, most (12, 67%) occurred on the right side, and the median size was 7.2 cm (range 3.8 – 18). Median time from diagnosis to development of brain metastasis was 3.9 months (range 0 – 244). Majority (10, 56%) had unifocal brain metastasis and the most common site were the frontal lobes (14, 77.8%). 8 (44%) were symptomatic with headache (5, 27.8%) as the initial symptom. The most common brain-specific therapy involved radiation (11, 61%), and 10 (56%) received systemic therapy after brain metastasis discovery. Protocol involvement was noted in 8 (44%) patients. Median OS was 70.6 months (range 2.1 – 283.4), the 5-year OS was 55%, and the median survival time from brain metastasis discovery to last follow up or death was 25.6 months (range 2.1 – 162). No specific variable was associated with a significantly improved survival.

Conclusion: For a significant number of these patients, brain metastasis appears to occur soon after development of metastatic disease. Median survival following development of brain metastasis exceeds 20 months. As a result, ASPS patients with brain metastasis should still be considered for therapeutic options.

Poster 013 3019420

EXPANDING THE HISTONE MUTATION LANDSCAPE IN SARCOMA

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Objective: Epigenetic dysregulation is increasingly recognized as contributing to sarcoma biology, particularly in the setting of bone tumors. Epigenetic states are controlled in large part by posttranslational modifications (PTMs) of histones, which form nucleosomes to package the genome in its physiologically relevant form. These PTMs are combinatorial and regulate genome stability, cell division, and cell fate. The complexes that 'read', 'write', and 'erase' histone PTMs harbor cancer-associated mutations, including in polycomb complex members in MPNST.

Recently, histones have been reported as driver genes based on high frequency mutations in diffuse intrinsic pontine gliomas (H3K27M), giant cell tumor of bone (H3G34W/L; also rarely seen in osteosarcomas), and chondroblastomas (H3K36M). H3K36M is sufficient to induce sarcomagenesis in a mesenchymal progenitor cell model.

We hypothesized that these known 'oncohistones' as well as additional histone mutations are present in other sarcoma subtypes. Our goal is to motivate future mechanistic studies.

Methods: We conducted a retrospective analysis of sequencing data from sarcoma samples in both publicly available whole exome sequencing studies (e.g. The Cancer Genome Atlas) and from institutional cancer gene specific panels (MSK-IMPACT). Missense somatic mutations occurring in core histone genes were analyzed along with data on sarcoma subtype, tumor mutation burden, and specific amino acid substitutions.

Results: We identified 44 sarcoma samples harboring at least one somatic histone missense mutation (Table 1). Within the histone-mutated dataset, bone sarcomas and undifferentiated pleomorphic sarcoma (UPS) accounted for nearly half of the represented subtypes, with 16 % of the mutations observed in Ewing sarcoma, 9 % in osteosarcoma, and 23 % in UPS. Mutations at H3G34 recurred six times including in two osteosarcomas, two UPS, and one unspecified subtype. Notably, one UPS sample harbored two different missense mutations in the HIST1H3B gene at the same residue (H3.1 G34D/S) likely indicating that both alleles were affected. An osteosarcoma harboring an H3G33 mutation was also observed, suggesting that the glycine adjacent to the previously described osteosarcoma associated H3G34 may be similarly important. A recurrent histone H3Y99C mutation was observed in a UPS and an embryonal rhabdomyosarcoma.

Notably, 18 of 44 samples had a tumor mutation burden (TMB) of < 2 mutations/Mb, thereby increasing the possibility of a functional role for the histone mutation given relatively few other mutations. Interestingly, in one osteosarcoma the only mutation detected on the MSK-IMPACT panel was H3R53G. Two of the low TMB context mutations occurred in desmoplastic small round cell tumors and an additional two occurred in Ewing sarcomas. This raises the possibly that histone mutations could potentiate the activity of the EWS fusions classically seen in these tumors.

Finally, given that the known oncohistone mutations occur in the H3 N-terminal tail, we looked for additional histone mutations that could affect the reading, writing, or erasing of regulatory PTMs in this region. We identified four instances of N-terminal domain arginine mutations at H3 R2, R8, or R26, which are just N-terminal to lysines that harbor key regulatory PTMs and are themselves post-translationally modified. Thus, mutations at these positions could affect important PTM-dependent chromatin functions.

Conclusion: A comprehensive analysis of sarcoma genomic sequencing data including fusion-associated and genomically complex sarcomas reveals recurrent oncohistone mutations previously found in bone tumors and also mutations at residues not previously reported to be mutated in sarcomas. It will be important to determine the mechanism of these mutations in driving sarcomagenesis and if these mutations modulate one or more histone-regulated processes including cell fate determination.

Table 1. Histone mutation data.

Gene	Protein Change*	Cancer Type	Study	Mutations/Mb
HIST1H3H	A115T	Angiosarcoma	MSK-IMPACT Clinical Sequencing Cohort (MSKCC)	9.24
HIST1H3B	R27P	Dedifferentiated Liposarcoma	Sarcoma (TCGA, PanCancer Atlas)	1.10
HIIST1H3H	A76G	Dedifferentiated Liposarcoma	Sarcoma (TCGA, PanCancer Atlas)	1.83
HIST1H3H	Q77L	Desmoplastic Small-Round-Cell Tumor	MSK-IMPACT Clinical Sequencing Cohort (MSKCC)	1.68
HIST1H3F	R3C	Desmoplastic Small-Round-Cell Tumor	MSK-IMPACT Clinical Sequencing Cohort (MSKCC)	1.68
HIST1H3F	Y100C	Embryonal Rhabdomyosarcoma	MSK-IMPACT Clinical Sequencing Cohort (MSKCC)	5.88
HIST1H3D	R9P	Ewing Sarcoma	Ewing Sarcoma (Institut Cuire, Cancer Discov 2014)	0.40
HIST1H4D	G12C	Ewing Sarcoma	Ewing Sarcoma (Institut Cuire, Cancer Discov 2014)	0.60
HIST1H2BF	V42L	Ewing Sarcoma	Pediatric Ewing Sarcoma (DFCI, Cancer Discov 2014)	2.63
HIST1H2BA	A83D	Ewing Sarcoma	Pediatric Ewing Sarcoma (DFCI, Cancer Discov 2014)	3.07
HIST1H2BA	I71T	Ewing Sarcoma	Pediatric Ewing Sarcoma (DFCI, Cancer Discov 2014)	3.10
HIST1H3H	A89V	Ewing Sarcoma	MSK-IMPACT Clinical Sequencing Cohort (MSKCC)	3.36
HIST1H2AJ	R12C	Ewing Sarcoma	Pediatric Ewing Sarcoma (DFCI, Cancer Discov 2014)	8.27
HIST1H3C	E51K	Gastrointestinal Stromal Tumor	MSK-IMPACT Clinical Sequencing Cohort (MSKCC)	1.68
HIST1H3C	F68L	Gastrointestinal Stromal Tumor	MSK-IMPACT Clinical Sequencing Cohort (MSKCC)	2.52
H3F3A	R9C	Gastrointestinal Stromal Tumor	MSK-IMPACT Clinical Sequencing Cohort (MSKCC)	5.66
HIST1H4C	R68P	Leiomyosarcoma	Sarcoma (TCGA, PanCancer Atlas)	0.83
HIST1H2AG	G3R	Leiomyosarcoma	Sarcoma (TCGA, PanCancer Atlas)	1.93
HIST1H3C	A136G	Malignant Peripheral Nerve Sheath Tumor	MSK-IMPACT Clinical Sequencing Cohort (MSKCC)	2.52
HIST1H4C	A39S	Myxofibrosarcoma	Sarcoma (TCGA, PanCancer Atlas)	18.93
HIST1H3B	E134K	Myxofibrosarcoma	Sarcoma (TCGA, PanCancer Atlas)	25.07
H2AFJ	R4L	Myxofibrosarcoma	Sarcoma (TCGA, PanCancer Atlas)	38.73
HIST1H3G	G34V	Osteoblastic Osteosarcoma	MSK-IMPACT Clinical Sequencing Cohort (MSKCC)	3.36
HIST1H3G	R54G	Osteosarcoma	MSK-IMPACT Clinical Sequencing Cohort (MSKCC)	0.94
H3F3A	G35W	Osteosarcoma	MSK-IMPACT Clinical Sequencing Cohort (MSKCC)	3.36
H3F3A	G35V	Osteosarcoma	MSK-IMPACT Clinical Sequencing Cohort (MSKCC)	3.36
H3F3A	G35W	Sarcoma, NOS	MSK-IMPACT Clinical Sequencing Cohort (MSKCC)	1.89
HIST1H3D	I75S	Sarcoma, NOS	MSK-IMPACT Clinical Sequencing Cohort (MSKCC)	1.89
HIST1H2BD	D52N	Sarcoma, NOS	MSK-IMPACT Clinical Sequencing Cohort (MSKCC)	4.72
HIST1H3B	R135K	Sarcoma, NOS	MSK-IMPACT Clinical Sequencing Cohort (MSKCC)	43.70
HIST1H3J	R84C	Solitary Fibrous Tumor/Hemangiopericytoma	MSK-IMPACT Clinical Sequencing Cohort (MSKCC)	2.52
H3F3A	L61F	Spindle Cell Rhabdomyosarcoma	MSK-IMPACT Clinical Sequencing Cohort (MSKCC)	13.21
HIST1H3C	R54C	Synovial Sarcoma	Sarcoma (TCGA, PanCancer Atlas)	0.93
H3F3B	G35V	Undifferentiated Pleomorphic Sarcoma/Malignant Fibrous Histiocytoma/High-Grade Spindle Cell Sarcoma	Sarcoma (TCGA, PanCancer Atlas)	0.57
H3F3B	H40R	Undifferentiated Pleomorphic Sarcoma/Malignant Fibrous Histiocytoma/High-Grade Spindle Cell Sarcoma	Sarcoma (TCGA, PanCancer Atlas)	0.57
HIST1H2AC	A13T	Undifferentiated Pleomorphic Sarcoma/Malignant Fibrous Histiocytoma/High-Grade Spindle Cell Sarcoma	Sarcoma (TCGA, PanCancer Atlas)	1.27
HIST2H2BE	E94D	Undifferentiated Pleomorphic Sarcoma/Malignant Fibrous Histiocytoma/High-Grade Spindle Cell Sarcoma	Sarcoma (TCGA, PanCancer Atlas)	1.63
HIST1H4J	R4C	Undifferentiated Pleomorphic Sarcoma/Malignant Fibrous Histiocytoma/High-Grade Spindle Cell Sarcoma	Sarcoma (TCGA, PanCancer Atlas)	2.47
HIST1H3G	Y100C	Undifferentiated Pleomorphic Sarcoma/Malignant Fibrous Histiocytoma/High-Grade Spindle Cell Sarcoma	MSK-IMPACT Clinical Sequencing Cohort (MSKCC)	14.15
HIST1H3B	G35D	Undifferentiated Pleomorphic Sarcoma/Malignant Fibrous Histiocytoma/High-Grade Spindle Cell Sarcoma	Sarcoma (TCGA, PanCancer Atlas)	18.63
HIST1H3B	G35S	Undifferentiated Pleomorphic Sarcoma/Malignant Fibrous Histiocytoma/High-Grade Spindle Cell Sarcoma	Sarcoma (TCGA, PanCancer Atlas)	18.63
HIST1H3A	T33I	Undifferentiated Pleomorphic Sarcoma/Malignant Fibrous Histiocytoma/High-Grade Spindle Cell Sarcoma	MSK-IMPACT Clinical Sequencing Cohort (MSKCC)	23.53
HIST1H3B	A25V	Undifferentiated Pleomorphic Sarcoma/Malignant Fibrous Histiocytoma/High-Grade Spindle Cell Sarcoma	MSK-IMPACT Clinical Sequencing Cohort (MSKCC)	50.00
HIST1H3D	S58L	Uterine Leiomyosarcoma	MSK-IMPACT Clinical Sequencing Cohort (MSKCC)	1.89

*residue count includes the initiator methionine.

Poster 014 3042534

DEVELOPMENT OF A PLASMA MICRORNA BIOMARKER FOR PEDIATRIC OSTEOSARCOMA

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Objective: Osteosarcoma (OS) is the most common bone cancer in children and young adults. Despite decades of chemotherapy intensification and improved surgical techniques, the 5-year overall survival remains stagnant at 65-70%. Currently, there are no specific non-invasive biomarkers that are routinely used for prognosis, to evaluate disease response, or to monitor for relapse after therapy.

MicroRNAs (miRNAs) are stable, small non-coding RNA molecules that are conserved across multiple species and are post-transcriptional regulators of protein expression implicated in regulating physiologic and pathologic processes, including cancer. They are ideal candidates for plasma biomarker development due to their stability in plasma, ease of isolation and detection, and the unique expression patterns associated with disease states. For these reasons, we hypothesized that plasma miRNAs could be utilized as noninvasive biomarkers for the presence of OS and tumor responsiveness to therapy.

Methods: We used plasma from a genetically engineered mouse model of OS to screen 752 murine miRNAs using qPCR and identified and validated four candidate miRNAs that can be used to detect disease and monitor response to therapy in both immunodeficient and immunocompetent animal models. The candidate miRNAs were further analyzed in independent training (n=70) and validation (n=190) sets of human plasma samples by qPCR. Statistical analysis was performed utilizing the $2^{-\Delta\Delta Ct}$ method and significance was defined as a p-value <0.05 for control versus disease group analysis. Receiver operator characteristic curve (ROC) analysis was performed on the training samples and optimal cutpoints of the ΔCt were determined with the Youden index. Cutpoints were evaluated for specificity and sensitivity in the validation set using qPCR.

Results: The four candidate miRNAs identified in the animal model were miR-205-5p, miR-214-3p, miR-335-5p, and miR-574-3p. In the human validation set, mir-205-5p was decreased 2.38 fold, whereas miR-574-3p and miR-214-3p were increased 6.89 and 1.53 fold in 190 plasma samples. The validation set was underpowered to detect a statistically significant difference in miR-335-5p. Post-hoc analysis of miR-214-3p in the training set showed significant correlation with metastatic disease and preliminary results in the training set indicate that it can be used as a prognostic marker for metastatic OS patients (Fig. 1). Survival data has not been released to confirm this finding in the validation set. Serial plasma analysis of OS patients treated at our institution show the potential for utilizing the miRNA signatures as a biomarker of chemotherapeutic responsiveness in real-time in humans (Fig 2).

Conclusion: To our knowledge, this is the most comprehensive development of a plasma miRNA biomarker in OS. Our study has several strengths that include utilizing a novel mouse model for candidate miRNA discovery, identifying and using endogenous miRNAs for the relative quantification analyses, evaluating the specificity and sensitivity in separate training and validation human sets, and using the plasma miRNA biomarker to assess therapeutic responsiveness in both animals and patients during tumor directed therapy. Ongoing studies are being conducted at our institution to evaluate its utility as a screening measure for disease relapse after therapy completion. As per guidelines for biomarker development, the next step will be to prospectively evaluate the miRNA signature on a clinical trial.

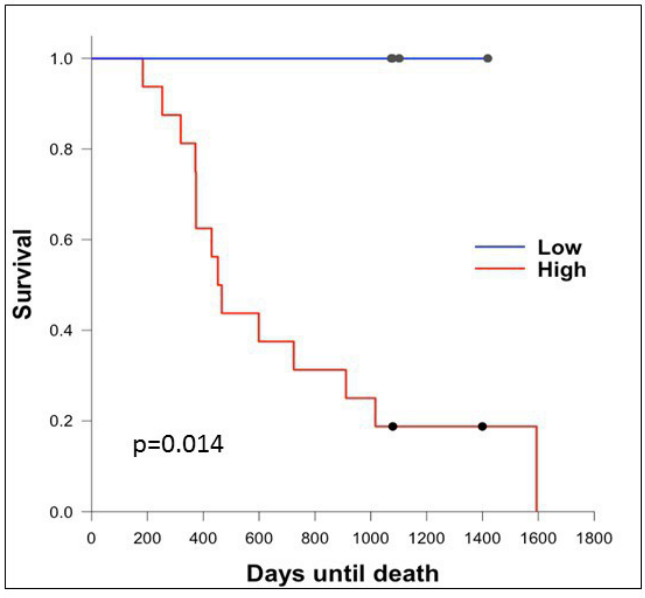

Fig 1. Plasma miR-214-3p levels in metastatic OS patients at diagnosis. Metastatic patients with low levels of plasma miR-214-3p have significantly better outcomes than patients with high levels at diagnosis.

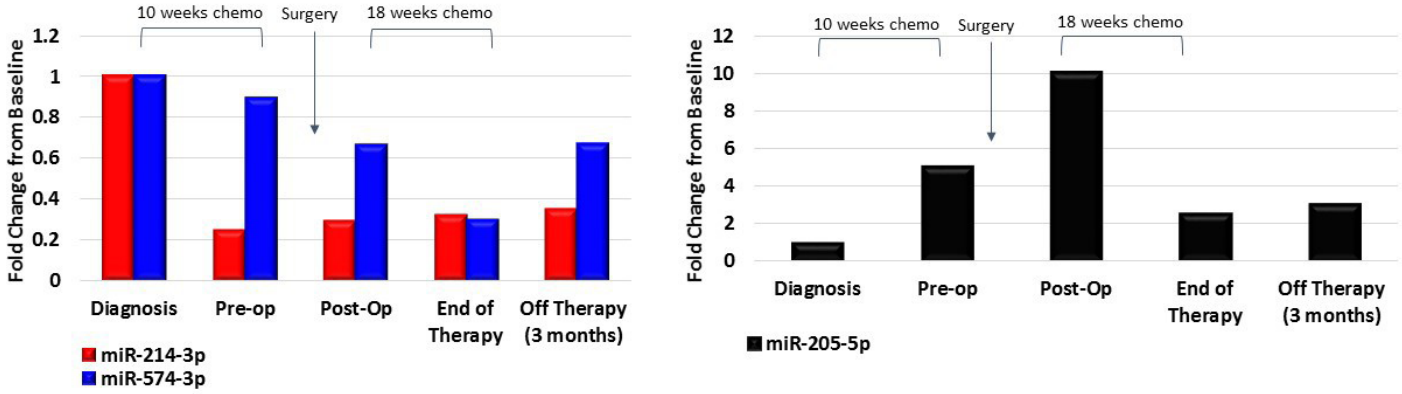

Fig 2. Serial plasma miRNA levels in a patient during and after tumor directed therapy. Patient had localized osteosarcoma with greater than 90% tumor necrosis. miR-214-3p (red) and miR-573-3p (blue) were decreased from baseline during therapy and at 3 months off of therapy while in remission, whereas miR-205-5p (black) was increased from baseline.

Poster 015 3042930

SHIFTING THE PARADIGM IN PRECLINICAL CANCER MODELING: A MOUSE-DOG-HUMAN PERSONALIZED MEDICINE PIPELINE TO IDENTIFY NOVEL THERAPEUTICS FOR OSTEOSARCOMA

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Objective: While the overall incidence of osteosarcoma (OS), in the human population is low, less than 1,000 new diagnoses each year, it is a disproportionately lethal cancer with few improvements in therapies since the advent of multimodal chemotherapy. Given the low prevalence of disease in humans, pet dogs provide a unique opportunity to serve as an adjunct to human patients. Canine OS is significantly more prevalent in the dog population with over 50,000 new diagnoses per year and similarities between the two species have been well established. We aimed to validate a mouse-dog-human (MDH) personalized medicine pipeline that utilizes comparative oncology to identify novel therapies for potential clinical application.

Methods: We generated one canine and one human osteosarcoma patient derived xenograft mouse model and cell line, D418X and 17-3X, respectively. Cell lines were generated by serial cloning of tumor cells until PCR analysis demonstrated purely dog or human cells. To identify novel therapeutic candidates for osteosarcoma, we performed a pilot drug screen of 119 FDA approved cancer therapeutics in five human (17-3X, 143B, U2OS, MG63, SA-OS) and four canine (D418X, D17, Moresco, Abrams) OS cell lines. To identify additional candidate drugs for our newly developed PDX cell lines, 17-3X and D418X, we performed an expanded drug screen using the NIH Bioactive 2,100 compound assay. The top drugs identified from the drug screens, bortezomib (proteasome inhibitor), verdinexor (CRM1 inhibitor) and alvespimycin (HSP inhibitor), were validated *in vivo*. Eight to 10-week-old SCID/beige mice were injected subcutaneously with 150 ul of homogenized PDX tissue-PBS suspensions at 150 mg/ml concentration. When the tumor volumes reached 100-150 mm^3, mice were randomized (n=5 per group) and treated with 100 ul of 5%DMSO, 1 mg/kg bortezomib (i.p), 25 mg/kg alvespimycin (i.p) and 5 mg/kg verdinexor (i.p) twice a week.

Results: In order to validate the utility of studying both species, we performed linear regression analysis of the 119 drug screen data between the human and canine OS cell lines and found a high positive correlation with R^2 value of 0.891. Hierarchical clustering of percent killing values from the screen showed indistinguishable results from both species and identified proteasome inhibitors as top drug candidates for all OS cell lines alongside standard of care therapies. An expanded drug screen with the newly developed D418X and 17-3X PDX cell lines identified proteasome inhibitors and other novel drug candidates such as CRM1 and HSP inhibitors. Verdinexor was found to significantly inhibit tumor growth ($p<0.05$) in both human and canine PDX mice compared to control tumors treated with DMSO. Though bortezomib conferred *in vitro* sensitivity across both human and canine OS cell lines, *in vivo*, bortezomib significantly reduced tumor growth ($p<0.05$) in D418X mice but not 17-3X mice. Alvespimycin, a HSP inhibitor, did not show *in vivo* efficacy in either species, highlighting the need for *in vivo* validation following *in vitro* drug screens.

Conclusion: Through the study of human and canine OS, our cross-species MDH pipeline has identified a targeted agent for OS, verdinexor. Our platform enables us to study disease in two species that receive similar clinical management and treatment. On the individual level, this pipeline provides the patient and the clinician with unique information about tumor biology and response to novel therapeutics; however, on a population level, this cross-species approach could make significant contributions to discovering novel standard of care therapies.

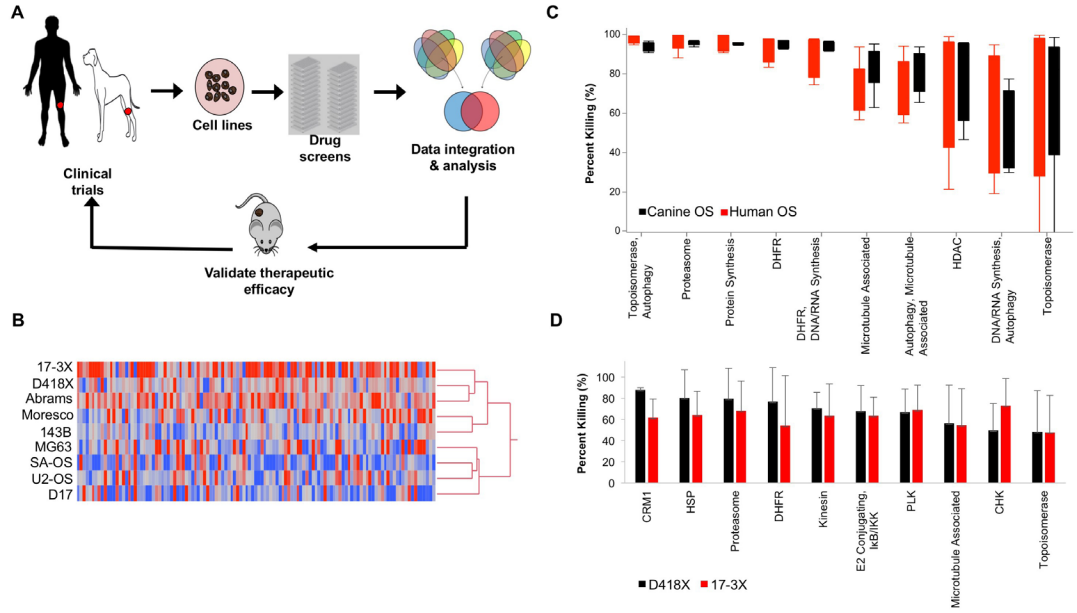

Figure 1: Our mouse-dog-human (MDH) personalized medicine pipeline demonstrated that canine and human OS cell lines perform similarly in cancer therapeutic drug screens, and identified novel therapeutic targets for osteosarcoma in both species. A. Schematic demonstrating the components of our mouse-dog-human personalized medicine pipeline B. Cluster analysis for percent killing in drug screens showed that canine and human OS cell lines are undistinguishable with no distinct clusters being identified. C. Top drug targets that are efficacious in four canine and five human OS cell lines include standard of care therapies, such as doxorubicin (topoisomerase, autophagy) along with novel drug candidates for OS, such as botezomib (proteasome inhibitor). D. Expanded drug screening with a 2,100 bioactive compound assay for the newly developed human (17-3x) and canine PDX (D418) cell line identified additional novel drug targets, HSP inhibitors and CRM1 inhibitors.

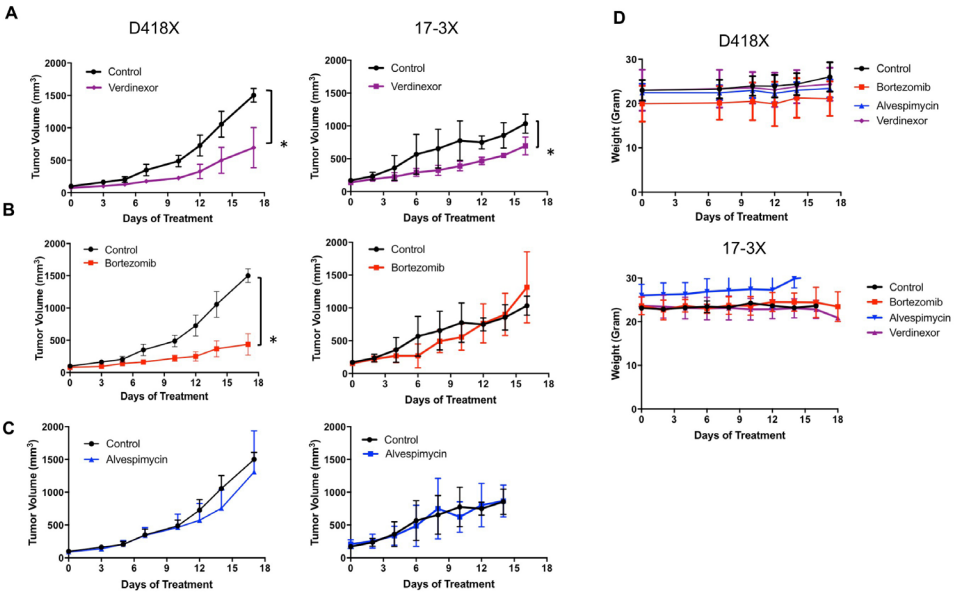

Figure 2. We have identified a novel drug for OS, targeted agent, verdinexor, based in vitro and in vivo efficacy in both human and canine OS. A. Administration of verdinexor caused significant tumor growth inhibition compared to control ($p<0.05$) in PDX mouse models of OS from both species. B. Though both D418X and 17-3x were were sensitive to bortezomib in vitro, only D418 showed sensitivity to bortezomib in vivo ($p<0.05$). C. Neither D418X or 17-3X showed in vivo sensitivity to alvespimycin with no difference in treatment and control tumors. D. In both PDX mouse models, there was no significant change in weight between mice treated with control or drug. Animals (n=5 per group) were treated with control 100 ul (i.p) of 5%DMSO, 1mg/kg of bortezomib (i.p), 5 mg/kg of verdinexor (i.p), 25 mg/kg alvespimycin (i.p).

Poster 016 3025705

XENOSARC: PATIENT-DERIVED XENOGRAFT (PDX) MODELS OF SOFT TISSUE SARCOMA (STS) – AND UPDATE ON A PRECLINICAL PLATFORM FOR EARLY DRUG TESTING

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Objective: STS constitutes a rare family of mesenchymal tumors with more than 70 subtypes described. The limited treatment options available for advanced STS underline the need for reliable preclinical models to test novel therapeutic strategies.

Methods: A panel of PDX models was established by subcutaneous implantation of fresh tumor specimens in immunodeficient, athymic nude NMRI mice. Once tumor growth was observed, pieces of tumor were re-transplanted to next generations of animals. At each passage tumor fragments were collected for detailed characterization. A model was considered established after observing stable histological and molecular features for at least two passages.

Results: Between 09/2011 and 11/2017, 228 STS samples from 203 consenting patients treated at the University Hospitals Leuven, Belgium, have been transplanted. Untill now 33 stable PDX models have been established, maintaining the histopathological and molecular features of the original tumor. Detailed clinical information about a donor patient, including sensitivity to given therapy, is linked to every model. The higher engraftment rate was observed in samples collected from patients who developed metastasis throughout the course of disease (38% *vs*. 23%, $p<0.05$). Moreover, patients whose tumor successfully engrafted had significantly poorer overall survival (OS) than those whose tumor did not grow in mice (median OS 83 *vs*. 259 months; $p<0.05$).

XenoSarc platform includes models of gastrointestinal stromal tumor (6 models), myxofibrosarcoma (6), leiomyosarcoma (5), dedifferentiated liposarcoma (4), malignant peripheral nerve sheath tumor (2), synovial sarcoma (1), pulmonary intimal sarcoma (1), CIC-DUX4 fusion-positive round cell sarcoma (1), epithelioid haemangioendothelioma (1), mesenchymal chondrosarcoma (1), pleomorphic rhabdomyosarcoma (1), telangiectatic extraskeletal osteosarcoma (1), and high-grade undifferentiated pleomorphic sarcoma (3). These models are well-characterized, with detailed data on copy number changes and expression profile. In addition we have constructed tissue microarray (TMA), which can be used for target identification. Some of these models have already been successfully used for *in vivo* testing of novel agents, including both targeted and cytotoxic (pro-)drugs, and results served as a rationale for several prospective clinical trials. In addition, 17 other xenografts are still in early stages of engraftment, not yet fulfilling our criteria of an “established model”.

Conclusion: Our XenoSarc platform contains a number of well-annotated models, characterized by stable histological and molecular features. This platform is a reliable tool for the evaluation of new anticancer treatments for STS and for studying the biology of these rare diseases. The platform is made available to collaborators from academia and industry.

Poster 017 3029268

BMP-2 SIGNALLING INFLUENCES TUMOUR BIOLOGY IN PRE-CLINICAL MODELS OF OSTEOSARCOMA

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Objective: Impaired bone healing biology secondary to soft tissue deficits and chemotherapy contribute to non-union, fracture and infection following limb salvage surgery in Osteosarcoma patients. Approved bone healing augments such as recombinant human bone morphogenetic protein-2 (rhBMP-2) have great potential to improve osteosynthesis and mitigate these complications. rhBMP-2 use in sarcoma surgery is limited, however, due to concerns of pro-oncogenic signalling within the tumour resection bed. To the contrary, recent pre-clinical studies demonstrate that BMP-2 may induce Osteosarcoma differentiation and limit tumour growth. Further pre-clinical studies evaluating the oncologic influences of BMP-2 in Osteosarcoma are needed. The objectives of this study are to evaluate how BMP-2 signalling affects Osteosarcoma cell proliferation and metastasis both in vitro and within an active tumor bed.

Methods: An intratibial xenograft murine model of Osteosarcoma was utilized. A well differentiated, low grade Osteosarcoma cell line (SaOS-2) and a poorly differentiated, high-grade Osteosarcoma cell line (143b) were assessed for proliferative capacity and invasion *in vitro* and *in vivo*. 143b and SaOS-2 cells were engineered to over-express BMP-2 to facilitate both *in vitro* and *in vivo* assessment of elevated BMP-2 signalling. *In vitro* proliferation was assessed in the presence and absence of osteogenic differentiation media (ODM); invasion was assessed using a scratch wound healing assay. Osteosarcoma cells were injected into the intramedullary proximal tibia of immunocompromised (NOD-SCID) mice and local tumour growth and metastases were assessed using weekly bioluminescence imaging (BLI) and tumour volume measurements for 4-6 weeks. At the experimental end point we assessed radiographic tumour burden using *ex-vivo* micro-CT, as well as tibial and pulmonary gross and histologic pathology.

Results: Osteosarcoma developed in 100% (13/13) of mice injected with 143b cells, and 82% (18/22) of mice injected with SaOS-2 cells. Osteosarcoma was confirmed on histology. BMP-2 over-expression in 143b cells resulted in increased cellular proliferation *in vitro* ($p = 0.014$); an effect that was lost when grown in ODM ($p = 0.65$) (Figure 1A-B). 143b cells over-expressing BMP-2 demonstrated faster *in vitro* wound healing ($p = 0.03$) (Figure 1C). Furthermore, in 143b tumours, BMP-2 over-expression significantly increased tumour volume ($p = 0.001$) and enhanced osteolysis detected on micro-CT, but did not affect rates of lung metastasis (67% vs. 71%, BMP-2 vs. Control) (Figure 1D-F). BMP-2 over-expression reduced SaOS-2 in vitro proliferation when grown in ODM ($p < 0.001$), and had no effect on *in vitro* wound healing ($p = 0.28$) (Figure 2A-C). BMP-2 over-expression also reduced *in vivo* SaOS-2 tumour burden at 6 weeks as assessed by photon counts ($p < 0.0001$) (Figure 2D), and decreased tumour-associated matrix deposition as assessed by trabecular thickness ($p = 0.02$) (Figure 2E-F), but did not affect rates of lung metastasis (0% vs. 0%).

Conclusion: Using intratibial murine models of Osteosarcoma we have assessed the impact of elevated BMP-2 signaling on an active tumour bed. Our results indicate BMP-2 signalling incites a proliferative effect on poorly differentiated 143b Osteosarcoma cells, but conditionally reduces proliferative capacity in a well-differentiated Osteosarcoma cell line (SaOS-2). This dichotomous effect may be partially mediated by the osteoblastic differentiation of Osteosarcoma tumours, and the inherent ability for Osteosarcoma cells to undergo BMP-2 mediated terminal differentiation (Figure 3). Importantly, these results do not support the clinical application of BMP-2 in Osteosarcoma limb salvage surgery due to the potential for stimulating growth of poorly differentiated Osteosarcoma cells within the tumour bed. rhBMP-2 is a pro-inflammatory growth factor; therefore, additional studies assessing the effects of BMP-2 in an immune-competent mouse model are ongoing.

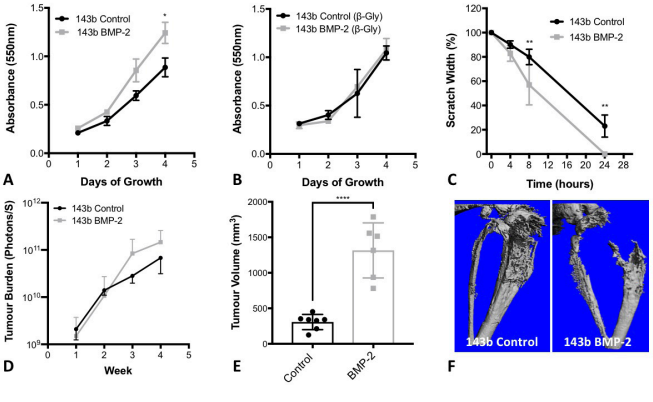

Figure 1. BMP-2 signalling promotes 143b tumour burden. BMP-2 signalling had a proliferative effect on 143b cells when grown in regular media (A), which was no longer seen when grown in the presence of beta-glycerophosphate (B). BMP-2 signalling promoted *in vitro* wound healing (C). BMP-2 signaling stimulated local tumour growth and osteolysis as assessed by bioluminescence (D), tumour volume (E) and micro-CT (F)

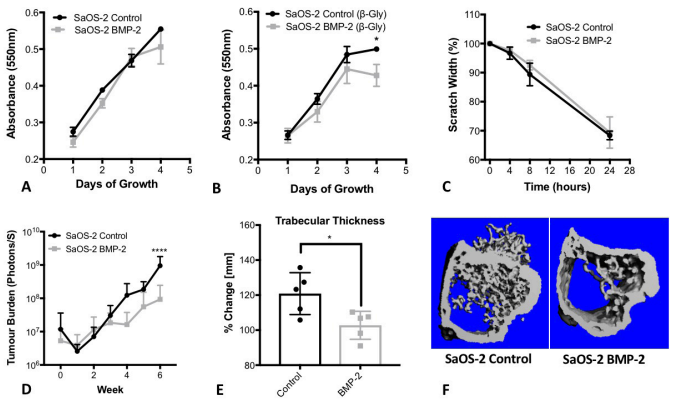

Figure 2. BMP-2 signalling conditionally limits SaOS-2 growth, but not invasion. BMP-2 signalling had no effect on proliferation when grown in regular media (A), but impeded growth in the presence of beta-glycerophosphate (B). BMP-2 had no effect on *in vitro* wound healing (C). BMP-2 signaling limited tumour proliferation at 6 weeks as assessed by bioluminescence (D), and trabecular thickness (E), as determined from micro-CT (F).

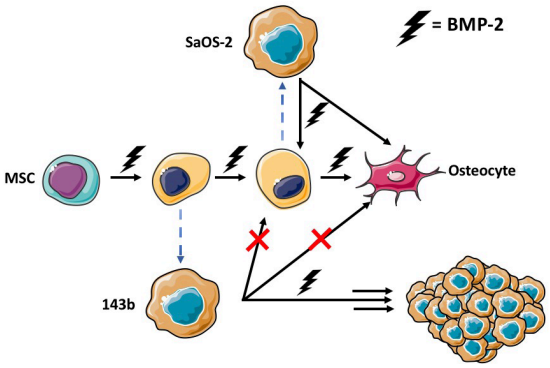

Figure 3. Modelling the putative effects of BMP-2 signalling in Osteosarcoma. BMP-2 stimulates osteogenic differentiation, and Osteosarcoma cells are derived from the osteoblastic lineage. 143b cells are poorly differentiated and may be blocked from BMP-2 induced differentiation; SaOS-2 cells are well differentiated and may be stimulated to further differentiate by BMP-2. *MSC = Mesenchymal Stem Cell.*
Adapted from Luo X, Chen J, Song W-X, et al. Osteogenic BMPs promote tumor growth of human osteosarcomas that harbor differentiation defects. Lab Invest. 2008;88(12):1264-1277. doi:10.1038/labinvest.2008.98. Cartoon images from Servier Medical Art (licenced under a Creative Commons Attribution 3.0 Unported License).

Poster 018 3036616

PHENOTYPIC CHARACTERIZATION OF IGFR2R KNOCKOUT IN HUMAN OSTEOSARCOMA CELLS

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Objective: Osteosarcoma is the most common non-hematologic primary bone malignancy. The overall 5-year survival rate of osteosarcoma remains approximately 70%, and the lack of significant changes to this rate over the past 30 years supports the need for additional treatment modalities. Aberrant growth receptor signaling has been implicated in the development of many cancers. The cation-independent mannose-6-phosphate/insulin-like growth factor-2 receptor (IGF2R) is overexpressed in osteosarcoma cell lines. To date, IGF2R overexpression has been leveraged to demonstrate the feasibility of a rhenium-188(^{188}Re)-labeled IGF2R-specific monoclonal antibody in inhibiting osteosarcoma xenograft tumors. However, there is limited understanding of the endogenous role of IGF2R overexpression in osteosarcoma. As IGF2R is considered to be a decoy receptor for insulin-growth factor I and in this context a tumor suppressor gene, its paradoxical overexpression in osteosarcoma suggests alternative functions.

We sought to determine the functional role of IGF2R in osteosarcoma. To this end, we investigated the phenotypic consequences of loss of IGF2R expression in a panel of human osteosarcoma cell lines.

Methods: To determine whether IGF2R overexpression is necessary and/or sufficient for osteosarcoma cell survival and growth, we first selected the high-IGF2R expressing cell lines HOS, HOS-143B, U20S, and SaOS, as well as the patient-derived xenograft cell line M17. Derivative IGF2R-knockout cell lines were generated either by transient transfection or lentivirus-mediated delivery of a CRISPR/CAS9 and an IGF2R-specific sgRNA followed by clonal expansion of single cells and screening for presence of homozygous IGF2R knockout. Proliferation of control and IGF2R knockout osteosarcoma cell lines were assessed *in vitro* using standard viability assays with varying levels of serum. Differential responsiveness of IGF2R overexpression and knockout cell lines to standard chemotherapeutic agents (doxorubicin) were also assessed by viability assays. Alterations in cellular morphology according to the absence or presence of IGF2R were assessed by standard cell microscopy. Lastly, to determine whether natively overexpressed IGF2R is involved in downstream cellular signaling, we compared the activity of MTOR between control and knockout cell lines using Western blot analysis for various MTOR targets.

Results: High efficiency of IGF2R knockout was confirmed at the protein level in pools of CRISPR/sgRNA treated HOS, HOS-143B, U20S, SaOS, and M17 cell lines, suggesting that IGF2R is not required for osteosarcoma cell survival. Expansion of single cell clones consistently showed good efficiency of IGF2R mutation with subsequent loss of expression of IGF2R at the protein level. In U20S cells, loss of IGF2R expression resulted in decreased proliferation by approximately 50%, an effect that was potentiated in the absence of supplemental serum growth factors. There was no difference in susceptibility of U20S cells to doxorubicin according to IGF2R status. Clonally expanded cell lines exhibited different cell morphologies ranging from spindle-type to round, although this was not consistently linked with IGF2R expression status. A wide range of proliferation in isolated clones was also appreciated and will be evaluated in future studies. Lastly, downstream MTOR signaling appeared to change according to both levels of baseline IGF2R expression and at different concentrations of serum.

Conclusion: Decreased proliferation of IGF2R-knockout osteosarcoma cell lines compared to high-expressing parent cells suggests IGF2R may impact osteosarcoma cell growth and may, in fact, function as an oncogene. Expansion of our investigation of the phenotype of IGF2R knockout in additional osteosarcoma cell lines, as well continued evaluation of the molecular signaling events downstream of IGF2R represent the next steps in our study, and will provide better understanding of the basis for IGF2R overexpression in osteosarcoma.

Poster 019 3041727

THE ODC1/POLYAMINES/C-MYC AXIS PROMOTES OSTEOSARCOMA TUMORGENESIS BY REGULATING GLUTAMINOLYSIS

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Objective: Osteosarcoma (OS) is the most common primary malignant bone tumor in children and adolescents. ODC1, the first enzyme in polyamines metabolism, has emerged as an important target for cancer therapy and many studies have focused on the correlation with ODC1 and nutrient uptake, but no molecular connection to glutaminolysis has been reported. Here, we show that ODC1 promotes gultamine metabolism by activating c-myc pathways in human OS cells.

Methods: High-throughout liquid- and gas-chromathography-based mass spectrometry (LC/MS and GC/MS) for a global metabolic profiling/subtraction of four pairs of high/low metastatic OS cell lines. *In vivo* nuclear magnetic resonance (NMR)-based stable isotope tracer methodologies for probing OS metabolism. Gene knockdown and over-expression for exploring the consequense(s) and mechanism(s) of altered ODC1 gene expression.

Results: By comparing the identity and level of the metabolites between high/low metastatic cells, we found that polyamines pathway was differentiated activated. Moreover, ODC1 was up-regulated in high metastatic OS cell lines. The results from *in vivo* NMR indicated that ODC1 inhibitor DFMO treatment caused marked changes in glutamine metabolites. Mechanistically, we demonstrated that ODC1-induced glutaminolysis probably via polyamines pathway-dependent c-Myc upregulation. Genetic and pharmacologic inhibition of ODC1 suppressed cell growth *in vitro* and *in vivo*, and combination with CB-839, a GLS1 inhibitor, exerted synergistic cytotoxic effect on human OS cells.

Conclusion: Our data support that ODC1/polyamines/c-Myc signaling promotes glutaminolysis contributing to OS cell growth. Therefore, ODC1 may be a promising target to reverse malignant progression of OS.

Poster 020 3042199

THE TYPE OF NR4A3 FUSION PARTNER DICTATES AN AXON GUIDANCE SWITCH IN EXTRASKELETAL MYXOID CHONDROSARCOMAS

***Monica Brenca**[1]; Silvia Stacchiotti[2]; Kelly Fassetta[1]; Maurizio Polano[1]; Dominga Racanelli[1]; Milijana Janjusevic[1]; Marta Sbaraglia[3]; Sabrina Rossi[3]; Silvia Brich[2]; Gian Paolo Dagrada[2]; Chiara Colombo[2]; Chiara Castelli[2]; Alessandro Gronchi[2]; Annalisa Astolfi[5]; Valentina Indio[5]; Maria Abbondanza Pantaleo[5]; Piero Picci[4]; Paolo Casali[2]; Angelo P. Dei Tos[3]; Silvana Pilotti[2]; Roberta Maestro[1]*
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Objective: Extraskeletal myxoid chondrosarcoma (EMC) is a very rare soft tissue sarcoma with uncertain differentiation. A distinct genetic feature of this tumor is the translocation of the NR4A3 gene that fuses, in the majority of cases, with either EWSR1 or TAF15. Although recent reports associate the expression of TAF15-NR4A3 to aggressive forms of EMC, how the different types of NR4A3 chimera affect the tumoral phenotype is still largely undefined. To shed light on this issue we compared the transcriptional profile of EWSR1- NR4A3 positive and TAF15- NR4A3 positive EMCs.

Methods: Twelve EMC FFPE samples (7 EWSR1-NR4A3 and 5 TAF15-NR4A3) were retrieved from the pathology files of INT National Cancer Institute of Milan, Treviso General Hospital and Rizzoli Institute. NR4A3 rearrangement was confirmed by FISH.

H-tert immortalized, E1A and Ras transformed human primary fibroblasts (tBJ/ER) were engineered to ectopically express the NR4A3 and relative chimeras.
RNA-seq was performed on an Illumina Hiseq 1000 apparatus (ave 70e6 paired-end reads per sample). PCA, hierarchical clustering and functional annotations were performed with different tools.
Immunohistochemistry and qRT-PCR were used to validate differential expressions.

Results: TAF15-NR4A3 and EWSR1-NR4A3 displayed a distinct transcriptional profile. Functional annotation of differentially expressed genes indicated an over-representation of axon guidance molecules provided of oncogenic features and a reduced expression of axon cues with tumor suppressive activities in TAF15-NR4A3 vs EWSR1-NR4A3 variant. Intriguingly, the differential pattern observed in tumors was well recapitulated in cell lines engineered to express the two gene fusions.

Conclusion: This study indicates that the axon guidance pathway represents the major discriminant between TAF15-NR4A3 or EWSR1-NR4A3 positive EMCs. The finding that the ectopic expression in vitro of the two chimeras recapitulates the differential modulation of axonal cues observed in tumors, supports the notion that the type of fusion partner of NR4A3 promotes an axon guidance switch and dictates the biology of the two EMC variants.

Poster 021 3042292

THE MECHANISMS OF ZOLEDRONIC ACID-INDUCED AUTOPHAGY ON OSTEOSARCOMA CELLS

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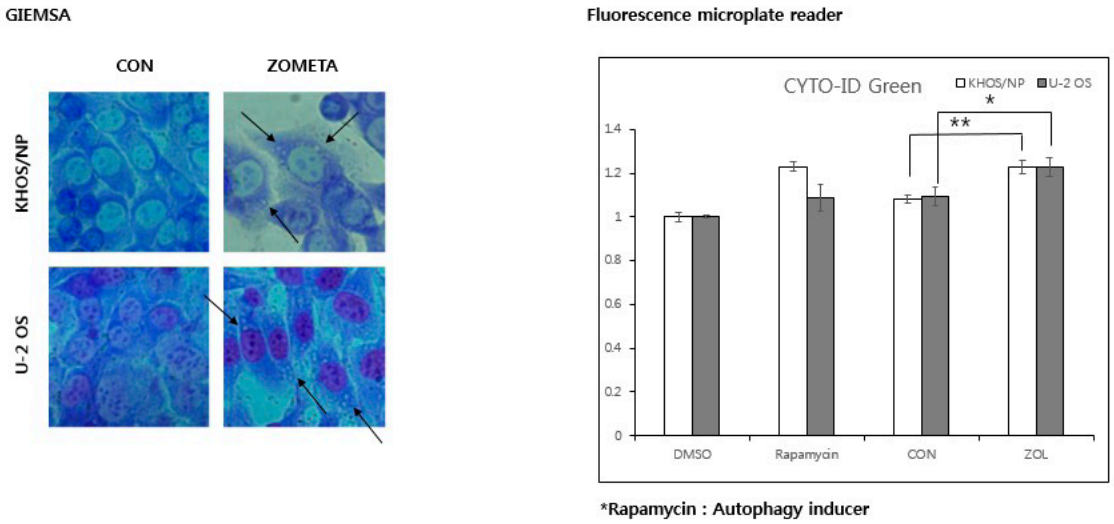
Objective: We have recently shown that the Zoledronic acid (ZOL), a third-generation nitrogen-containing bisphosphonate, inhibits growth, proliferation and colony formation, arrests the cell cycle and induces cleavage of PARP-1 in osteosarcoma cell lines. Here we report on the mechanism behind the anticancer properties of ZOL.

Methods: The cytotoxic effect of ZOL on osteosarcoma cells (KHOS and U2OS, patient primary cells) was investigated employing a panel of tests used for the detection of apoptosis and autophagy. Apoptosis and autophagy were defined by caspase activity, Annexin-V and acridine orange (AO) staining. Autophagy markers such as LC3B, Beclin, ATG5 and mammalian target of rapamycin (mTOR) pathway related proteins were assessed by western blotting and ELISA techniques.

Results: ZOL did activate caspases 3 and it alter the percentage of Annexin V positive stained cells. And accumulation of acidic vacuoles with distinct chromatin morphology and an increase in punctuate localization of green fluorescent protein-LC3B, and ZOL-induced changes in the expression of Beclin and ATG5 were all indicative of ZOL-induced autophagy.

Conclusion: We found inhibition of mTOR phosphorylation leading to suppression of the mTOR/p70S6K signaling pathway. Our findings provide the first evidence to show that ZOL triggers autophagy through the deactivation of mTOR/p70S6K signaling pathway.

Fig3. ZOL induces autophagy



*Rapamycin : Autophagy inducer

Fig3. ZOL induces autophagy

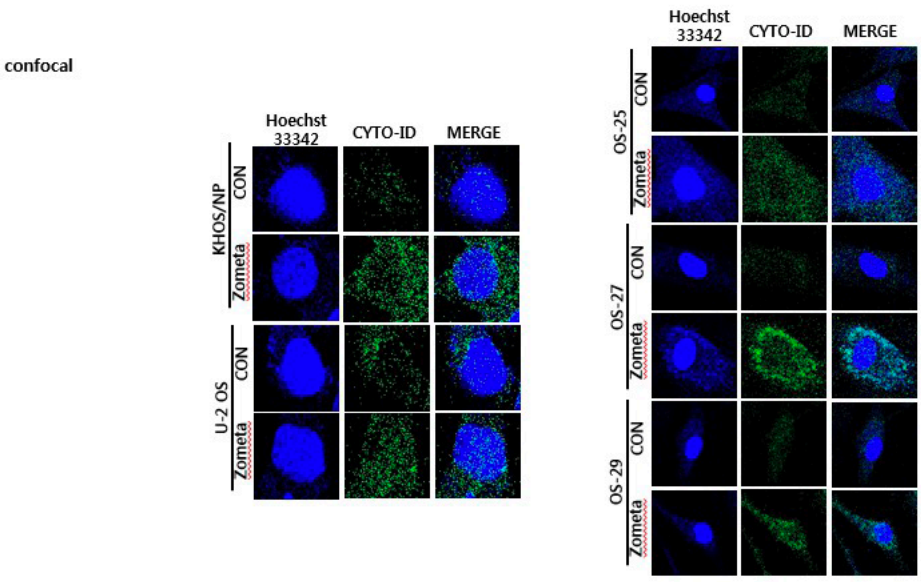
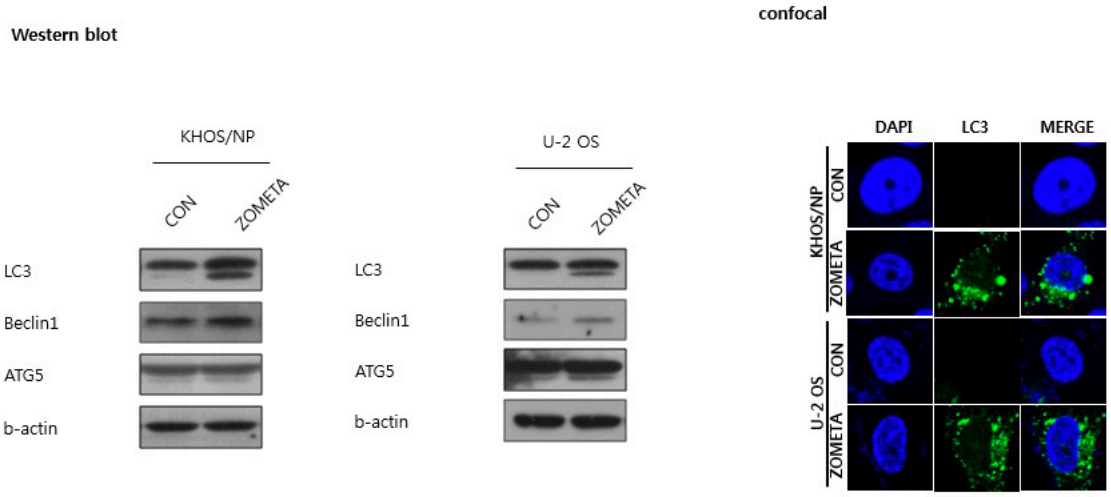


Fig3. ZOL induces autophagy



Poster 022 3042653

ATRX MUTATIONS INCREASE TUMORIGENICITY IN OSTEOSARCOMA

Suzanne Bartholf DeWitt[1]*; Jason Somarelli*[2]*; So Young Kim*[2]*; Vidya Seshadri*[2]*; Robert Floyd*[2]*; David Kerr*[2]*; Randall T. Kreulen*[2]*; Willa Chen*[2]*; Gireesh B. Reddy*[2]*; Sneha Rao*[2]*; Rachael Thomas*[3]*; Brian Brigman*[2]*; Matthew Breen*[3]*; Benjamin Alman*[2]*; William Eward*[2]

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Objective: 1) To determine the effect of *ATRX* mutations on OS tumor biology.
2) To investigate the underlying mechanisms of increased tumorigenicity in OS with *ATRX* mutations.

Methods: Human 143B OS cells were stably transduced with a non-silencing shRNA or one of two independent shRNA constructs for *ATRX* knockdown. The *ATRX* knockdowns were confirmed via qPCR, immunofluorescence, and western blotting. Control and *ATRX* shRNA knockdown cells were injected subcutaneously in SCID-beige mice in a Duke IACUC-approved study, and tumor growth rates were compared. In parallel, RNA-Seq was performed on these *ATRX* knockdown

cell lines, and all cell lines were assessed for ALT pathway activation following the methods described by Lau et al. (Nucleic Acids Research, 2013). CRISPR-Cas9 was used to knockout *ATRX* in the human MG63 osteosarcoma cell line, and the wild-type or knockout MG63 cell lines were screened with 2100 bioactive small molecule inhibitors for drugs to identify drugs for which ATRX loss of function led to increased drug efficacy.

Results: *ATRX* knockdown enhanced tumor growth and local invasion following xenograft injections. The whole transcriptomic profiling by RNA-Seq showed significant downregulation of extracellular matrix pathways, supporting a role for *ATRX* in matrix remodeling and invasion. The ALT pathway was not activated upon *ATRX* knockdown, suggesting that the increase in tumor growth was not due to activation of this method of telomere length maintenance. In the drug screen assay, *ATRX* loss significantly increased sensitivity to an integrin-inhibitor. We further validated this integrin-inhibitor sensitization upon *ATRX* loss using IC_{50} assays. Interestingly, integrins are known key interactors with extracellular matrix components.

Conclusion: Our results support the conclusion that decreased *ATRX* expression in OS is associated with more aggressive tumors exhibiting increased proliferation and invasion. Results from both RNA-Seq and the bioactive drug screen support altered extracellular matrix remodeling, which may suggest a change in invasive properties of OS cells with *ATRX* expression loss. In the future, we plan to use both *in vitro* and *in vivo* methods to further explore these mechanisms and test the integrin-inhibitor as a potential new therapeutic for OS tumors with loss of *ATRX* expression.

Fig. 1a: Stable shRNA-mediated knockdown and CRISPR knockout of *ATRX* expression:

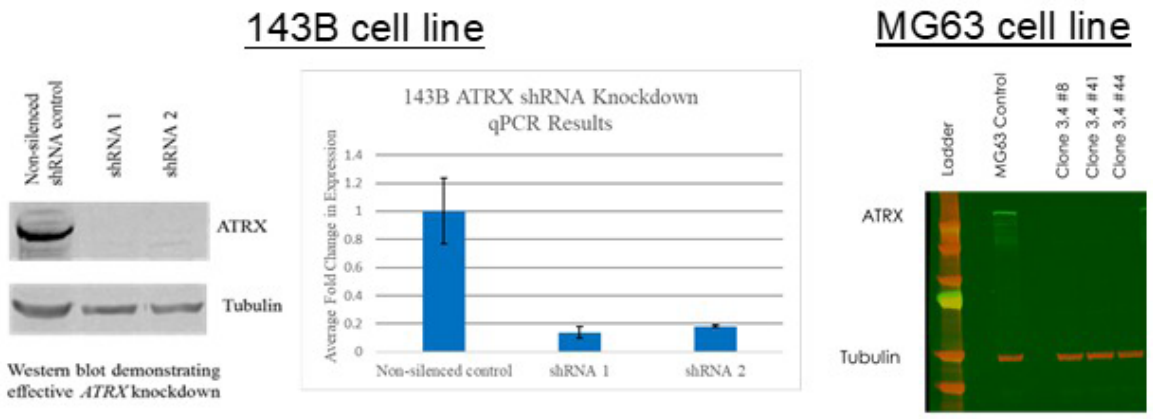


Fig. 1b: Loss of *ATRX* expression increased tumor growth in an ALT-independent manner

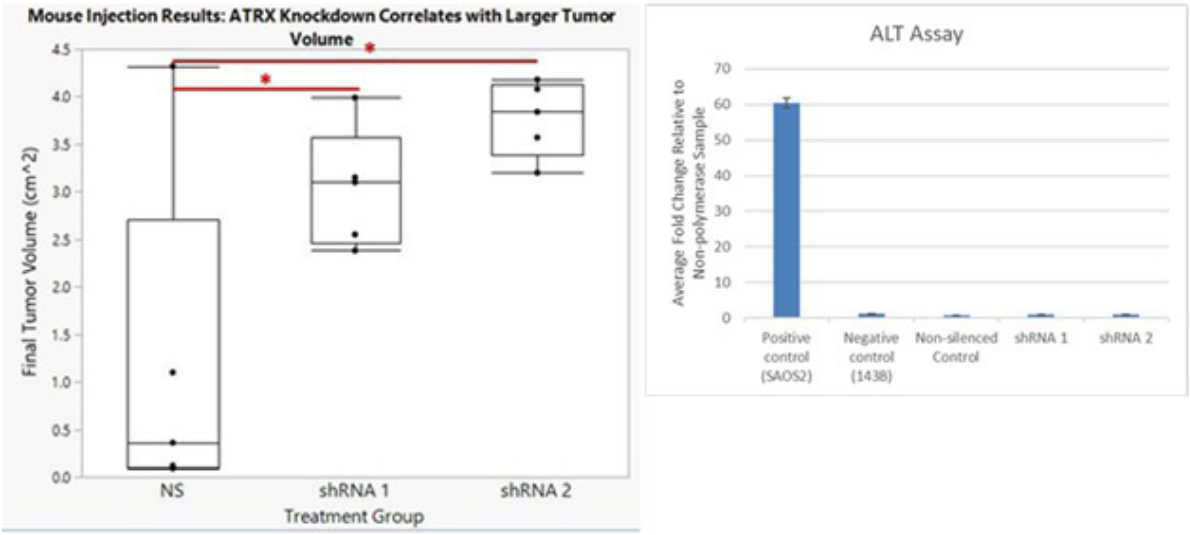


Fig. 2a: *ATRX* drives genes involved in extracellular matrix remodeling and deposition

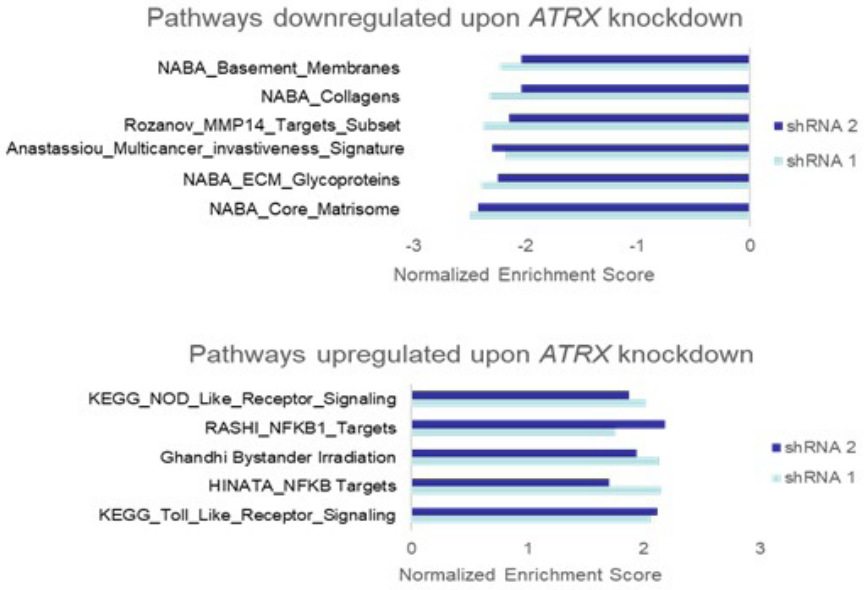
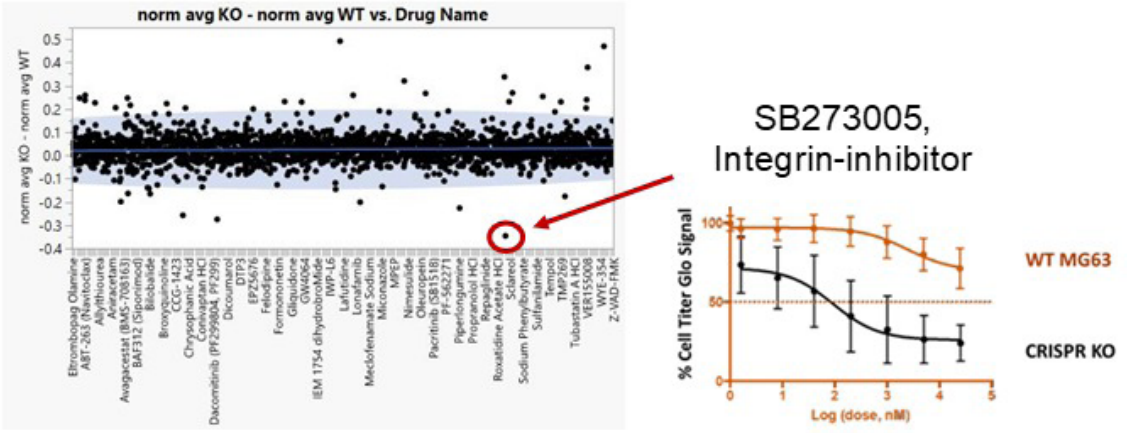


Fig. 2b: Drug screen finds *ATRX* loss sensitizes OS cells to integrin-inhibitor; confirmed with IC50 assays



Poster 023 3042613

DOXORUBICIN, GEMCITABINE, IFOSFAMIDE, AND THE EZH2 INHIBITOR EPZ-011989 IN EPITHELIOID SARCOMA: A COMPARISON OF DIFFERENT REGIMENS IN A PATIENT-DERIVED XENOGRAFT

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Objective: Epithelioid sarcoma (ES) is a rare soft tissue sarcoma with two variants, the proximal- and the distal-type. Retrospective data point to the activity of anthracycline- and gemcitabine-based regimens. EZH2 inhibitors are under evaluation in clinical trials. The differential activity of these agents is unknown and unlikely to be prospectively evaluated. We decided to comparatively assess some medical agents in a proximal-type INI1-deleted ES patient-derived xenograft (PDX). In addition to chemotherapeutic drugs, we assessed the activity of the EZH2 inhibitor EPZ-011989 based on the notion that INI1 loss impairs the function of the SWI/SNF chromatin-remodelling complex, leading to a dependence of tumor cells on the activity of EZH2.

Methods: The ES-1 PDX model was established by subcutaneously xenotransplanting tumor fragments obtained from a patient with a primary, proximal-type, INI1 deleted ES of the forearm into immunodeficient (SCID) mice. After tumor propagation in SCID mice for three consecutive passages, the PDX was considered established. Mice were randomized to receive doxorubicin (D) and ifosfamide (I), as single agents or in combination (D+I), gemcitabine (G) and the EZH2 inhibitor EPZ-011989 (E) (8 mice/experimental group). Drug activity was assessed in terms of tumor volume inhibition (TVI%). Whole transcriptome sequencing (using Illumina NextSeq500 platform) and western blotting were performed on ES-1 samples obtained before and after mouse treatment with E.

Results: Single agent D and I showed a modest antitumor effect, while D+I induced an almost complete inhibition of tumor growth (max TVI: 94%). A comparable antitumor activity was caused by single agent G (max TVI: 98%). Conversely, a tumor growth stabilization was initially induced by E, followed by a progressive reduction of tumor volume starting from the end of treatment (max TVI: 89%). Consistent with its mechanism of action, E inhibited trimethylation and increased acetylation of H3K27, as detected in ES-1 samples at different intervals from the end of treatment, which were paralleled by a reduced expression of EZH2 protein. GSEA analysis of transcriptome data showed “senescence and autophagy” processes among the most enriched pathways in E-treated tumors. Consistently, an accumulation of the autophagy markers LC3-II and SQSTM1/p62 was detected in ex-vivo ES-1 samples obtained at different time points from mice treated with E. The same evidence was found in the ES-1 cell line, established from the PDX model, after in vitro exposure to different concentrations of the EZH2 inhibitor. Conversely, no cells positive for senescence-associated β-galactosidase staining were observed, suggesting a lack of senescence involvement in ES-1 response to E.

Conclusion: Our preclinical results in a proximal-type ES INI1-deleted PDX model showed that D+I, G, and E induced a strong antitumor activity. These data support clinical use of G and D+I and also confirm that EZH2 is a therapeutic target in proximal-type ES.

Consistent with the reported role of EZH2 as a negative regulator of autophagy, we showed that inhibition of this enzyme resulted in the induction of autophagy-associated markers in ES-1 tumors and cells. Mechanisms underlying the autophagic response are currently being investigated. The extent to which these preclinical findings can be applied to distal ES subtype is left to be defined.

Poster 024 3042633

REACTIVATION OF WILD TYPE P53 BY MDM2 INHIBITION IN SYNOVIAL SARCOMAS

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[1]Microbiology, Tumor and Cell Biology, Karolinska Institutet, Stockholm, Sweden; [2]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA; [3]Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, BC, Canada

Objective: *TP53* mutations frequent in most cancers, are rare in synovial sarcomas. However, the expression of SS18-SSX, is associated with increased stability of MDM2 subsequent ubiquitination and degradation of p53, a possible explanation for the lost of p53 function in these tumors. SS18-SSX is a transcritpional regulator that forms a complex with SWI/SNF and polycomb proteins to drive oncogenic transcription. p53 also interacts with subunits of the SWI-SNF to regulate gene transcription in response to cell damage in normal cells.
The objective of this study is to investigate the effects of MDM2 inhibition in combination with the DNA damaging on a) the proliferation of synovial sarcoma cells. b) the transcription of p53 target genes and c) the interaction of SS18/SSX with SWI-SNF and p53.

Methods: We investigated the activity of the MDM2 inhibitor Idasanutlin in combination with the DNA damaging agent doxorubicin on the proliferation of synovial sarcoma and normal mesenchymal cells in real time. We investigated the activity of ninety p53 target genes following MDM2 inhibition in these cells using PCR arrays. Using proximity ligation assay and immunioprecipitsation terchniques we investigated if p53 interacts with SS18 and/or SS18-SSX.

Results: We found that the MDM2 inhibitor Idasanutlin in combination with doxorubicin have a synergistic anti-proliferative effect on synovial sarcoma cells but not in normal mesenchymal stem cells. Exposure to Idasanutlin, leads to increased levels p53 with a resulting activation of p53 target genes such as Bax and Casp9 (involved in the apoptotic response), MyoD (myogenic differentiation) and EGR1 (a tumor suppressor gene repressed by the SS18-SSX). Transcription of WT1, IGF1R, MycN and Sox1, also p53 targets, was repressed following MDM2 inhibition. Using proximity ligation assay, and immunoprecipitation techniques we found that p53 interacts with SS18 in normal cells

following exposure to Idasanutlin. In synovial sarcomas SS18-SSX interacts with p53, suggesting that in these tumors, the SS18-SSX/p53 interaction may result in aberrant p53 transcription.

Conclusion: Our results confirm that in synovial sarcomas, MDM2 inhibitors in combination with genotoxic drugs restores p53 tumor suppression function resulting in cell death. This is a therapeutic oportunity worth to be further explored. Mechanistically, we propose that in normal cells, the wild type p53 protein forms a transcriptional complex with the endogenous SS18 to drive transcription in rresponse to cell damage.Interaction of p53 with SS18-SSX reprograms p53 normal transcription favouring synovial sarcoma genesis.

Poster 025 3026307

MACHINE LEARNING ANALYSIS OF GENE EXPRESSION DATA REVEALS NOVEL DIAGNOSTIC AND PROGNOSTIC BIOMARKERS AND IDENTIFIES THERAPEUTIC TARGETS FOR SOFT TISSUE SARCOMAS

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Objective: Based on morphology it is often challenging to distinguish between the many different soft tissue sarcoma subtypes. Moreover, outcome of disease is highly variable even between patients with the same disease. Here we used machine learning analysis to identify novel diagnostic and prognostic markers and therapeutic targets for soft tissue sarcomas.

Methods: We modeled a deep neural network to compare gene expression data from soft tissue sarcomas (206 cases) from The Cancer Genome Atlas (TCGA) and control tissues (9662 samples) from the Genotype-Tissue Expression (GTEx) project. Soft tissue sarcoma subtypes in the TCGA dataset were analyzed with t-Distributed Stochastic Neighbor Embedding (t-SNE) and subtype defining genes were identified using random forest. Kaplan Meier analysis was used to identify prognostic genes, which were validated in a k-nearest neighbor analysis in an independent dataset from the French Sarcoma Group (310 samples). Regulatory networks were used to identify new targeted therapies. To confirm some of our findings we used immunohistochemistry (38 leiomyosarcoma cases) and qRT-PCR on samples (five synovial sarcomas and four MPNSTs) from our archives. Targeted therapies were tested on cell lines (one synovial sarcoma: SYO-1 and four leiomyosarcomas: IP566, JA192, LMS04, LMS05).

Results: We investigated the overlap of gene expression patterns of soft tissue sarcomas with gene expression patterns of human tissues without malignancies from the GTEx project using clustering with PCA and a deep neural network. Three groups of tumors were identified that overlap in their molecular profile as seen with unsupervised t-SNE clustering. The three groups corresponded to subtypes that are morphologically overlapping. Using a random forest algorithm, we identified novel diagnostic markers for soft tissue sarcoma that distinguished between synovial sarcoma and MPNST, and that we validated using qRT-PCR in an independent series. In the current diagnostics molecular testing for the SS18-SSX fusion specific for synovial sarcoma is required, which is laborious and time consuming. Next, we identified prognostic genes that are strong predictors of disease outcome. The prognostic genes were further validated in expression data from the French Sarcoma Group. One of these, *HMMR*, was validated in an independent series of thirty-eight leiomyosarcomas using immunohistochemistry on tissue micro array, where high expression was associated with a shorter disease-free interval. Furthermore, a regulatory network reconstruction of kinases and transcription factors combined with data from the Connectivity Map showed, amongst others, that HDAC inhibitors could be a potential effective therapy for multiple soft tissue sarcoma subtypes. With a proliferation assay on cell lines we confirmed that leiomyosarcomas and synovial sarcomas are highly sensitive to HDAC inhibitors. HDAC inhibitors were previously found to be effective treatments for synovial sarcomas but had not been tested on leiomyosarcomas.

Conclusion: In conclusion, machine learning algorithms uncovered diagnostic biomarkers, prognostic genes and identified potential novel therapeutic targets for soft tissue sarcomas. This study thereby illustrates the power of different machine learning algorithms to improve our understanding of rare cancers using existing datasets.

Poster 026 3042679

THE DEVELOPMENT AND CHARACTERTIZATION OF A HUMANIZED XENOGRAFT MURINE MODEL FOR OSTEOSARCOMA

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Objective: Osteosarcoma therapy has stagnated, with little meaningful improvement in nearly 40 years. There exists an ongoing need for the development and evaluation of novel therapeutic approaches. Current preclinical xenograft murine models are commonly employed in the development and evaluation of novel therapies but have recognized limitations, such as a defective innate immune system. Furthermore, with the growing interest in immunotherapy, the creation andadoption of models that more accurately represent the human biological condition are of paramount importance. We sought to develop and characterize a humanized xenograft osteosarcoma murine model: 1) Can human osteosarcoma grow within a humanized mouse model? 2) What is the lymphocyte infiltration pattern associated with tumor growth within this model? 3) What is the origin of vasculature within the tumor?

Methods: Three to five-week-old immunocompromised NOD-*scid* IL2rγ^{null} (NSG) mice were radiated with 250 cGy using a Cs^{137} source irradiator. Mice were reconstituted with 10^5 human $CD34^+$ cells isolated and purified from approximately 80-100ml of umbilical cord blood. Engraftment validation was confirmed by measuring peripheral blood levels of human $CD45^+$ at 10-16 weeks post engraftment. Humanized mice were engrafted with 1 x 10^6 - 2.5 x 10^6 standard and patient-derived osteosarcoma cell lines and thereafter characterized radiographically and histologically. Lungs were weighed and lung to body weight ratio was calculated. Tumor lymphocyte presence and infiltration patterns were detected using anti-mouse CD45, anti-human CD45, anti-human CD8, anti-human CD3 antibodies. The origin of the vasculature within the tumor was determined using endothelial marker antibodies, anti-mouse CD31 and anti-human CD31. Slides were scanned using the Aperio autoscanner. Image analysis was performed on the largest continuous focus of viable tumor on each slide and density (positive labeling cells/area mm^2) was calculated.

Results: Three of four tumor lines successfully engrafted in both the tibia and subcutaneous flank. The plain radiographs of the orthotopically-implanted tibias were characterized by lytic changes, cortical destruction, and soft-tissue extension, which are consistent with the human condition. Histologic findings included hyper-cellularity, necrosis, and cortical bone destruction, as commonly seen and described in human osteosarcoma tumors. Lung metastases occurred in the three tumor lines that successfully engrafted in both the tibia and subcutaneous flank. Human $CD45^+$ leukocyte cells were demonstrated within the bone marrow, the primary tumor, and the metastatic lesions, including the lungs and liver. There was minimal to no staining of mouse $CD45^+$ cells within the bone marrow, primary lesions or metastatic lesions. Both CD3 and CD8 immunohistochemistry studies labeled variable amounts of human T-cells in tumors. Staining was positive for both human and mouse $CD31^+$, indicating the presence of both human and mouse endothelial cells within primary and metastatic lesions.

Conclusion: A humanized xenograft murine model permits reliable heterotopic and orthotopic tumor implantation and growth, making it a feasible and scalable tool for pre-clinical trials. Human T-cells are the predominant tumor-infiltrating cells within both the primary and the metastatic lesions and, thus, offer a more relevant means for assessing novel therapeutics, particularly immunotherapies. Tumor vasculature appears to derive from both host and tumor origin. This may serve as an alternate or additional therapeutic target. These results are encouraging and support the humanized xenograft murine model as a novel and relevant preclinical tool for future therapeutic investigation. Going forward, we plan to further characterize the model by better defining the timeline for humanization, the infiltrative CD45 + leukocyte subpopulation, and the effect of immunotherapies on osteosarcoma tumor growth and development.

Poster 027 3042837

COMBINATION OF CISPLATIN AND HIV PROTEASE INHIBTOR NELFINAVIR SHOWS SYNERGISTIC EFFECTS AGAINST THE GROWTH OF HUMAN OSTEOSARCOMA CELLS

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Objective: The five-year survival rate for patients diagnosed with osteosarcoma (OS) who present with metastatic, recurrent, or refractory disease is less than 20% and has remained unchanged for over three decades. The lack of improvement in survival can partly be attributed to the development of chemoresistance. Elucidating the mechanisms that contribute to

chemoresistance and implementing strategies to overcome it will be pivotal to improving survival for these patients. We have previously shown that ER stress induced transcription factor ATF6α is activated in OS and serves as an independent prognostic indicator, promoting resistance to chemotherapy in OS cells. Our objective is to examine whether inhibitors of regulated intramembrane proteolysis (RIP) pathway that activates ATF6α can work synergistically with chemotherapy to enhance OS chemosensitivity.

Methods: We used Western blotting, qPCR, siRNA, immunofluorescence, luciferase activity assay, FACS analyses, and apoptotic assays to examine the effects of RIP inhibition in OS chemosensitvity of cell lines U2OS, 143b and MG63.

Results: ATF6α is activated at significantly higher levels in OS cells and tumors when compared to normal osteoblasts and normal age matched tissue (lung, liver, smooth muscle, and kidney). The site-1 and site-2 proteases (S1P and S2P) activate ATF6α via the RIP mechanism. We examined whether S1P and S2P were expressed at higher levels and qPCR analysis showed that both proteases are expressed 2-4-fold higher in OS cells than normal osteoblasts. Furthermore, we found that both genetic and pharmacologic inhibition of both S1P and S2P significantly enhanced chemosensitivity in OS cells. siRNA mediated downregulation of S1P and S2P resulted in significant increase in cisplatin induced caspase-3 activation. Co-treatment of cisplatin with the HIV protease inhibitor, Nelfinavir, that inhibits S1P or PF42942 that inhibits S2P resulted in synergistic increase in cisplatin induced cell death. In agreement with the pro-survival role of RIP proteases S1P and S2P in OS, we also found that downregulation of another RIP activated osteoblast specific transcription factor OASIS, also significantly contributed to the enhanced sensitivity of OS cells to cisplatin induced cell death.

Conclusion: Therapeutic targeting of the RIP pathway or combination treatment with drugs that inhibit RIP holds promise as an innovative and effective treatment strategy for OS.

Poster 028 3042736

PROGNOSTIC IMPACT OF THE FGFR EXPRESSION IN LIPOSARCOMA ROLE OF FGFR AND MDM2 DUAL TARGETING

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Objective: Liposarcomas are the most common type of soft tissue sarcomas. Among liposarcomas, well-differentiated liposarcoma (WDLPS)/dedifferentiated liposarcoma (DDLPS) are the most frequent types. WDLPS never metastasize but are associated with a high risk of local recurrence and dedifferentiation especially when they are localized in the retroperitoneum. More than 50% of DDLPS will relapse locally. A significant proportion of patients will remain with a non-resectable disease that will metastasize in 20% of cases. Standard chemotherapy is poorly efficient and alternative options are so far limited.
Our objective is to find new therapeutic targets in liposarcomas. FRS2 (Fibroblast growth factor Receptor Sustrate 2), a crucial adaptor protein of the FGFR signaling pathway is amplified and overexpressed in most WDLPS/DDLPS suggesting that the FGFR pathway might be involved in liposarcoma tumorigenesis. Our aim is to demonstrate the relevance of the FGFR pathway in WDLPS and DDLPS tumorigenesis.

Methods: First, we have used immunohistochemistry to perform an exhaustive analysis of the pattern of expression and localisation of FGFR1-4 in WDLPS/DDLPS both in a large collection of 207 primary tumors and in our in-house panel of high quality and validated human WDLPS and DDLPS cell lines. Second, we have tested the effect of the pan-FGFR tyrosine kinase inhibitor JNJ-42756493 - as a single agent or in combination - on viability, cell cycle and apoptosis in our panel of 5 liposarcoma cell lines using flow cytometry. We have also assayed the effect of these
compounds on activation of the downstream pathways of FGFR signalling the ERK1/2 and PI3K/AKT pathways using western blot analysis.

Results: Expression studies
We have detected a high expression of FGFR1 and/or FGFR4 in a significant percentage of WDLPS and DDLPS. The prognostic value of FGFR expression by correlation to the patient clinical outcomes is under investigation and will be presented at the meeting.

Fonctional studies
We have shown that our liposarcoma cell lines are sensitive to the pan-FGFR inhibitor JNJ-42756493. Exposure of the cells to JNJ-42756493 induced a decrease in cell viability, cell cycle arrest in G1 and apoptosis. JNJ-42756493 treatment had a strong inhibitory effect on the ERK1/2 pathway whereas the effect on the PI3K/AKT pathway was not constant and much less pronounced. This led us to investigate the potential synergy of the JNJ-42756493 with the PI3K/mTOR antagonist BEZ235. Synergy between JNJ-42756493 and BEZ235 was observed for the WDLPS cell lines but not for the DDLPS cell lines. WDLPS and DDLPS are characterized by the systematic amplification and overexpression of MDM2. We therefore investigated the effects of the MDM2 antagonist RG7388 in combination with JNJ-42756493. Interestingly, we found that the combination of RG7388 and JNJ-42756493 exerts a highly synergistic effect on both viability and apoptosis in all our WDLPS and DDLPS cell lines. We are currently investigating the mechanics of the synergy between the FGFR and the MDM2 antagonists. We plan to use xenograft and PDX models to validate our in vitro findings in the in vivo setting with the ultimate goal to improve patient management.

Conclusion: We have shown that FGFR expression might constitute a powerful biomarker to select patients for clinical trials testing FGFR inhibitors. The availability of an early clinical trial unit in Institut Bergonié, managed by Prof. A. Italiano, will give the immediate opportunity to transfer our data to the management of metastatic DDLPS patients.

Poster 029 3042825

DISCOVERY SCREEN OF SMALL MOLECULE INHIBITORS OF THE PAX3-FOXO1 FUSION PROTEIN NOMINATES THERAPEUTIC COMBINATION STRATEGIES

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Objective: Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma of childhood. Despite aggressive therapy, the 5-year survival rate for patients with metastatic or recurrent disease remains poor. Previous studies have found that tumors driven by the PAX3-FOXO1 fusion protein are associated with a particularly poor outcome. This study was designed to discover novel therapeutic options for this disease using a high-throughput screen and a large small molecule library at the National Cancer Institute.

Methods: Patient derived RH4 cells were stably transfected with either a PAX3-FOXO1 enhancer sequence upstream of luciferase (pALK-Luc construct; for reporting on PAX3-FOXO1 activity) or a constitutively active CMV promoter (pCMV-Luc construct; to assay non PAX3-FOXO1 related transcription) were enriched for reporter expression levels and used for assay development. A high throughput screening assay was developed after optimization of cell seeding density, length of incubation of cells prior to and post treatment with test compounds, and effect of passaging among other factors. The assay was validated for sensitivity and reproducibility over three separate runs using 3000 randomly chosen screening compounds with high correlation (coefficient median R^2 = 0.87, range R^2 = 0.86-0.90). A pure compound library of ~63,000 compounds consisting of synthetic and natural products was used in a high throughput screening campaign for the identification of inhibitors of PAX3-FOXO1 luciferase reporter activity in Rh4 ALK-Luc cells with minimal effect on cell viability and activity in the Rh4 CMV-Luc reporter. RNAseq was performed on a subset of the discovered compounds to profile the effect of lead molecules on PAX3-FOXO1 transcription. Additional RMS cell lines were tested to validate the specificity of the findings in PAX3-FOXO1 driven tumors and *in vivo* studies were performed for a lead therapeutic combination.

Results: A primary screen of 62,643 compounds was completed using a 10uM screening dose. 573 active compounds were selected for dose response follow-up screening and from this, 64 lead compounds were identified. Of these compounds, 16 compounds had a described mechanism, including RMS active agents such as tubulin inhibitors, topoisomerase inhibitors, staurosporine analogues and histone deacetylase inhibitors. Forty-eight novel compounds were discovered and further characterization was performed using RNAseq expression profiling and gene set enrichment analysis. The combination of a bromodomain inhibitor plus a topoisomerase inhibitor was particularly potent in eliminating PAX3-FOXO1 transcriptional output and was chosen for further *in vivo* studies. Detailed mechanistic studies of this combination are currently underway.

Conclusion: To date, this is the largest small molecule screening effort designed to find specific inhibitors of the PAX3-FOXO1 fusion oncoprotein. The work adds to the understanding of the biology of this disease and nominates candidate drug combinations for clinical translation.

Poster 030 3042839

HIGH-THROUGHPUT DRUG SCREENING OF PATIENT-DERIVED SARCOMA TUMOR ORGANOIDS FOR PERSONALIZED THERAPY

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Objective: Tumor organoids are ideal preclinical models to rapidly predict drug responses as they recapitulate various features of primary tumors including heterogeneity, cell organization, and sensitivity to therapeutic agents. We have successfully and reliably created organoids from primary sarcoma specimens spanning an array of sarcoma histologies. By adapting our fully optimized high-throughput screening approach, we tested response of these organoids to hundreds of therapeutic agents. Our method is applicable not only to high-grade, therapy-naïve tumors but also low-grade or pre-treated sarcomas as well. In addition, drug response profiles can be generated within a week following surgery, allowing for rapid and effective therapy selection for patients.

Methods: Patient tumors were obtained from adult and pediatric cases at the time of surgery, processed to single cell suspension and seeded in Matrigel in 96 well plates following our established mini-ring methodology. Organoids are grown in three dimensions for 3-5 days then treated twice using a library of up to 430 investigational and FDA approved compounds. After the samples have been exposed to drugs for 48 hours, we assess response by measuring cell viability (ATP release assay). We also validate the models by comparing organoid histology to that of the original tumor.

Results: We have performed functional screenings of the first 15 patients enrolled in our ongoing, prospective study. The samples tested encompass different histologies, histologic grades, and patient treatment regimens. Tumor subtypes are delineated in Table 1. We obtained sufficient cells to establish organoids for 14/15 samples; 13/14 yielded viable models (93%). One heavily pre-treated necrotic osteosarcoma did not produce viable cancer cells. We generated 3D organoid models and obtained a drug-response profile for all viable samples. These included low-grade samples (chondrosarcoma, solitary fibrous tumor) as well as previously treated tumors (leiomyosarcoma, rhabdomyosarcoma), which can be difficult to establish as patient-derived xenografts (PDXs). The responses observed will allow therapy to be tailored for each patient.

Conclusion: We have successfully established organoids from different sarcoma subtypes to yield biologically and therapeutically relevant models. Results of our high throughput functional screening will be integrated into clinical decision-making through a Precision Medicine Sarcoma Tumor Board.

Tumor Subtype	Grade	Status	Therapy
Rhabdomyosarcoma	High	Primary	Yes (Chemo)
Chondrosarcoma	Low	Primary	No
Chondrosarcoma	High	Primary	No
Chondrosarcoma	N/A	Primary	No
De-differentiated liposarcoma	High	Primary	No
Leiomyosarcoma	N/A	Metastasis	Yes (Chemo/Radiation)
Leiomyosarcoma	High	Primary	Yes
Osteosarcoma	High	Metastasis	Yes (Chemo)
Osteosarcoma	High	Metastasis	Yes (Chemo)
Osteosarcoma	High	Primary	Yes
Osteosarcoma	High	Metastasis	No
Solitary fibrous tumor	Low grade	Primary	No
Undifferentiated spindle cell sarcoma	Low	Primary	No
Undifferentiated spindle cell sarcoma	Intermediate/High	Recurrence	No
Undifferentiated pleomorphic sarcoma	High	Metastasis	Yes (Chemo)

Table 1. List of tested sarcoma samples.

Poster 031 3042840

TARGETING ACTIVATING TRANSCRIPTION FACTOR 6 ALPHA (ATF6 A): A NOVEL APPROACH FOR THE TREATMENT OF PEDIATRIC OSTEOSARCOMA

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Objective: Osteosarcoma is the sixth most common form of cancer in children. The five-year survival rate for patients diagnosed with osteosarcoma (OS) who present with metastatic, recurrent, or refractory disease is only 15-30% and has remained unchanged for over 30 years. One of the contributing factors to the lack of improvement in survival is the development of chemoresistance. Therefore, finding and characterizing cellular mechanisms, which contribute to OS chemoresistance could be one promising strategy for designing therapies that can change the outlook for patients with this disease.We have previously shown that activation of UPR transducer ATF6apromoted chemoresistance of OS cells to cisplatin and irinotecan and that it served as an independent prognostic indicator irrespective of the metastatic status and percent necrosis in patients with OS. As inhibitors for this protein are unavailable, our objective here is to identify small molecules that inhibit ATF6aactivity.

Methods: We utilized Western blotting, qPCR and immunofluorescence and high-throughput screening tools and techniques to identify and validate small molecules that can disrupt ATF6aactivity and function.

Results: To identify small molecule inhibitors of ATF6a, we developed a U2OS osteosarcoma cell line that stably expressed the ATF6a-Luc or pGL3-BiP-Luc reporter plasmid that contain tandem repeats of ATF6aconsensus binding sites. The cell lines were screened for inhibition of ATF6areporter activity induced by Tunicamycin using a compound library of 604 anti-cancer agents and kinase inhibitors. Among the hits, CDK targeting agents including flavopiridol and dinaciclib significantly and specifically decreased ATF6a reporter activity in a dose dependent manner. Further analysis of the role of CDKs in ATF6aactivation and function is currently being investigated. Identification of inhibitors of ATF6acould lead to improved treatment of osteosarcoma patients.

Conclusion: Our findings emphasize an important role for ATF6ain the therapy resistance of osteosarcoma. Hence therapeutic targeting of the ATF6apathway holds promise as an innovative and effective treatment strategy for OS.

Poster 032 3042902

ELUCIDATING THE ROLE OF THE EPHRIN TYPE-A RECEPTOR (EPHA2) AS THERAPEUTIC TARGET IN OSTEOSARCOMA USING PATIENT-DERIVED TUMOR XENOGRAFTS

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Objective: Osteosarcoma (OS) is the most common primary malignant bone tumor in children and young adults. The clinical outcome of recurrent or metastatic disease has not significantly changed in the past decades despite aggressive multimodality therapy. Identification of novel therapeutic targets is critical to improve the dismal outcome of patients with OS. The cell surface receptor ephrin type-A receptor 2 (EphA2) has been identified as one the most abundant receptors in OS. EphA2 activates several molecular pathways that participate in the processes of cell proliferation, differentiation and migration. We hypothesize that targeting EphA2 would have an effect in tumor progression in OS.

Methods: We have developed 23 patient-derived tumor xenografts (PDXs) from patient with OS at different time points during their cancer treatment (at diagnosis, local control, metastasis and recurrence). We performed qPCR and fluorescent-activated cell sorting (FACS) on PDX tumors and derived cell lines to evaluate the expression of EphA2. The effect of ALW-II-41-27, an Epha2 small-molecule specific inhibitor, in cell proliferation and migration was evaluated *in vitro.*

Results: Osteosarcoma PDXs demonstrated high EphA2 mRNA expression as compared to normal bone. The level of EphA2 mRNA expression did not correlate with treatment resistance or metastasis in the evaluated tumor samples. We found that EphA2 surface expression was enriched in PDX cell lines using flow cytometry analysis. We FACS-sorted PDX cell lines in two distinct cell pools, expressing either high (EphA2Hi) or low (EphA2Lo) EphA2 levels, and then assessed their sarcosphere forming capacity and their expression of different stem cell genes. We found that EphA2Lo cells generated more sarcospheres, which is a surrogate of their self-reneal capacity, and had increase mRNA expression of OCT4, NANOG and SOX2 . Osteosarcoma PDX cell lines showed significant inhibition of cell proliferation in a dose dependent manner after 72hrs of treatment with ALW-II-41-27. *In vivo* studies evaluating the effect of ALW-II-41-27 on OS PDXs are ongoing.

Conclusion: EphA2 expression is increased in OS PDXs. The role of EphA2 in OS stem cell biology is still unknown. We believe that Epha2 interaction with other molecular pathways would be ligand-independent as it has been described in other malignancies. Our results suggest that EphA2 can be considered an attractive therapeutic target in OS.

Poster 033 3042984

PATIENT-DERIVED SARCOMA MODELS - FIRST RESULTS FROM THE SARQMA STUDY

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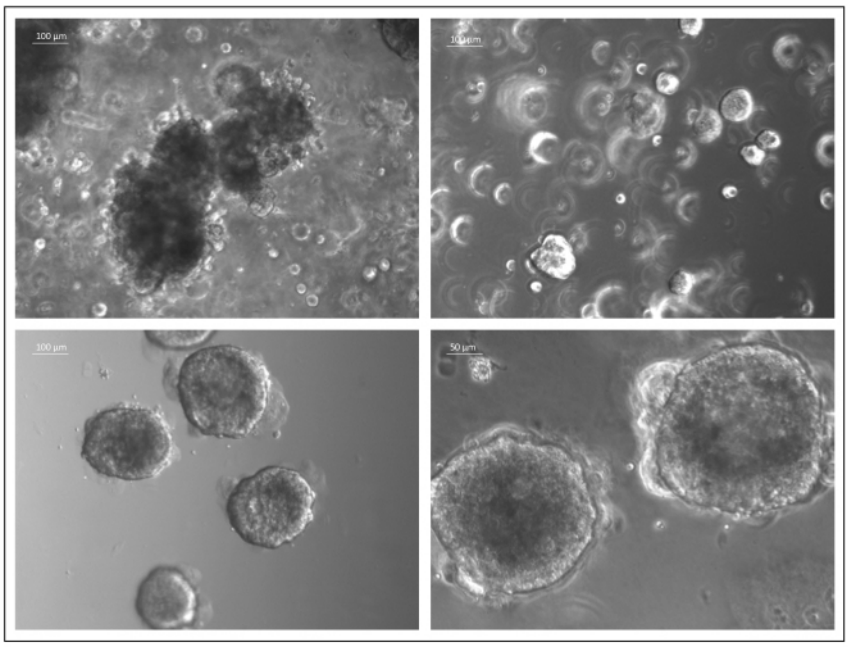
Objective: Over the past decade, the development of new targeted therapeutics directed against specific molecular pathways involved in tumor cell proliferation and survival has allowed an essential improvement in carcinoma treatment. Unfortunately, the scenario is different for sarcomas for which the main therapeutic approach still consists in the combination of surgery, chemotherapy, and radiation therapy. The lack of innovative approaches in sarcoma treatment stems from the high degree of heterogeneity of this tumor type, with more that 70 different histopathological subtypes, and the limited knowledge of the molecular drivers of tumor development and progression. Here we show that patient-derived 3D (PD3D) cell culture models allow for an *in vitro* system to systematically test single compounds and combinations thereof in a semi-automated manner, generating a pre-clinical dataset that in combination with clinical data, genomic and proteomics profiles may help to better understand the biology and ultimatively identify more potent treatment regimen in the future.

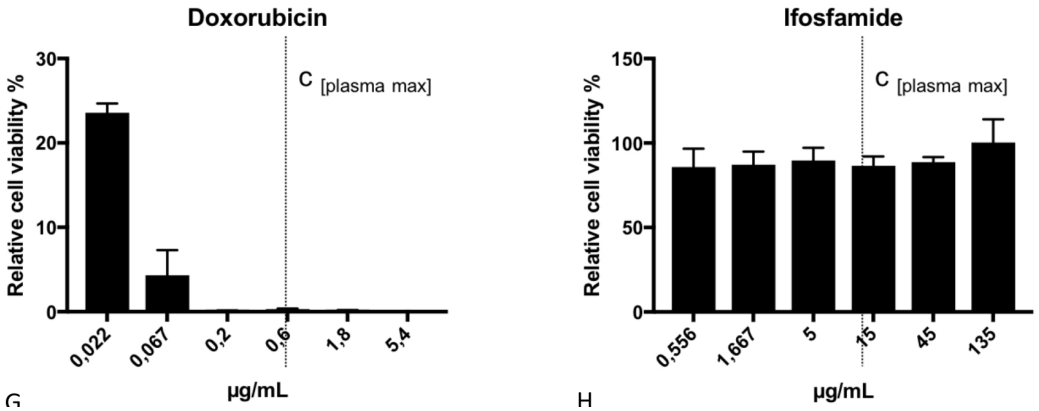
Methods: Fresh surgical specimen are transferred into the lab, where they undergo several steps of mechanical and chemical dissociation. Cell aggregates are then seeded into 24 well plates in matrix-like scaffolds and alllowed to grow until they reach >100µm (Fig 1). Organoids are then harvested and semi-automatically transferred to 384-well plates and treated with a set of compounds that resemble the standard-of-care treatment as well as novel compounds of interest. Finally, viability is calculated as previously published by us. In parallel, protein extracts of the PD3D models are used for DigiWest, a multiplexed westernblot allowing to interrogate up to 200 (phospho)-proteins.

Results: We recruited so far 50 patients of which In 49 cases a biopsy was conducted. In 23 of these cases to little material was available, or the macroscopic consistency did not fit for sarcoma diagnosis. Of these 23 samples 5 were reported as sarcoma tissue afterwards, while 5 of the taken 26 samples were not sarcomas according to the final histopathology reports (Fig 2). Two third of the patients were male, while the median age was 55 and the mean age was 56,19. Of all sarcoma samples 90,48% (19/21) were taken from tumors localized at the extremities, while the rest was located at the trunk. 52,38% (11/21) were growing in short term cell culture and were split at least to passage 1 (p1). 28,57% (6/21) were growing for long term analyses. Two of these six are myxoid liposarcomas, two are undifferentiated pleomorphic sarcomas or classified as not otherwise specified (UPS/NOS), one was a myxoid liposarcoma and one a biphasic synovial sarcoma. Despite relatively low cell culture take-rates, we here show that it is feasible to generate organoids from sarcoma tissues using them for extensive characterization in order to better understand their biology and mechanisms of treatment. High-throughput drug-screening allows for an extensive characterization of pharmacokinetic properties of individual sarcomas (Fig 3). Using the same source of material for additional (phospho)-proteomics provides multiple layers of understanding.

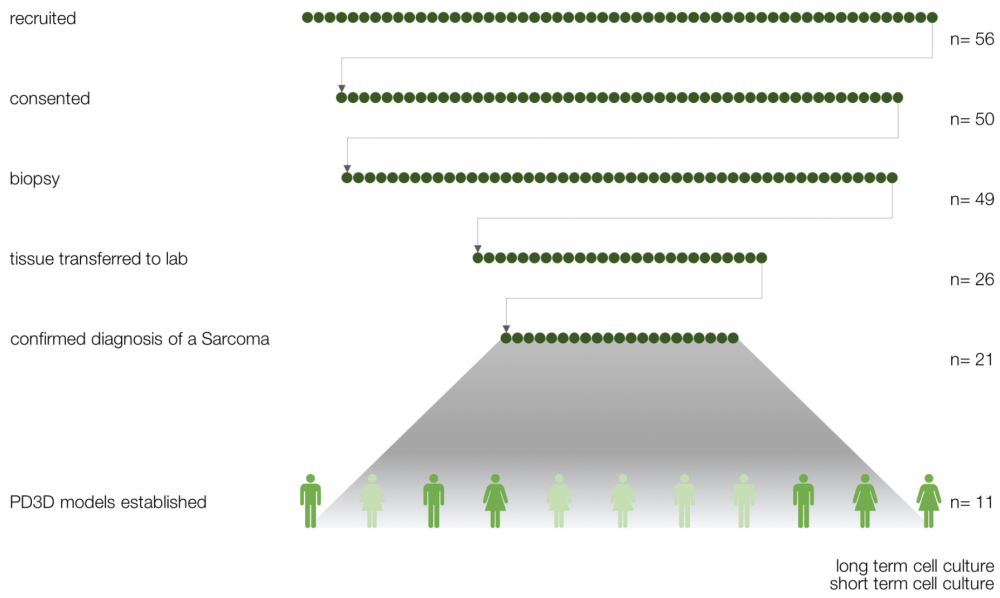
Conclusion: At present, the structure of clinical trials is not amenable to N of 1 studies, so applying the information garnered from this platform, particularly combination therapy drug screens, remains a significant hurdle. The major technical limitation to the successful establishment of organoid cultures was insufficient amounts of fresh tissue with viable tumor cells. Increasing the tumor tissue available for organoid prosuction would allow for culture media optimization and lead to a greater success rate. More viable tumor tissue could be made available through the acquisition of larger samples through surgical biopsies or resections.Nevertheless, by their recapitulation of the donor tissue architecture, they provide an interesting and important tool to study the hugh variety of soft-tissue tumors.



Sarcoma spheroid growing in Matrigel-based 3D cell culture



Relative cell viability on the basis of luminescence read out as ATP Assay (CellTiter-Glo) normalized to read out of untreated cells.



Overview of the recruitment process and number of patient derived samples from biopsy to cell culture success.

Poster 034 3042827

CLEAR CELL SARCOMA OF THE KIDNEY SHOWS ELEVATED LEVELS OF THE ONCOMETABOLITE AND EPIGENETIC MODIFIER L-2-HYDROXYGLUTARATE

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Objective: Clear cell sarcoma of the kidney (CCSK) is an uncommon high-grade pediatric renal sarcoma that accounts for 2-5% of all primary pediatric renal cancers. CCSKs have a relatively stable genomic profile other than *YWHAE-NUTM2B/NUTM2E* fusions or internal tandem duplication of *BCOR*. Interestingly, CCSKs show global CpG island hypermethylation compared to normal kidney and other primary pediatric kidney tumors. One proposed mechanism for global DNA hypermethylation in cancers is through the competitive inhibition of TET hydroxylases (a 2-ketoglutarate dependent dioxygenase) by elevated levels of oncometabolites such as D-2-hydroxyglutarate (D2HG), L-2-hydroxyglutarate (L2HG), succinate, and fumarate. Here, we show increased levels of the putative oncometabolite L2HG is in a small cohort of CCSKs.

Methods: Four frozen CCSK tissues (and corresponding normal kidney tissues) were retrieved from pathology archives. Tissue levels of the enantiomers L2HG and D2HG were measured by mass spectrometry. Briefly, the tissue extracts were derivatized with (+)-Di-O-acetyl-L-tartaric anhydride, a chiral derivatizing agent, followed by liquid chromatography-tandem mass spectrometry (LC-MS/MS). Deuterated stable-isotope, D,L-[3,3,4,4-$^{2}H_{4}$]-2-hydroxyglutarate, was used as internal standard and the results were normalized to protein content of the tissue extracts.

Results: L2HG levels ranged from 505.7 to 1654.4 pmol/mg protein (mean 839.1) in CCSK and 80 to 256.8 pmol/mg protein (mean 172.8) in normal kidney. D2HG levels ranged from 17.7 to 214 pmol/mg protein (mean 96.9) in CCSK and 105.2 to 490.7 pmol/mg protein (mean 280.5) in normal kidney. Total 2HG levels ranged from 565.4 to 1868.4 pmol/mg protein (mean 935.9) in CCSK and 185.2 to 747.5 pmol/mg protein (mean 453.3) in normal kidney. L2HG/D2HG ratio ranged from 6.9 to 30.9 (mean 13.4) in CCSK and 0.5 to 0.8 (mean 0.7) in normal kidney.

Conclusion: Our results in this limited cohort demonstrate increased levels of the oncometabolite and epigenetic modifier L2HG in CCSKs and suggest a possible mechanism for global CpG island hypermethylation in these renal cancers. Further studies are ongoing to elucidate the mechanism and effect of increased L2HG in CCSKs.

Poster 035 3025487

ANTI-TUMOR EFFECTS OF TAS-115 ON MURINE OSTEOSARCOMA CELL LINE(LM8) WITH HIGH METASTATIC POTENTIAL TO THE LUNG

***Naohiro Yasuda**[1]; Sho Nakai[1]; Takaaki Nakai[2]; Yoshinori Imura[3]; Hironari Tamiya[3]; Takaaki Tanaka[3]; Hidetatsu Outani[1]; Satoshi Takenaka[1]; Kenichiro Hamada[1]; Akira Myoui[1]; Hideki Yoshikawa[1]; Norifumi Naka[3]*
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Objective: Osteosarcoma (OS) is the most common malignant bone tumor in adolescents and childhood. Despite combination treatment with wide resection and chemotherapy, lung metastases occur in 40–50 % of OS patients. Survival for patients with metastatic or relapsed osteosarcoma has remained virtually unchanged over the past 30 years, with an overall 5–year survival rate of about 20%. Therefore, new therapies are needed for OS patients. TAS-115 is a novel multiple receptor tyrosine kinase(RTK)s inhibitor that has been shown to inhibit c-MET, VEGFRs, PDGFRs, and TAM tyrosine kinase. Recently, it was reported that TAS-115 had a favorable tolerability profile and exhibited antitumor activity in human gastric cancer, in human lung cancer and synovial sarcoma. Now, Phase I study for solid cancer including metastatic or relapsed OS is ongoing. However, the efficacy of this drug for OS remains unclear. Here we aimed to investigate the therapeutic potential of TAS-115 against OS.

Methods: We utilized syngeneic mouse spontaneous highly metastatic OS cell line, LM8. We established LM8 from the Dunn OS cell line by eight repeated intravenous injection of the cells derived from the lung nodule. We used a clone of LM8 cells that stably expresses luciferase to evaluate lung metastasis easily using In Vivo Imaging System (IVIS).

Animal studies:
1. LM8 cells (1×10^{7}) were inoculated subcutaneously into the flank of 5-week-old femaleC3H mice. Since one week after inoculation, TAS-115 was orally administered once daily at a dose of 50 or 200 mg/kg for 4 weeks. Lung metastasis and

subcutaneous tumor were evaluated using IVIS at 3 and 4 weeks after inoculation of LM8. Four weeks after inoculation, the mice were euthanized, and the tumor weight was measured.

2. LM8 cells (1×10^6) were injected into the lateral tail vein of 5-week-old female C3H mice. One week after injection of LM8, TAS-115 was orally administered once daily at a dose of 50 or 200 mg/kg for 3 weeks. Lung metastasis were evaluated using IVIS at 2 and 3 weeks after injection of LM8.
In vivo Imaging: 15 minutes prior to imaging, mice received the D-luciferin at 100 μg/body by intraperitoneal injection. A region of interest (ROI) of the same size and shape that covered the entire thoracic cavity was applied to every image. Total flux (ps-1) in the ROI was measured. Data were analyzed by using IVIS Living Image software. Phospho-RTK array: Mouse Phospho-RTK Array Kit (R&D Systems) was used to measure relative level of tyrosine phosphorylation of 39 distinct receptor kinases. LM8 cells were cultured with/without TAS-115 for 24h, subcutaneous tumor in mice, or lung nodule in mice were minced and lysed using lysis buffer. The arrays were blocked with blocking buffer and incubated with 300 μg of cell lysate overnight at 4°C. The arrays were washed, incubated with a horseradish-peroxidase-conjugated phosphotyrosine detection antibody, treated with chemiluminescent, and exposed to film.

Results: TAS-115 suppressed cell proliferation of LM8 in a dose-dependent manner (IC_{50}: 2.23μM). In Phospho-RTK arrays of in vitro, PDGFRα was strongly phosphorylated. Consistently, in xenograft models TAS-115 notably attenuated the growth of LM8 subcutaneous tumors and decreased lung metastasis. Furthermore, TAS-115 inhibited the growth of lung metastasis after iv injection of LM8. In Phospho-RTK arrays of in vivo, not only PDGFRα but also some other tyrosine kinases phosphorylation was observed in LM8 subcutaneous tumor and lung metastasis lysate. Intriguingly, TAS-115 treatment blocked the phosphorylation of AXL and FLT-3 as well as that of PDGFRα and their downstream effectors, leading to marked growth inhibition in LM8 cell line in in vitro and in vivo studies.

Conclusion: Taken together, we first demonstrate that TAS-115 has potent antitumor activity in OS cell line. TAS-115 may benefit OS patients whose tumors are dependent upon PDGFRα/AXL/FLT-3 signaling by functioning as a multiple tyrosine kinase inhibitor.

Poster 036 3026960

MESENCHYMAL STROMAL CELLS ENHANCE METASTASIS FORMATION IN OSTEOSARCOMA

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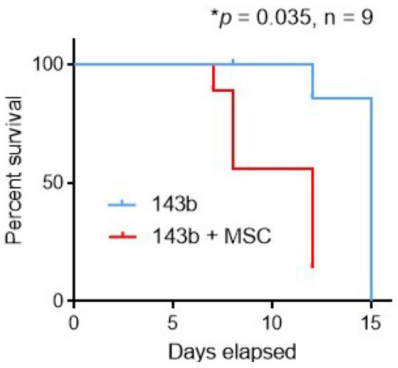
Objective: Previous attempts to fight metastasis in osteosarcoma (OS) have focused on cancer cells, without proper consideration of the complexity of tumor microenvironment (TME). We have recently demonstrated that in OS hypoxia and aerobic glycolysis (Warburg effect) promote proton accumulation in the TME, a microenvironment condition similar to the wound healing process. Interstitial acidosis favors the secretion of a plethora of growth factors, inflammatory cytokines, and chemokines by tumor-associated mesenchymal stromal cells (MSC), in turn supporting proliferation, stemness, invasiveness, and drug resistance of tumor cells. The most lethal attributes of tumor cells are not going to be neutralized blindly looking only at the tumor or only at the stroma: the interaction between the two is a critically important matter. We thus intended to test the hypothesis that also *in vivo* MSC might influence OS behavior.

Methods: We co-injected MSC and bioluminescent 143B OS cells (3:1) in an orthotopic mouse model. The orthotopic mouse model of OS was obtained by intratibial injection of cell suspensions of 143B cells, with or without MSC, in Balb/c nude mice, and the subsequent injection of MSC or vehicle in the tail vein once/week. The number of circulating tumor cells that arrived in the lung was determined by tissue digestion and cell counting, whereas the number and the area of lung metastasis were determined by using camera imaging of luciferase (LUC) activity. Subsequent histomorphological analysis of the primary tumor and of lung metastasis was performed through E&E staining, and vimentin and Ki67 stainings, as well as the staining of markers indirectly associated with intratumoral acidosis, like V-ATPase and LAMP2, or of markers of the NF-kB inflammatory pathway like RelA, and RelB.

Results: We found that in mice co-injected with MSC and 143B the growth rate of OS cells was significantly higher ($p<0.05$) than in mice injected with 143B cells alone. Furthermore, in the same model, MSC fostered the process of spontaneous tumor metastasis to the lung. In fact, the co-injection of MSC with tumor cells strongly enhanced the number of tumor cells that reached the lung tissue at 7 days from the injection, and the number of lung metastases that formed at 12-14 days from the injection (Fig. 1, $*p < 0.05$), as well as the total area of pulmonary nodules that were significantly higher ($p<0.01$) in mice co-injected with MSC plus 143B cells, as compared to mice injected with 143B alone. Notably, all mice co-injected with MSC

and 143B developed lung metastases, whereas only 1/3 of mice injected with 143B cells alone developed lung nodules. Analyses of the expression of specific markers related to proliferation, acidosis, and inflammation on tissue sections are still ongoing.

Conclusion: These findings demonstrate *in vivo* that MSC recruited to sites of rapid tumor growth modulate the TME, likely inducing a pro-inflammatory phenotype, to increase OS growth at the primary site and tumor dissemination. The results emphasize the importance of the stromal environment to OS progression and lead the way to innovative approaches targeting tumor-stroma interactions and MSC homing toward the tumor.



Poster 037 3027348

TNIK IS A NOVEL MOLECULAR TARGET FOR OSTEOSARCOMA TREATMENT AND CONTROLS OSTEOSARCOMA CELL FATE

Toru Hirozane[1]*; Mari Masuda*[2]*; Naoko Goto*[2]*; Teppei Sugano*[3]*; Naofumi Asano*[1]*; Eisuke Kobayashi*[4]*; Akira Kawai*[4]*; Keisuke Horiuchi*[5]*; Morio Matsumoto*[1]*; Masaya Nakamura*[1]*; Masaaki Sawa*[6]*; Hideo Morioka*[7]*; Robert Nakayama*[1]*; Tesshi Yamada*[2]

[1]Department of Orthopedic Surgery, Keio University School of Medicine, Tokyo, Japan; [2]Lab of Collaborative Research, National Cancer Center Research Institute, Tokyo, Japan; [3]Department of Pulmonary Medicine and Oncology, Nippon Medical School Hospital, Tokyo, Japan; [4]Division of Musculoskeletal Oncology, National Cancer Center Hospital, Tokyo, Japan; [5]Department of Orthopedic Surgery, National Defense Medical College, Tokyo, Japan; [6]Carna Biosciences, Inc., Kobe, Japan; [7]Department of Orthopedic Surgery, National Hospital Organization Tokyo Medical Center, Tokyo, Japan

Objective: Conventional chemotherapy has remained as a mainstay of the first-line treatment for osteosarcoma (OS) without no major development in molecular targeted therapy against this malignancy for decades. Therefore, there is a strong incentive to develop a more potent and effective treatment modality for patients with OS. Recently, several studies indicate that inhibition of the Wnt signaling pathway is a rational therapeutic strategy against OS. Our group has previously demonstrated that TRAF2 and NCK-interacting protein kinase (TNIK), an essential component of the Wnt signaling pathway and developed a novel TNIK inhibitor. Therefore, in the present study, we asked whether TNIK serves as a therapeutic target against OS and investigated the possibility of a TNIK inhibitor for OS treatment.

Methods: TNIK expression in OS cell lines and tissues were analyzed. We performed gene-silencing experiments using siRNAs against TNIK transcripts (*siTNIK*) and monitored OS cell growth by using real time cell analyzer. We next examined the effects of a TNIK inhibitor NCB-0846. ATP production was assessed in OS cell lines incubated with various concentration of NCB-0846. NCB-0970, a diastereomer of NCB-0846, which exhibits a lower level of TNIK-inhibitory activity compared to NCB-0846, was used as internal control as well as DMSO. Effects of NCB-0846 *in vivo* were confirmed by using human OS cells implanted immunodeficient mice model. RNA-seq was performed using the RNA extracted from vehicle or TNIK inhibitor-treated OS cells. Cancer stem cell (CSC)-like properties were assessed by soft-agar colony-formation assay, limiting dilution assay, ALDH activities, and the expression of CSC markers (SOX2, NANOG, OCT4, and MYC). Adipogenic phenotypes were qualitatively analyzed by Oil red O staining and green fluorescent molecular probe for the staining of cellular neutral lipid content. The expression of adipogenic markers were assessed by qPCR. Transduced OS cell lines were created and stable cell lines were obtained by using lentiviral vector expressing shRNAs against *TNIK* transcripts and puromycin resistance gene.

Results: We detected that the expression of *TNIK* was higher in OS compared to that in osteoblasts or mesenchymal stem cells by analyzing public database. Immunohistochemical analysis of OS tissue microarrays demonstrated that 49 out of 51 OS tissues were stained positive for TNIK (Figure 1). TNIK inhibitor suppressed OS cell proliferation both in vitro and in vivo. OS cell growth was also inhibited by *siTNIK* (Figure 2). Global gene expression analysis revealed that the modules relating to Wnt signaling pathway and maintenance of stem cell pluripotency were down-regulated. Soft-agar colony-formation assay and limiting dilution assay revealed that TNIK inhibitor decreased sphere formation activities in OS cells. Accordingly, TNIK inhibitor significantly suppressed ALDH activities and the expression of the proteins that are involved in the maintenance of CSCs (Figure 3, upper panel). Concomitantly, we found that TNIK inhibitor drove adipogenic transdifferentiation of OS cells with PPARγ activation (Figure 3, lower panel). TNIK knock-down OS cells created by shRNAs showed nearly identical results regarding CSC-like activities and adipogenic traits.

Conclusion: We present the feasibility of TNIK as a target for OS treatment. TNIK inhibition promotes adipogenic transdifferentiation of OS cells and eliminates CSCs.

Figure 1

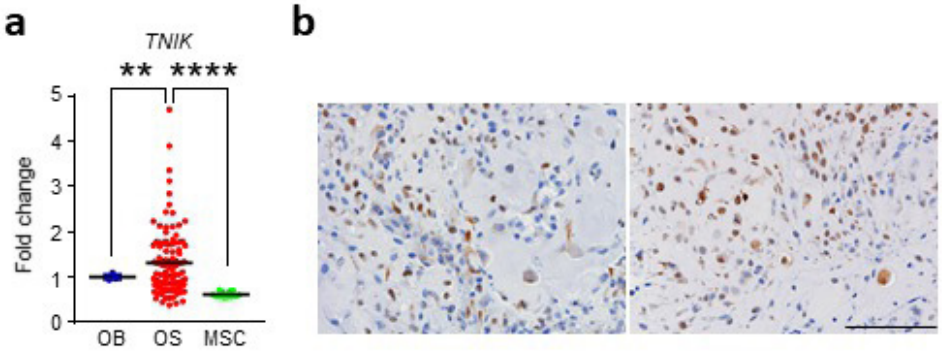


Figure 2

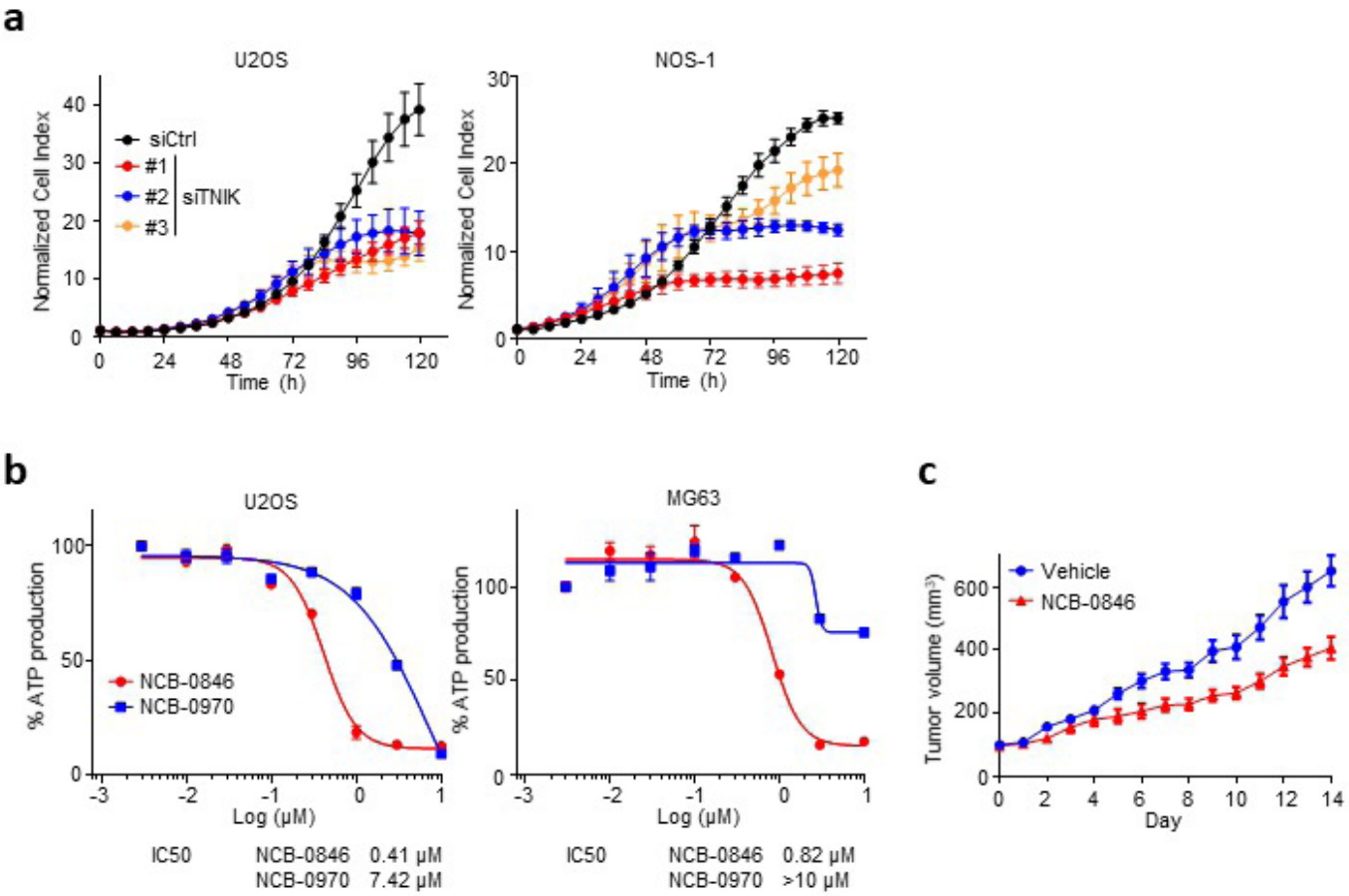
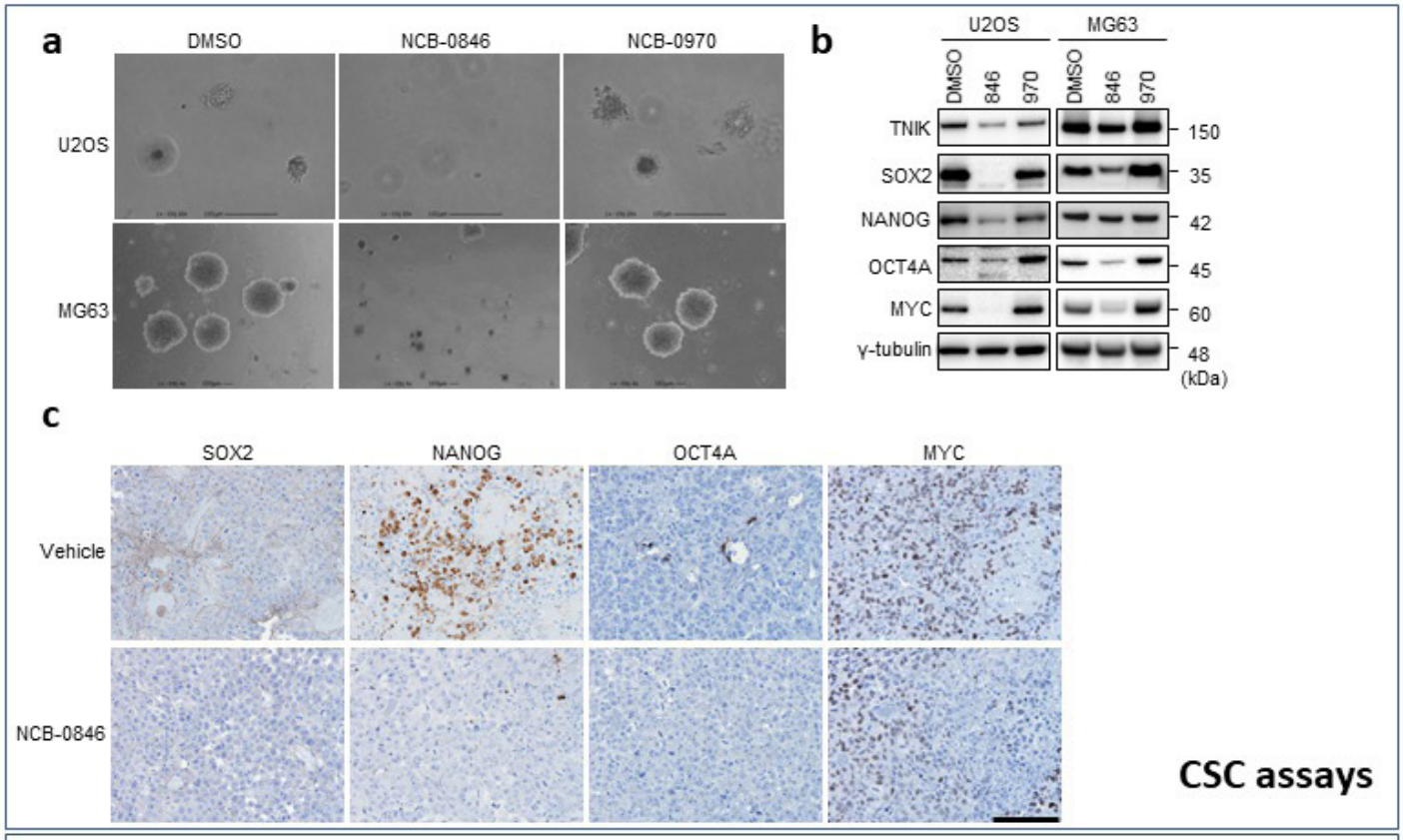


Figure 3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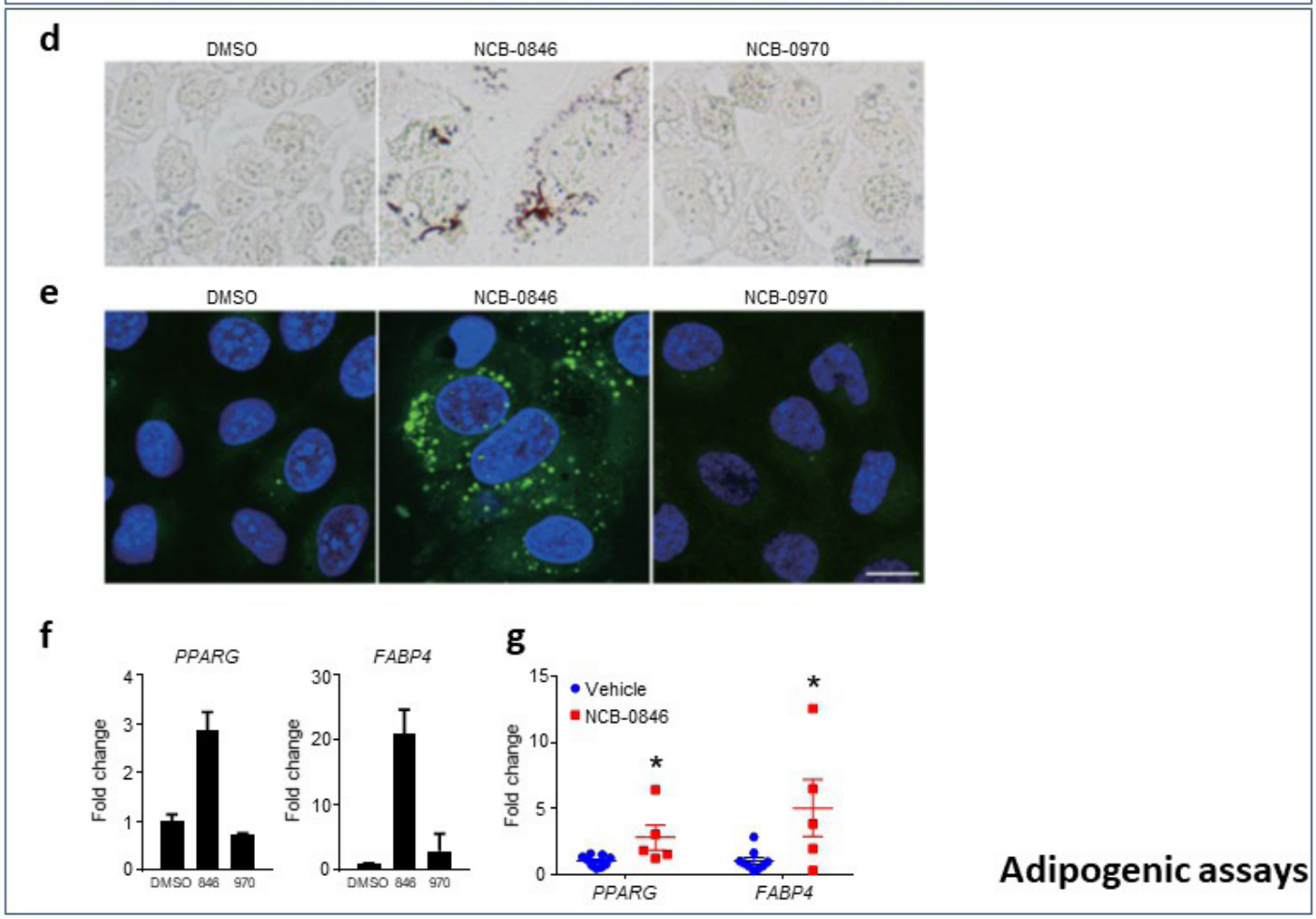
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Adipogenic assays

Poster 038 3028039

IRE1α-XBP1 INHIBITORS EXERTS ANTITUMOR ACTIVITY IN OSTEOSARCOMAS

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Objective: Bone and soft-tissue sarcoma are rare malignant tumors comprising numerous histological subtypes. Novel effective therapies are still required. In recent years, endoplasmic reticulum stress (ERs) responses have been suggested to be involved in the malignancy of various cancer types, prompting new studies focused on this area for the development of new therapies. Our previous study, based on comprehensive protein analyses, demonstrated an association between the ERs response and malignant behaviors in Ewing sarcomas (ESs). We also found that IRE1α inhibitors exert anti-tumor activity in ESs. In the present study, to develop novel therapies for osteosarcoma (OS), we investigated the functional activity of ERs and the anti-tumor effect induced by inhibitors of ERs in OS.

Methods: We conducted reverse transcription polymerase chain reaction (RT-PCR) and quantitative (q)-PCR to elucidate the expression of XBP1 and XBP1 splicing (XBP1s) variants in OS cell lines (143B, KHOS, KHOSR, U2OS, U2OSR) and surgical materials. We also performed XBP1 siRNA and conducted inhibitor assays using several IRE1α-XBP1 inhibitors. Furthermore, we analyzed the association between clinicopathological factors and the ERs status.

Results: The mRNA expression of XBP1 was confirmed to be increased in OS cell lines and surgical materials. Regarding the XBP1s status, half of the OS cell lines and surgical materials showed XBP1s, and the chemo-resistant group showed a markedly higher frequency of XBP1s in OS than the non-resistant group. The knockdown of XBP1 by siRNA inhibited the cell proliferation of the OS cell lines. Regarding inhibitor assays using IRE1α-XBP1 inhibitors, toyocamycin exerted a strong anti-tumor effect (IC50 <0.07 [0.007 to 0.07] μM) in the OS cell lines, with the chemo-resistant group showing particularly strong anti-tumor activity. The functional pathways (IRE1α, ATF6, PERK) of the ERs responses were analyzed under ligand and inhibitor stimulation.

Conclusion: We confirmed the association between the ERs response and the tumor activity in OS. We also found that IRE1α-XBP1 inhibitors suppressed cell growths in OS. In a future study, we will verify the antitumor effects and toxicity of IRE1α-XBP1 inhibitors in OS *in vivo*. We believe that our findings may lead to the development of novel therapeutic strategies for OS.

Poster 039 3036627

ESTABLISHMENT OF PATIENT-DERIVED XENOGRAFT MODELS OF MUSCULOSKELETAL SARCOMA SERIALLY EVALUATED WITH COMPREHENSIVE GENE EXPRESSION PROFILING

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Objective: Cell lines and cell line xenograft mouse models of human malignancy have been gold standards for basic research and valuable preclinical models for evaluating the efficacy of therapeutics. Recently, patient-derived xenograft (PDX) models of various malignancies have been established and shown to more accurately recapitulate the molecular and histological heterogeneity of the primary tumor in the patient. We report newly established 8 strains of PDX model for musculoskeletal sarcoma serially evaluated with comprehensive gene expression profiling.

Methods: Fresh tumor tissues obtained from biopsy or surgical specimen were implanted subcutaneously in NOG (NOD. Cg-*Prkdc*^{scid}*Il2rg*^{tm1Sug}/ShiJic) mice. When the tumor masses grew (passage 0, P0), the P0 tumor was resected and divided into equal sized specimens and implanted subcutaneously into the other NOG mice (P1). In the same manner, P2 and P3 generations were established. The tumor specimens from each passage were serially compared with the primary tumors by pathological finding and comprehensive gene expression profiling. The present study was approved by Institutional Animal Care and Use Committee of Fukushima Medical University (approval number: 27011, 29035

Results: From April 2013, 8 strains of PDX model of musculoskeletal sarcoma (1 strain of small-cell osteosarcoma, leiomyosarcoma, embryonal rhabdomyosarcoma, pleomorphic rhabdomyosarcoma, and angiosarcoma, and 3 strains of undifferentiated pleomorphic sarcoma) from 70 tumor specimens. All the PDX models were transplantable between

NOG mice and pathological characteristics were similar to the primary tumors. Moreover, comprehensive gene expression profiling of each PDX model in each passage resembled those of the primary tumors.

Conclusion: In the present study, comprehensive gene expression profiling showed the maintained genetic characteristics between all the 8 strains of PDX model and the primary tumors. These PDX models might be quite useful for investigating biological behaviors and developing new treatment such as molecular-targeting antitumor drugs or immunological drugs for musculoskeletal sarcomas.

Poster 040 3037703

IMAGING THE INTERACTION OF OSTEOSARCOMA CELLS WITH HOST STROMAL CELLS AND TUMOR SCAFFOLD COLLAGEN IN THE TUMOR MICROENVIRONMENT

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Objective: Host stromal cells are tightly associated with tumor progression and metastasis in cancer. However, little has understood in osteosarcoma. The purpose of the present study is to image the interaction between osteosarcoma cells and host stromal cells in the primary and metastatic tumor microenvironment.

Methods: Human osteosarcoma 143B cells were previously stably transfected with an α_v integrin-GFP vector. 143B expressing α_v integrin-GFP cells were transplanted orthotopically in the tibia of transgenic nude mice expressing ubiquitously expressing red fluorescent protein (RFP). The primary tumors acquired RFP-expressing stroma and were passaged orthotopically in the tibia in non-colored nude mice, which maintained the RFP stroma. The interaction of α_v integrin-GFP expression in 143B cells with RFP-expressing host stromal cells was observed by the confocal microscopy Olympus FV1000®. Collagen fibers were imaged simultaneously in reflectance mode.

Results: The RFP-expressing stroma included cancer-associated fibroblasts (CAFs) and tumor-associated macrophages (TAMs) in the tumors which persisted even three weeks after passage to non-colored nude mice. CAFs expressing RFP were aligned between collagen fibers and cancer cells expressing α_v integrin-GFP. Six weeks after transplantation, pulmonary metastases expressing α_v integrin-GFP could be imaged. TAMs expressing RFP accompanied metastasized osteosarcoma cells expressing α_v integrin-GFP in the lung.

Conclusion: The present study demonstrates the importance of α_v integrin interaction with stromal elements in tumor growth and pulmonary metastasis of osteosarcoma.

Poster 041 3037788

ACIDIC MICROENVIRONMENTS IN SOFT-TISSUE SARCOMA PROMOTES FOXM1 EXPRESSION AND TUMORIGENESIS

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Objective: Acidic microenvironment is one of the characteristic features of malignant tumors. Accumulating evidence indicates that the acidic microenvironments critically influence malignant behaviors of cancer including proliferation, invasiveness, metastasis and chemoresistance. For sarcoma, it was reported that sarcomas were significantly more acidic than benign soft tissue tumors. However, the precise role of acidic microenvironment in sarcoma is still unclear. In the present study, we report on the relationship between the acidic environment and the transcription factor Forkhead Box M1 (FOXM1).

Methods: pH in the soft tissue tumor was measured immediately after resection using pH meter. The human dedifferentiated liposarcoma cell line SW872 were cultured in pH 7.4 and 6.4 DMEM with 10% fetal bovine serum and 100 U/ml penicillin and 100 µg/mL streptomycin. Microarray expression data was obtained from SW872 cells cultured at pH 7.4 and pH 6.4. Total RNA was extracted from the fresh frozen sample that obtained by open biopsy or resection. All experiments were conducted according to the ethical guidelines of the Institutional Review Boards and approved by the Ethics Committee of the Tokushima University.

Results: The average pH of resected tumor was 6.56±0.36 in malignant tumor (n=18), 7.19±0.26 in benign tumor (n=25), 7.35±0.25 in normal tissue (n=16) (Fig.1), suggesting that malignant tumor showed a significant acidic environment

compared with benign tumor and normal tissue ($p<0.05$). SW872 liposarcoma cells treated with acidic medium (pH6.4) showed increased cell proliferation and invasion at 24 hours compared with cells at normal pH medium (Fig.2). Microarray analysis revealed some cancer related genes were elevated in acidic pH. Notably, expression of FOXM1 was remarkable among them. We examined the expression of FOXM1 in resected specimens of benign soft tissue tumor (n= 16) and malignant tumor (n= 11). As a result, FOXM1 was significantly highly expressed in malignant tumors (Fig.3a). Expression of FOXM1 was significantly elevated in SW872 cells cultured at pH 6.4 compared with cells at pH7.4 (Fig. 3b). Down-regulation of FoxM1 by thiostrepton reduced proliferation and migration ability of SW872 cells.

Conclusion: These data suggest that acidic microenvironment formed in malignant tumor activates FOXM1 and promotes sarcoma aggressiveness.

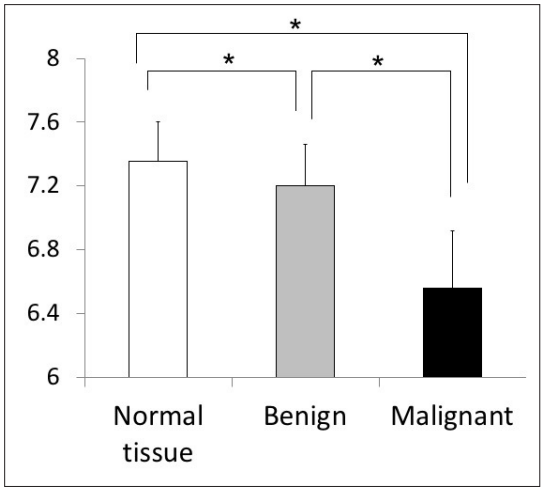

Figure 1. The pH of normal tissue (muscle and adipose tissue), benign and malignant tumor. The malignant tumors were significantly more acidic than the benign tumor and normal tissues.

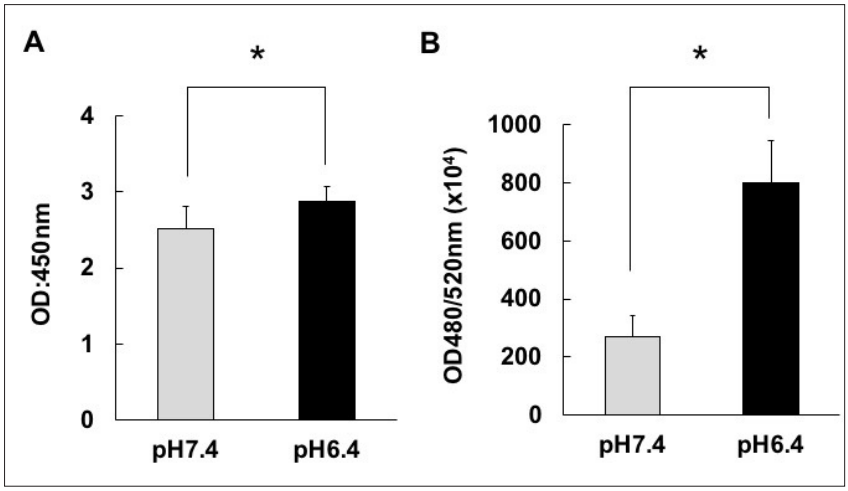

Figure 2. Acidic microenvironment promotes SW872 cell proliferation and cell invasion. (A) WST assay (B) Invasion assay.

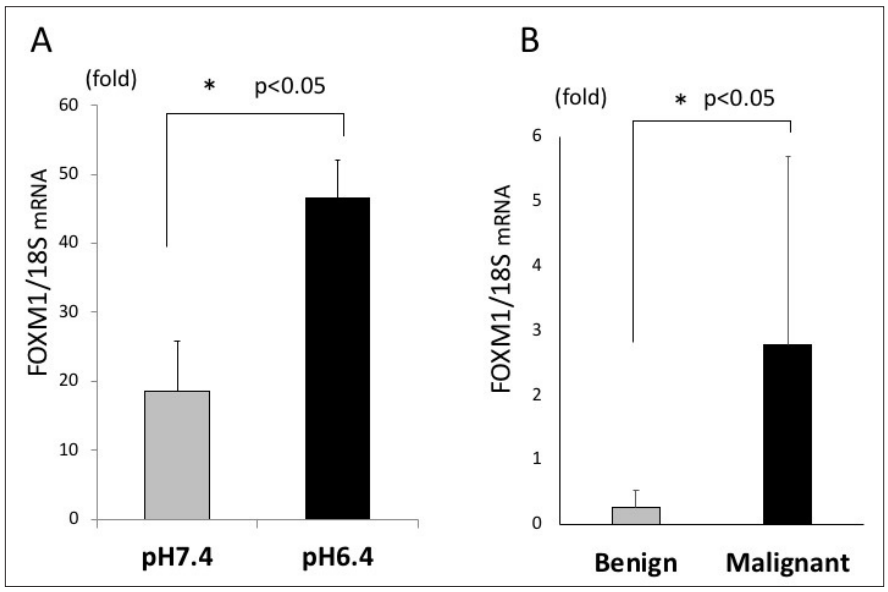

Figure 3. FOXM1 mRNA expression. Acidic microenvironment upregulated mRNA level of FOXM1 in SW872 cells (A). There was a significant difference in FOXM1 expression between the benign and malignant tumor (B).

Poster 042 3037829

CYTOTOXIC AND ANTI-METASTATIC EFFECTS OF MYCOPHENOLATE MOFETIL IN OSTEOSARCOMA: DRUG REPURPOSING FROM PROTEOMIC DATA

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Kriengsak Lirdprapamongkol[3]*; Sarawoot Yama*[4]*; Jisnuson Svasti*[3]*; Dumnoensun Pruksakorn*[1]
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Objective: Osteosarcoma, a highly aggressive primary malignant bone tumor, is an incompletely curable disease. Because of the heterogeneity of osteosarcoma, therefore the new therapeutic options for improving outcomes have not yet been discovered. In our previous study (Chaiyawat, 2017), we have explored the potential protein targets in osteosarcoma through proteomics data review, extraction and cross-reference with identifiers of targets of FDA-approved drugs. We found that, inosine monophosphate dehydrogenase (IMPDH), the first rate limiting step enzyme of the de novo pathway of guanosine nucleotide synthesis, was an overexpressed protein in the metastatic and chemoresistant osteosarcoma. IMPDH is a target of mycophenolate mofetil (MMF; FDA-approved non-cancer drug) which has been clinically used in organ transplantation to prevent graft rejection. In the body, MMF is metabolized to mycophenolic acid (MPA). MPA exhibits potent anti-growth, anti-metastatic and anti-angiogenic effects in various types of cancer. Previous study showed that IMPDH2 overexpressed osteosarcoma cells were poorly sensitive to cisplatin and methotrexate, indicating the important role of IMPDH2 in chemo-sensitivity of osteosarcoma cells. Evidence suggests that MPA might be used in osteosarcoma. We hypothesized that MMF are promising candidate for drug repurposing in osteosarcoma. We therefore evaluated MMF, the IMPDH inhibitor currently available as a clinical therapeutic drug, for its antineoplastic activity in osteosarcoma.

Methods: MNNG-HOS, U2-OS, SaOS-2, MG-63 and 143B human osteosarcoma cell lines were subjected to MPA treatment. In order to investigate mechanism of its anticancer activities, we performed several *in vitro* assays including cytotoxic assay, colony forming assay, cell cycle analysis, apoptosis assay, cell invasion and migration assays. *In vivo* anti-tumor growth and anti-metastatic effects of MMF were determined by using 143B cell line-derived xenograft nude mice model. Subcutaneous xenograft and tail vein-lung metastasis experiment were performed and tested with MMF at dose of 50, 100 and 200 mg/kg/day.

Results: In Figure 1, MPA showed cytotoxic effect with IC_{50} values less than 10 μM in all test osteosarcoma cell lines, whereas therapeutic range of MPA in renal transplantation without toxic effect is 3.125-10.9 μM. MPA treatment caused cell cycle arrest at S and/or G2/M phase, and effectively induced apoptosis in all cell lines. Interestingly, MPA significantly suppressed invasive ability of osteosarcoma cells *via* the inhibition of cell migration. In animal experiments, MMF treatment at dose 200 mg/kg/day significantly reduced the average tumor volume of mice, compared with vehicle control mice. The percentage of tumor growth inhibition (%TGI) of the MMF-treated mice at 200 mg/kg/day was 40.0 ± 15.6 % (Figure 2). Interestingly, the lung metastasis experiment showed MMF treatment at all doses significantly decreased number of lung metastatic nodules, compared with the control mice (Figure 3). MMF at 50, 100 and 200 mg/kg/day are approximately equivalent to the 250, 500 and 1000 mg/day doses used in human. Whereas, a recommended dose clinically used in organ transplantation is 2000-3000 mg/day. Therefore, our study indicates that MMF with non-toxic dose has promising results in preclinical studies of osteosarcoma, suggesting this drug can be clinically effective and safety.

Conclusion: MMF treatment showed promising anti-tumor growth and anti-metastatic effects in osteosarcoma under the safety dose range of clinical use. Since IMPDH2 is the important enzyme plays role in resistance of osteosarcoma to standard chemotherapy, therefore targeted IMPDH2 by MMF is a potent strategy to control osteosarcoma. Thus, a clinical trial study is urgently required for repurposing of MMF into chemotherapeutic regimens of osteosarcoma.

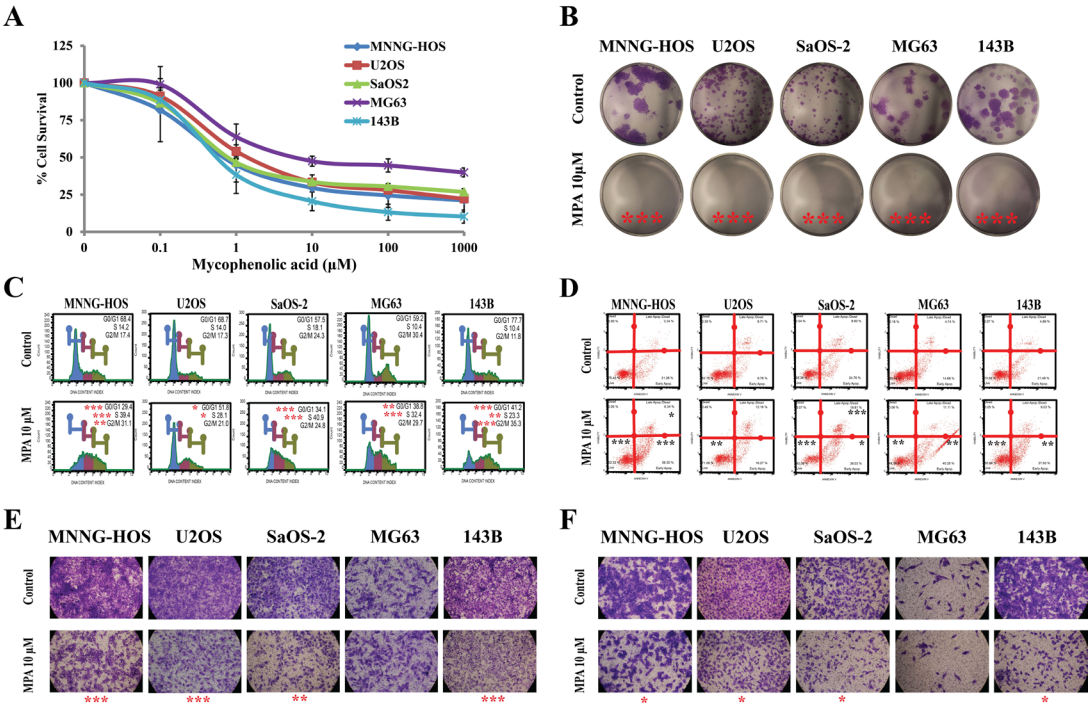

Figure 1. Cytotoxic and anti-metastatic effects of MPA on human osteosarcoma cell lines including MNNG-HOS, U2OS, SaOS-2, MG63 and 143B. (A) Osteosarcoma cells were treated with different concentrations (0.1-1000 μM) of MPA for 72 hours and MTT assay were performed to determine number of surviving cells. MPA at a concentration of 10 μM was used to treat osteosarcoma cells in the following assays; (B) colony-forming assay, (C) cell cycle analysis, (D) apoptotic cell death analysis, (E) cancer invasion assay and (F) cell migration assay.

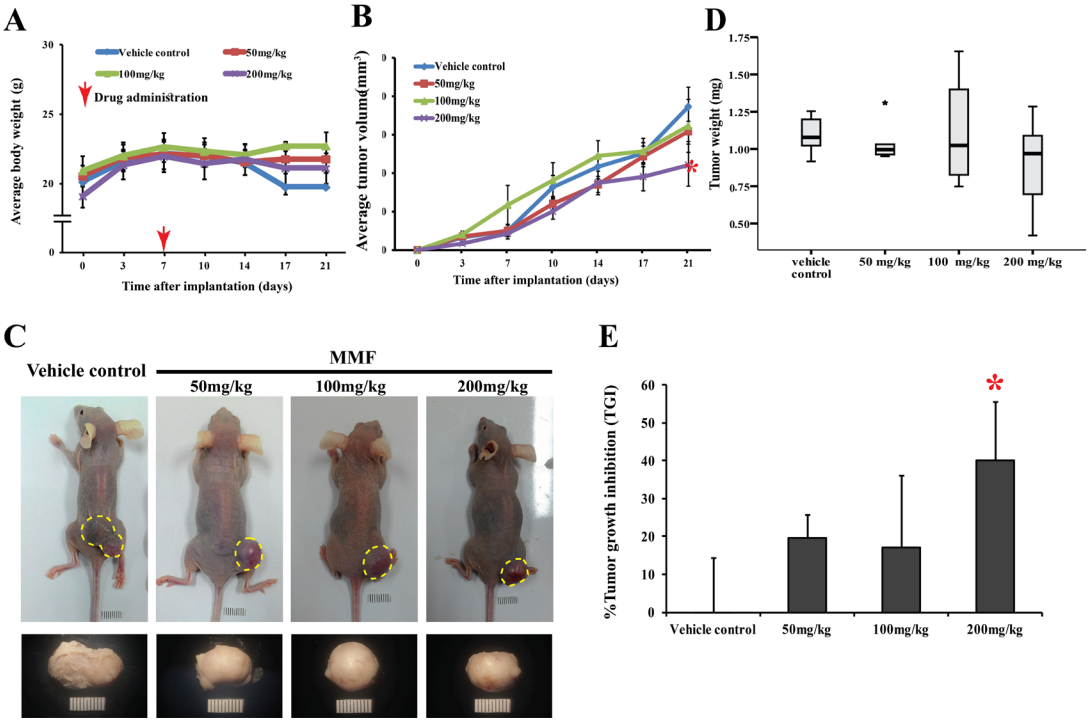

Figure 2. Anti-tumor effect of MMF on subcutaneous osteosarcoma xenograft in BALB/c nude mice. The mice were subcutaneously inoculated with 143B osteosarcoma cells into right posterior flank. After one week, the mice were randomized into 4 groups and were fed with different doses of MMF for 2 weeks. (A) Body weight and (B) tumor volume were measured every 3-4 days. After 2 weeks, mice were sacrificed, and (C) tumors were photographed and (D) weighted. (E) The percentage of tumor growth inhibition (%TGI) was calculated for each treatment group (t) versus vehicle control group (c) using initial (*i*) and final (*f*) tumor volume according to the formula: $\%TGI = (1 - [t_f - t_i] / [c_f - c_i]) \times 100$.

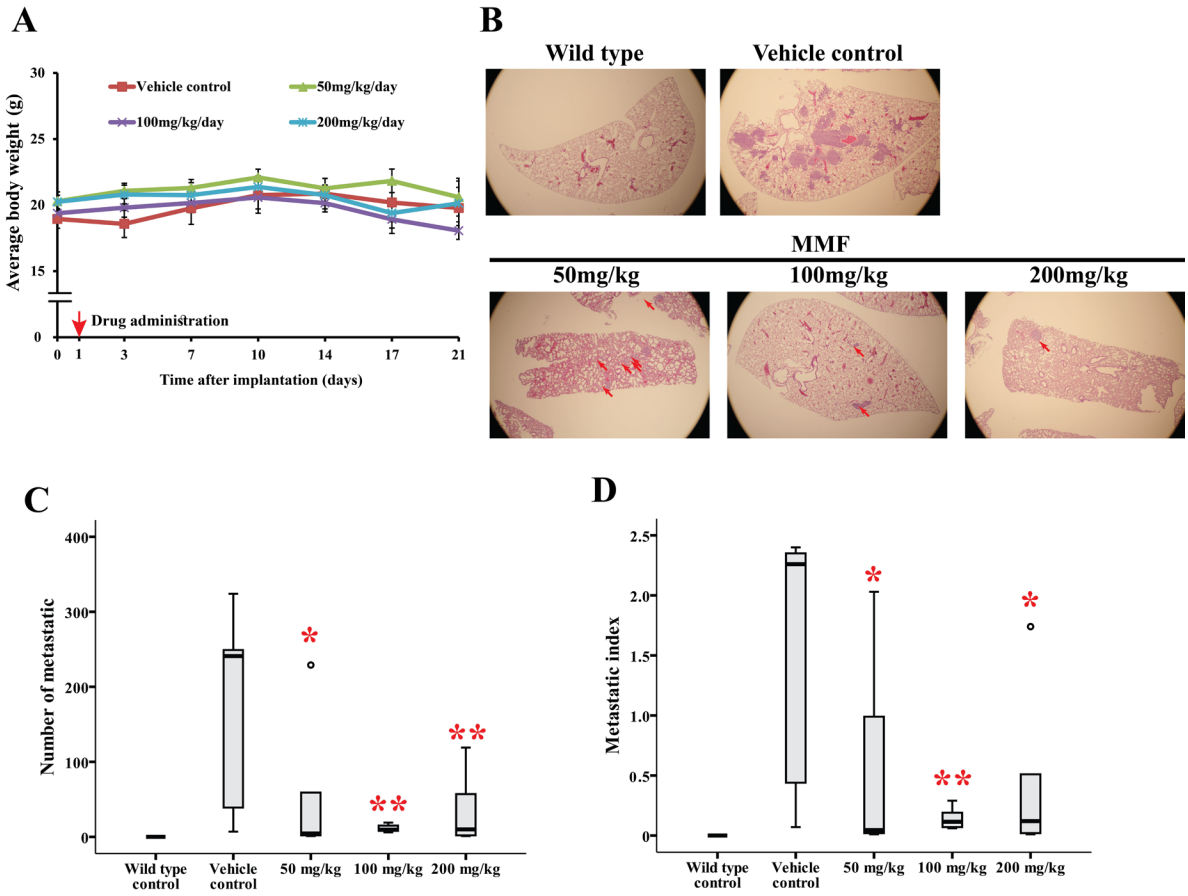

Figure 3. Anti-metastatic effect of MMF on lung metastasis of osteosarcoma xenograft in BALB/c nude mice. The 143B osteosarcoma cells were injected into tail vein of mice. On the following day (day 1), the mice were randomized into 4 groups and fed with different doses of MMF for 3 weeks. (A) Body weight was measured every 3-4 days. After 3 weeks, mice were sacrificed and lungs were collected and (B) histological studies were performed. (C) The numbers of metastatic tumor nodule in lungs were counted under a light microscope. (D) The metastatic index was calculated by the ratio of tumor nodule number per total lung area.

Poster 043 3040744

COMPLEX AUTOCRINE AND PARACRINE INTERACTIONS IN A SERIES OF SINGLE-BACKGROUND MURINE FIBROSARCOMA CELL LINES

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Objective: Cancer cell heterogeneity is an important clinical problem with implications both into clinical cancer progression and therapeutic response. One possibility how to experimentally tackle cancer heterogeneity is to dissect a complex tumour into discrete cancer cell lines, each with a unique and stable combination of transformation-related traits. Molecular comparison of the cancer cell lines then yields important insights into their complex relationships.

Methods: Towards this end, we established, from the H-2K/v-jun transgenic fibrosarcoma model, a unique single-background progression series of murine sarcoma cell lines, consisting of the slowly proliferating nonmotile and noninvasive cell line JUN-2, rapidly proliferating, motile and invasive cell line JUN-3, and the cell line JUN-2fos-3 that exhibits a unique transformation pattern, with little deregulation of cell growth and proliferation, but pronounced motility and invasiveness. This unique distribution of transformation related-traits made us possible to identify, using the genome-wide transcriptomic analysis, two separate groups of genes tentatively involved in sarcoma progression in a single analysis – on one hand, proliferation-related genes could be identified by their differential expression in JUN-3 compared to both JUN-2 and JUN-

2fos3, and, on the other hand, motility and invasiveness-related genes could be identified by their common expression pattern in JUN-2fos3 and JUN-3 cells compared to JUN-2. The high-throughput gene expression analysis has been performed using the GeneChip Mouse Genome 430 2.0 Array (ThermoFisher Scientific). Analysis of metabolic activity of sarcoma cells has been performed on the Seahorse XF Analyzer (Agilent).

Results: In total, we identified 277 upregulated and 212 downregulated unique transcripts in JUN-2 and JUN-2fos3 compared to the JUN3 cells (adjustP < 10^{-4}). Simultaneously, we showed 29 upregulated and 112 downregulated unique transcripts in JUN3 and JUN2fos3 compared to JUN2 cell cultures (adjustP < 10^{-4}). Initial inspection of JUN-3-overexpressed genes revealed a remarkable enrichment for growth factors or their receptors (amphiregulin, epiregulin, FGF-10 and -13, HGF, as well as PDGFRα), suggesting an autocrine growth regulation, as well as an enrichment for known motility factors in both JUN-3 and JUN-2fos3 cell lines (Ccl-8, Sema3A, Tspan2) hinting at autocrine motility regulation. Indeed, we could show that JUN-3 cells grew in a serum-independent manner and pharmacological inhibition of the Ccl-8 signaling significantly downregulated JUN-3 cell motility. Interestingly, JUN-3-conditioned medium dramatically downregulated proliferation of JUN-2 cells, and this could be followed to a dramatic decrease of their metabolic activity, suggesting the secretion of prominent growth inhibitor(s) as well. JUN-3 cells thus activate their own proliferation while at the same time inhibiting proliferation of other cell clones within the tumour. This observation could provide a new mechanistic explanation of the phenomenon of clonal dominance, a frequently observed aspect of cancer heterogeneity.

Conclusion: We believe that our progression series of single-background sarcoma cell lines can be very instrumental in deciphering both basic biological principles operating in sarcoma progression and intratumoural heterogeneity, and in pinpointing potential new sarcoma prognostic markers and/or promissing therapeutic targets. Supported by the Czech Grant Agency project No 17-17636S.

Poster 044 3042297

CXCR4 INHIBITORS AS CHEMOSENSITIZER IN BONE MARROW-DERIVED MESENCHYMAL STEM CELL-MEDIATED OSTEOSARCOMA AND SYNOVIAL SARCOMA CELL APOPTOSIS AND MIGRATION

Serena Pollino[1]*; Laura Pazzaglia*[1]*; Elisa Bientinesi*[1]*; Barbara Dozza*[2]*; Enrico Iucarelli*[2]*; Maria Serena Benassi*[1]*; Emanuela Palmerini*[3]

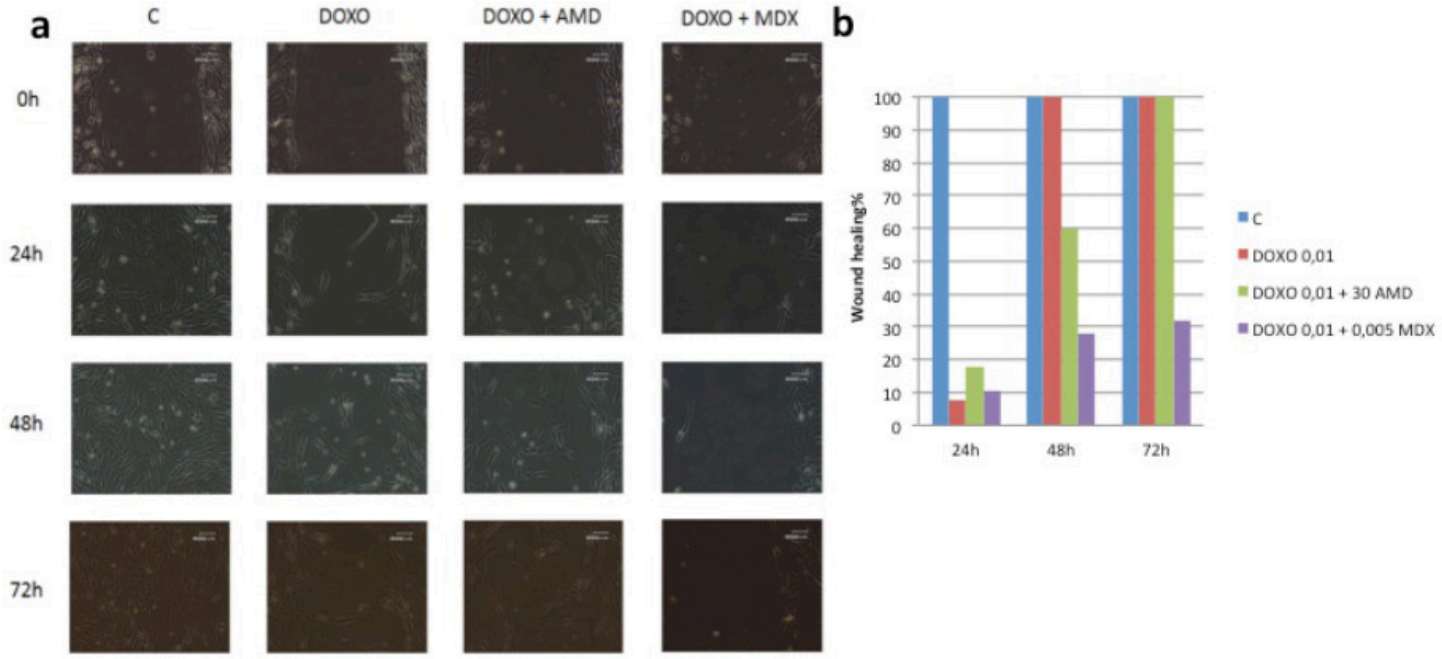
[1]Experimental Oncology Lab, Ortopedico Rizzoli, Bologna, Italy; [2]Osteoarticolar Regeneration Lab, Ortopedico Rizzoli, Bologna, Italy; [3]Chemotherapy Unit, Ortopedico Rizzoli, Bologna, Italy

Objective: CXCR4 antagonists can block CXCR4/stromal cell-derived factor 1 (SDF-1)interaction and has been shown effective in inhibiting tumor cell metastasis by targeting various pathways. Few are the studies on the combined effect of CXCR4 antagonist and chemotherapy on sarcoma cells migration, survival and growth. Also, bone marrow-derived mesenchymal stem cells (BM-MSCs) are recruited into the microenvironment of developing tumors, where they contribute to metastatic processes. Our goal was to investigate whether CXCR4 inhibitors and chemotherapy can act synergistically in sarcoma.

Methods: MDX1338, a fully human IgG(4) monoclonal antibody that specifically recognizes human CXCR4 and AMD3100, a highly specific chemokine receptor CXCR4 antagonist were employed in osteosarcoma (U2OS) and synovial sarcoma (SW982) cultured in BM-MSCs conditioned medium. Proliferation, apoptosis, and migration were assessed.

Results: Our data showed that U2OS and SW982 express CXCR4 in 98% and 83% of cells respectively and SDF1 in 80% and 41% of cells respectively. By the evidence that the treatment with MDX1338 and AMD3100 could reduce SW982 and U2OS proliferation and migration, and increase the apoptotic fraction, we evaluated the effect of combined treatments of CXCR4 inhibitors and doxorubicin. Combined treatment with doxorubicin and MDX1338 or AMD3100 was not synergic in terms of cell vitality, with over-imposable curves with doxorubicin alone or combined with CXCR4 antagonists both in synovial sarcoma and in osteosarcoma cell lines. On the opposite, a significantly increase of apoptosis and reduction of cell migration at 48h was demonstrated in SW982 cell lines when MDX1338 or AMD3100 were combined with doxorubicin, as compared to control and doxorubicin alone (FIGURE). Similarly, in U2OS cell lines, a significant increase of apoptosis was observed when AMD3100 (30µg/ml) was combined with 0.1 µM doxorubicin as compared to doxorubicin alone, associated with a slight decreaseof cell motility, while with MDX1338 the apoptotic rate increase was not significant.

Conclusion: Our results confirm that CXCR4 inhibitors may sensitize sarcoma cells cultured in BM-MSCs conditioned medium to chemotherapy , significantly increasing apoptosis in synovial sarcoma and osteosarcoma (AMD3100). Last, the combined treatment doxorubicin with CXCR4 inhibitors induced a cell migration slowdown, more evident in SW982 cells. The combined effect of trabectidin and CXCR4 inhibitors in synovial sarcoma cell lines is under investigation.



SW982 migration after combined treatments

Poster 045 3042289

THE PHOSPHATASE PTPRG CONTROLS FGFR1 ACTIVITY AND INFLUENCES SENSITIVITY TO FGFR KINASE INHIBITORS

Michal Kostas[1]; Ellen M. Haugsten[1]; Yan Zhen[2]; Vigdis Sørensen[2]; Patrycja Szybowska[2]; Elisa Fiorito[1]; Susanne Lorenz[1]; Antoni Wiedlocha[2]; ***Jørgen Wesche[1]***

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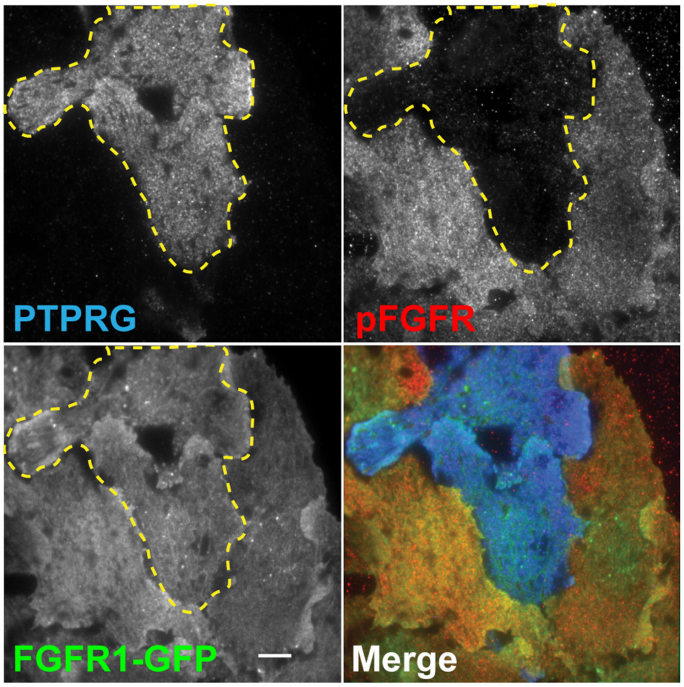
Objective: Recently, FGFR1 was found to be overexpressed in osteosarcoma and represents a possible target for precision medicine. However, because targeted cancer therapy based on FGFR inhibitors has so far been less efficient than expected, a detailed understanding of the target is important.

Methods: We have here applied proximity-dependent biotin labeling combined with label-free quantitative mass spectrometry to identify determinants of FGFR1 activity in an osteosarcoma cell line.

Results: Many known FGFR interactors were identified (e.g. FRS2, PLCG1, RSK2, SRC), but the data also suggested novel determinants. A strong hit in our screen was the tyrosine phosphatase PTPRG. We show that PTPRG and FGFR1 interact and colocalize at the plasma membrane where PTPRG directly dephosphorylates activated FGFR1. We further show that osteosarcoma cell lines depleted for PTPRG display increased FGFR activity and are hypersensitive to stimulation by FGF1. In addition, PTPRG depletion elevated cell growth and negatively affected the efficacy of FGFR kinase inhibitors.

Conclusion: Thus, PTPRG may have future clinical relevance by being a predictor of outcome after FGFR inhibitor treatment.



Poster 046 3042323

EUTHYROID HYPOTHYROXINEMIA [EH] MODULATED BY EXOGENOUS L -TRIIODOTHYRONINE MAY EXTEND SURVIVAL IN ADVANCED SARCOMA-AN UPDATED FOLLOW-UP

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Objective: There is preclinical and experimental evidence that physiological thyroxine [T4] is pro-oncogenic in solid tumors but that physiological triiodothyronine [T3] is 10-100 times less potent . Translational clinical studies in patients with terminal cancers have reported that lowering serum free thyroxine [hypothyroxinemia] in patients metabolically supported by exogenous T3 (EH) is associated with extended survival.The objective of this study was to substitute the less pro-oncogenic L-tri-iodothyronine [T3] for exogenous L-thyroxine [T4] in hypothyroid metastatic sarcoma patients and monitor outcomes.

Methods: All patients had Stage 4 soft tissue sarcoma deemed incurable by conventional means.Patients were converted abruptly from L-T4 (50-100 mcg daily), before, after or during the oncological treatment.Serum FT4 and TSH were regularly monitored to enable adjustments to drug therapy. After a week 'washout' period exogenous L-T3 12.5-37.5 mcg/day begun in two daily divided doses. In all patients FT4 levels had declined below the reference range to a nadir by 4 weeks. Survival is calculated from date of L-T4 cessation.

Results: Seventeen patients are included. M:F ratio 9;8,Median age 65 [range 31-70]. TUMOR TYPES: Liposarcoma -1 , Uterine Leiomyosarcoma (ULMS) - 7. Breast sarcoma - 2, Synovial sarcoma - 2, Undifferentiated pleomorphic sarcoma (UPS) including one cardiac sarcoma - 3, Fibrosarcoma -1, low grade uterine LMS -1. RESPONSE: 3 Patients CR (1 synovial, 1 UPS, 1 ULMS), 5 had PR, 4 had SD, 5 had PD. Median follow up is 20 months [4-60 months], Median Survival is not yet reached. One patient [Synovial sarcoma] is disease free (DF) at 84 months, one patient with breast and chest wall sarcoma is DF at 52 months after resection of the tumor, One patient with Leiomyosarcoma of uterus is alive without disease (DF after metastatectomies) for more than 33 months.

Conclusion: L-T3 supplemented patients with metastatic sarcoma have prolongation of survival. The LMS subset have an exceptional median survival of 19 months(5-33mo). The exceptional longevity observed in some patients suggests that induced EH might be a therapeutic option in incurable sarcoma patients. Prospective studies of induced EH in hypo and euthyroid patients might now be reasonably investigated.

Poster 047 3042408

NOVEL BIOINFORMATICS APPROACH FOR SARCOMA PROTEOGENOMICS; MUTATED NUCLEOTIDES AND AMINO-ACIDS GENERATOR (MUNAGE)

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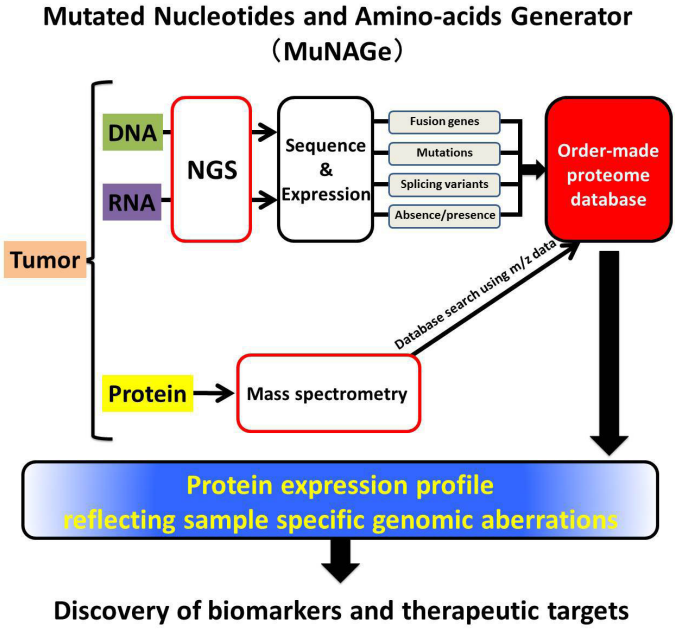
Objective: Proteogenomics is an approach to investigate the molecular backgrounds of diseases by integrating genome and proteome. Sarcomas are diseases caused by the accumulated genomics aberrations. Genomic aberrations are translated to proteomic ones, and transform the normal mesenchymal cells into fully malignant cells, controling the malignant behaviors of sarcoma cells. There are many proteomic events that play an important role but cannot be examined by the genomic approach. Those include the aberrant regulation of post-translational modifications, and protein amount. In this sense, the integrative and comprehensive understanding of genome and proteome is the essential approach to the disease mechanisms in sarcomas. Next-generation sequencing is a key technology in genomics, and a driving force technology in proteomics is mass spectrometry.

Through the experience of extensive sarcoma proteomics, we realized the inherent and overlooked problem in mass spectrometry. To identify proteins using mass spectrometry data, we always use the public protein database. However, the proteins with aberrant amino acid sequences, which are unique to individual protein tissue samples, are not recorded in the public database for mass spectrometric protein identification. As a consequence, although mass spectrometry detects the signals from peptides with aberrant amino acid sequences, we cannot identify them, and only proteins with normal sequence are studied by proteomics. This is a general problem of cancer proteomics using mass spectrometry. Proteins with unique amino acid aberrations should be strong candidates for biomarkers and therapeutic targets, because they are specific to tumors. Thus, it is critically problematic that we cannot observe them using a conventional proteomic approach. To address this issue, we aimed to create a novel bioinformatics tool, by which the individual genome data are translated to proteome database for mass spectrometric protein identification.

Methods: Software for proteogenomics was created using Python version 2.7.12 on Linux Mint version 18.1. Argparse version 3.2 was used as parser for command-line arguments. Biopython version 1.69 was used to manipulate FASTA files and translate RNA sequences to amino-acid sequences. This study included the genome and proteome data of cell lines. The RNA-seq data were obtained from Databse of Transcriptional Start Sites, and DNA Data Bank of Japan (https://dbtss.hgc.jp), and the genome data were given by Dr. A. Suzuki (The University of Tokyo). The proteome data were generated by Finnigan LTQ Orbitrap XL mass spectrometer equipped with a nanoelectrospray ion source (Thermo Fisher Scientific). Peptide search against the MuNAGe database was performed by Mascot version 2.5.1 (Matrix Science).

Results: We developed novel proteogenomics software, and named it as Mutated Nucleotides and Amino-acid generator (MuNAGe). MuNAGe constructs a sample-specific virtual proteome database for mass spectrometric protein identification. We compared the results of protein identification using the database generated by MuNAGe or the Swiss-Prot, a pulic proteome database. We found that the number of proteins identified by the database generate by MuNAGe was significantly larger than that of proteins detected using the Swiss-Prot. In addition, the proteins detected only by the database generated by MuNAGe included the cancer-associated proteins with unique mutations. As the input and output file formats for MuNAGe are general ones, our approach can be widely applied to the genome and proteome data of any clinical materials.



Conclusion: MuNAGe reveals a novel features of proteogenomics, which cannot be obtaied otherwise. We participate to the International Cancer Proteogenomics Consortium (ICPC). We will share our proteogeonomics data of sarcomas as well as MuNAGe in the ICPC. We anticipate that proteogenomics will identify proteins with unique mutations, that can be used as candidate drug targets or biomarkers in sarcomas.

Poster 048 3042413

EFFECT OF ANLOTINIB, A NOVEL SMALL MOLECULAR TYROSINE KINASE INHIBITOR, ON GROWTH, METASTASIS AND ANGIOGENESIS IN OSTEOSARCOMA

Yingqi Hua[1]*; Gangyang Wang*[1]*; Mengxiong Sun*[1]*; Tao Zhang*[1]*; Wei Sun*[1]*; Hongsheng Wang*[1]*; Fei Yin*[1]*; Zhuoying Wang*[1]*; Jing Xu*[1]*; Zhenfeng Duan*[2]*; Zhengdong Cai*[1]

[1]*Shanghai General Hospital, Shanghai, China;* [2]*David Geffen School of Medicine at UCLA, Los Angeles, CA, USA*

Objective: Osteosarcoma is the most common primary malignant bone tumor in children and adolescents, with highly aggressive and early systemic metastases. The survival rates for osteosarcoma remain relatively low over the past two decades. Studies aiming to find new or alternative therapies for patients with refractory osteosarcoma are urgently needed. Anlotinib, a novel multi-targeted tyrosine kinase inhibitor (TKI), has exhibited encouraging clinical activity in a variety of solid tumors, whereas its effect on osteosarcoma has never been investigated. Therefore, this study aimed to investigate the anti-tumor activity and underlying mechanism of anlotinib in osteosarcoma.

Methods: Various *in vitro* and *in vivo* models of human osteosarcoma were used to determine the anti-proliferative, anti-angiogenesis and anti-metastasis efficacy of anlotinib.

Results: Our results showed that anlotinib markedly suppressed the growth and increased the chemotherapy sensitivity of osteosarcoma. In addition, anlotinib potently inhibited migration and invasion and reversed epithelial-mesenchymal transition (EMT) in osteosarcoma cells. A phospho-RTK antibody array showed that the antitumor mechanism and targets of anlotinib. Immunoblot analysis confirmed that anlotinib effectively suppressed the phosphorylation of MET, VEGFR2 and the downstream signaling pathway activation. Furthermore, we demonstrated that anlotinib also blocked hepatocyte growth factor (HGF)-induced cell migration, invasion and VEGF-induced angiogenesis. Notably, a 143B-Luci orthotopic osteosarcoma model further showed that intraperitoneal injection of anlotinib significantly inhibited growth and lung metastasis of implanted tumor cells.

Conclusion: Our preclinical work indicates that anlotinib acts as a novel inhibitor of VEGFR2 and MET that blocks tumorigenesis in osteosarcoma.

Poster 049 3042579

EFFECT OF CHEMOTHERAPY ON CANCER STEM CELLS AND TUMOR-ASSOCIATED MACROPHAGES IN A PROSPECTIVE STUDY OF PREOPERATIVE CHEMOTHERAPY IN SOFT TISSUE SARCOMA

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Objective: Cancer stem cells may differ in their response to chemotherapy from other tumor cells. We examined changes in putative stem cell markers, angiogenesis, and macrophage infiltration before and after chemotherapy in patients with soft tissue sarcoma (STS).

Methods: This study examined the expression of the putative cancer stem cell markers CD44, ALDH1, and CD133; the angiogenesis marker CD31; and the macrophage marker CD68 by immunohistochemistry in STS before and after 4 cycles of chemotherapy with pegylated-liposomal doxorubicin and ifosfamide in 31 patients with high-grade STS in a prospective clinical trial.

Results: None of the markers clearly identified cancer stem cells in STS samples. CD31 staining was generally similar before and after chemotherapy. CD68 positive macrophages represented an unexpectedly prominent component in viable tumor areas in pre-treatment STS biopsies, ranging from <5% to >50%. Furthermore, macrophages expressed CD44 and ALDH1. High macrophage infiltration appeared more frequent in undifferentiated pleomorphic sarcomas than in the other diagnoses studied, though the sample sizes were small. Synovial sarcomas had lower CD68 staining (fewer macrophages) when compared with all other diagnoses. Pre-chemotherapy CD68 staining (macrophage density) correlated positively with the baseline SUVmax, and negatively with the percent of viable tumor cells in post-chemotherapy resection samples. In other words, cases with more CD68 positive cells at biopsy had fewer viable tumor cells at resection, suggesting a better response to chemotherapy.

Conclusion: In conclusion, CD133, CD44, and ALDH1 are not likely to be useful markers of cancer stem cells in STS. However, our observation of infiltrating macrophages in STS specimens indicates that these immune cells may contribute significantly to STS biology and response to chemotherapy, and could provide a potential target of therapy.

Poster 050 3042624

DRUG SENSITIVITY TESTING ON PATIENT-DERIVED SARCOMA CELLS PREDICTS PATIENT RESPONSE TO TREATMENT AND IDENTIFIES C-SARC INHIBITORS AS ACTIVE DRUGS FOR TRANSLOCATION SARCOMAS

Bertha Brodin[1]*; Antroula Papakonstantinou*[2]*; Elisabet Lidbrink*[2]*; Otte Brosjö*[3]*; Asle Hesla*[3]*; Henrik Bauer*[3]*; Swapnil Potdar*[4]*; Olli Kallioniemi*[5]*; Christina Linder-Stragliotto*[2]
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Objective: The objective of this study was to evaluate the use of phenotypic and genotypic screening on patient- derived cells as a tool for identifying potential treatments for sarcoma patients with refractory disease.

Methods: We cultured and characterized patient-derived sarcoma cells and evaluated their sensitivity to 525 anti-cancer agents at five different concentrations. The drug library was composed of FDA approved drugs and agents in clinical trials. In total, 14 soft tissue sarcomas, 9 bone sarcomas and 5 healthy mesenchymal primary cell cultures were analyzed. The sarcoma biopsies and derived cells were characterized by gene panel sequencing and cancer-driver gene expression. Tumor cell representativity in translocation-associated sarcomas grown *in vitro* was evaluated by detecting specific fusion oncoproteins *in situ* using proximity ligation assay.

Results: Soft tissue sarcomas and healthy mesenchymal cell cultures were established from patient biopsies with a success rate of 62 %. Gene panel sequencing showed identical gene mutations in the patient tumor biopsy and derived cultured

cells. Similarly, fusion oncoproteins were expressed in both translocation-sarcoma biopsies and the derived cultured cells, confirming high representativity of sarcoma cells in the cultures. The drug sensitivity testing identified targeted inhibitors active on sarcomas but less toxic for bone marrow and normal mesenchymal cells. Dasatinib was identified as an active drug in all translocation sarcoma tested. The drug sensitivity of the patient-derived sarcoma cells correlated with the response to the actual patient treatment.

Conclusion: Our results show that patient derived sarcoma cells can be used in genotypic and phenotypic screens to identify potentially efficient drugs to treat sarcoma patients with poor treatment options.

Poster 051 3042658

THE EFFECT OF BUPIVACAINE AND LIDOCAINE ON OSTEOSARCOMA CELLS

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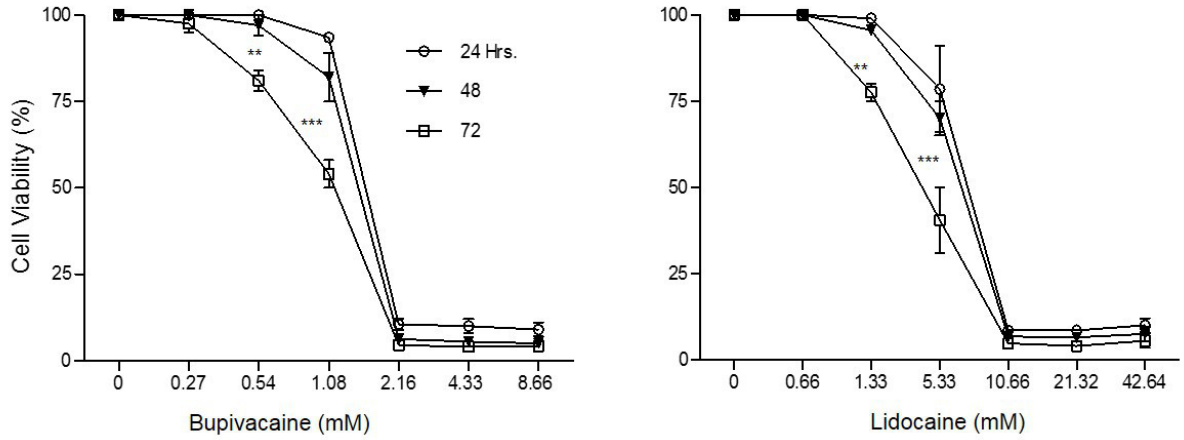
Objective: Osteosarcoma (OS) is an aggressive malignant tumor of the skeletal system characterized by the direct formation of immature bone by tumor cells. OS typically affects the long tubular bones of children. Local anesthetics (LAs) have been shown to be toxic to certain malignancies. To our knowledge this is the first study investigating the effects of LAs on OS. The purposes of this study were to assess whether bupivacaine or lidocaine could induce apoptosis in an OS cell line and to evaluate the underlying mechanism.

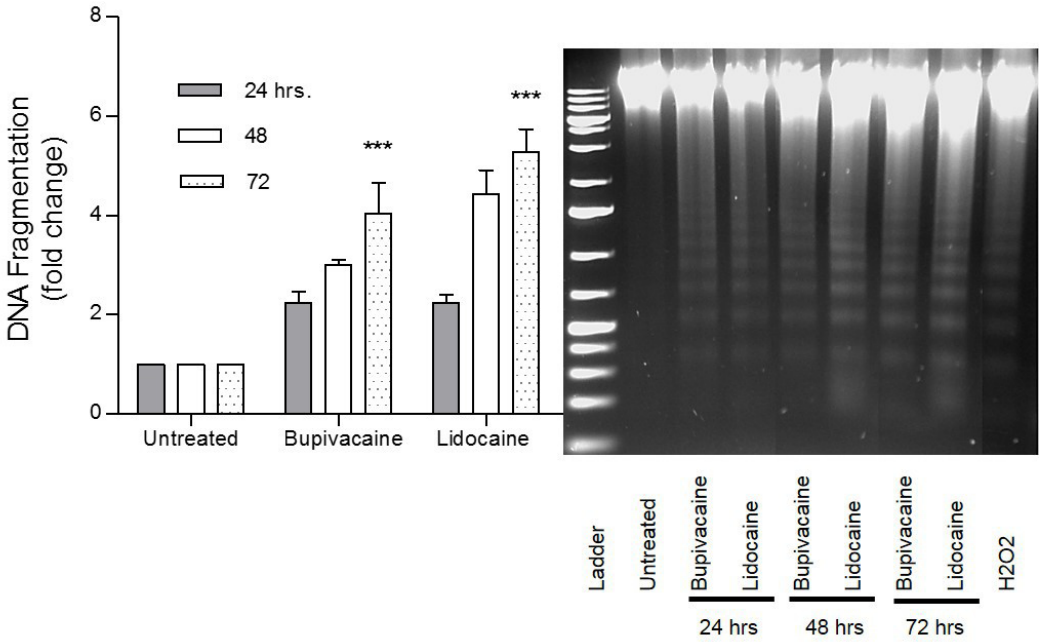
Methods: Rat OS cells (UMR-108) were exposed to various concentrations of LAs. Cell viability, cytotoxicity, apoptosis induction, DNA fragmentation and the expression of apoptosis-related markers were examined by MTT assay, colony formation assay, flow cytometry, agarose gel electrophoresis and western blot, respectively.

Results: Bupivacaine and lidocaine induced apoptosis of rat OS cells in a dose- ($p<0.05$) and time-dependent ($p< 0.01$) manner. Apoptosis was confirmed by cell morphology, annexin positivity, and activation of caspase-3 ($p<0.001$). The molecular data showed that LAs could significantly down-regulate the expression of Bcl-2 ($p<0.001$), survivin $P<0.001$), pro-caspase-3 ($p< 0.001$), PARP ($p<0.01$), up-regulate expression of Bax ($p< 0.05$), and cause cleavage of both caspase-3 and PARP ($p<0.01$).

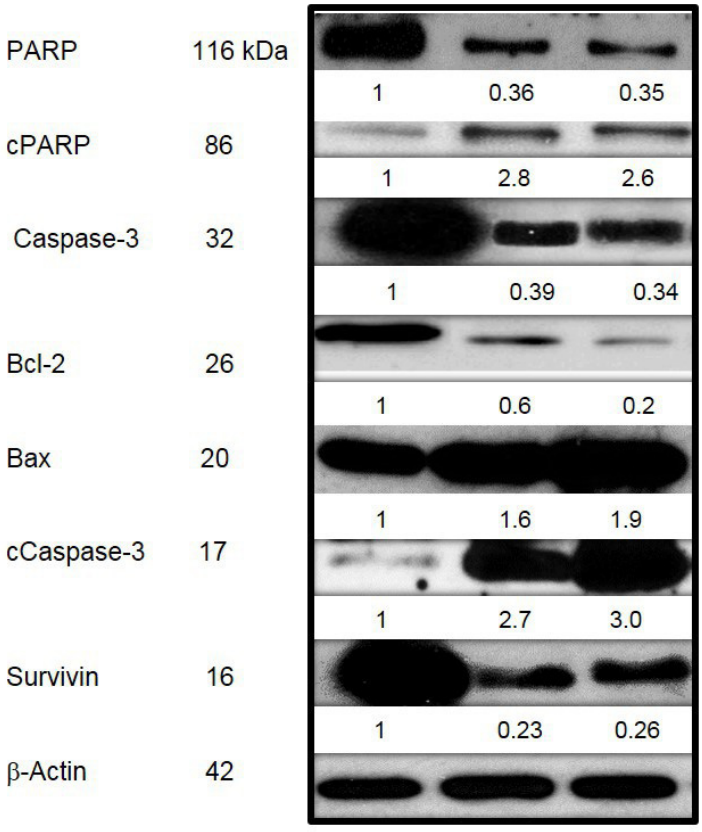
Conclusion: These findings demonstrate that LAs are cytotoxic to rat OS cells, decrease colony formation, and cause the cell morphology to resemble that of apoptotic cells. LAs also induce apoptosis in a dose- and time-dependent manner. The caspase-dependent pathway was, at least in part, involved in the bupivacaine and lidocaine mediated apoptosis.



Effect of LAs on OS cells. The UMR-108 cells were treated with bupivacaine and lidocaine for 24, 48 and 72 hours. Then MTT assays were performed at 24, 48 and 72 hour intervals and compared to the control. The percentage of viable cells were then compared to the control ($p< 0.01$ **, $p< 0.05$ *, $p> 0.05$ ns).



DNA fragmentation of OS cells occurred in a time-dependent manner. UMR-108 cells were exposed to bupivacaine (1.08 mM) and lidocaine (5.3 mM) for 24, 48, and 72 hours. The genomic DNA was applied to 1.5% agarose gels containing µg/ml of ethidium bromide. A DNA step ladder, (1 kb) and the DNA from apoptotic UMR-108 cells induced by H_2O_2 (0.4 mM) were used as positive control. The DNA fragmentation pattern was examined in photographs taken under UV illumination ($p< 0.01$ **, $p< 0.05$ *, $p> 0.05$ ns).



LAs modulate the expression of apoptosis related proteins. UMR-108 cells were exposed to bupivacaine (1.08 mM) and lidocaine (5.3 mM). Equal amounts of protein from each sample were loaded and separated through 12% SDS-PAGE gels and then transferred to PVDF membranes. The following antibodies were used; Bcl-2, Bax, caspase-3, cleaved caspase-3 PARP, cleaved PARP, and b-actin. The bands were visualized by an enhanced chemiluminescence kit per instructions. Data were normalized to corresponding values of b-actin densitometry.

Poster 052 3042684

THE PROTEIN EXPRESSION OF NF1; P16INK4A, PTEN AND THEIR INVOLVED SIGNAL PATHWAY FATORS IN UNDIFFERENTIAED PLEOMORPHIC SARCOMA

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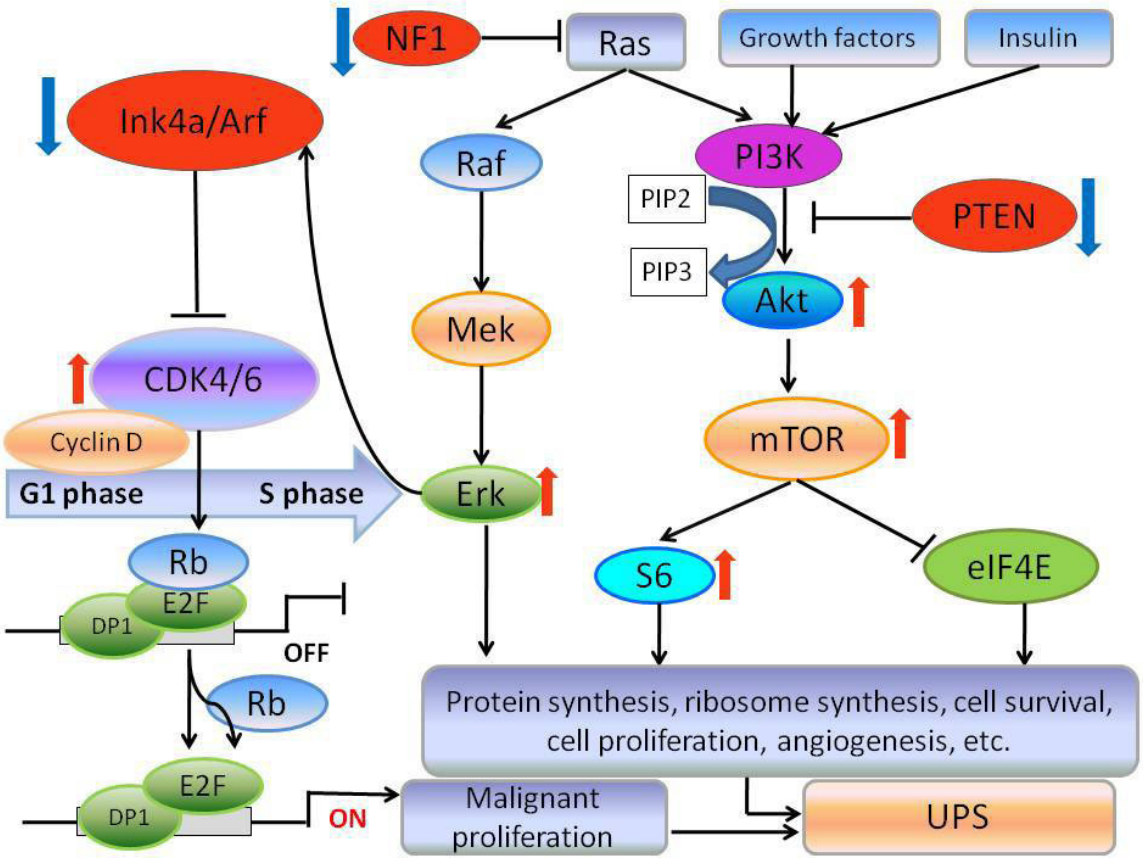
Objective: Undifferentiated pleomorphic sarcoma (UPS) with the highest constituent ratio is the important subtype of Soft tissue sarcomas (STS). NF1, $p16^{Ink4a}$ and PTEN are antioncogenes, however, the protein expression of NF1, $p16^{Ink4a}$, PTEN alone/together, and their involved signal pathway factors in UPS is unknown. In order to explore the protein expression of NF1, $p16^{Ink4a}$, PTEN and the important protein of their involved signal pathways in UPS, and to provide evidence and clue for the occurrence of soft tissue sarcoma.

Methods: 68 pairs of sarcoma tissues and adjacent normal muscle tissue were collected from surgical resection in Department of bone and soft tissue sarcoma in Henan Province Cancer Hospital. The protein expression of NF1, $p16^{Ink4a}$, PTEN was detected using immunohistochemistry, and the ratio of two or three low-expressed protein was analyzed. Then the important phosphorylated protein expression of p-Akt, p-mTOR, p-S6 and p-Erk in these three antioncogenes-involved signal pathways in UPS sarcoma tissues and adjacent tissues was determined using immunohistochemistry, the combination of CDK6 and Cyclin D1 was detected using immunofluorescence double staining and confocol.

Results: In 68 cases of UPS sarcoma tissues, the positive rates of NF1, $p16^{Ink4a}$ and PTEN were decreased compared to those in adjacent tissues (P<0.05). Furthermore, in 68 UPS patients, 4 patients (5.88%) were found with NF1(-)$p16^{Ink4a}$(-) PTEN(+) or NF1(+)$p16^{Ink4a}$(-) PTEN(-) in sarcoma tissue, 14 patients (20.59%) with tumor suppressor protein expression of NF1 (-) $p16^{Ink4a}$ (+) PTEN (-); and 19 patients (27.94%) with low protein expression of NF1 (-) $P16^{Ink4a}$ (-) PTEN (-). In addition, the protein expression of p-Akt, p-mTOR, p-S6 and p-Erk in UPS sarcoma tissues were increased compared with those in adjacent tissues (P<0.05). And the rate of positive cell of the combination of CDK6 and Cyclin D1 in UPS sarcoma tissues was (19.50±3.66)%, but there was no positive cell in adjacent tissues.

Conclusion: Low protein expression of NF1, $p16^{Ink4a}$ and PTEN alone/together, and the activation of their involved Ras-Raf-Mek-Erk, PI3K-Akt-mTOR-S6, CDK6-Cyclin D1 signal pathways were associated with the occurrence of UPS.



Poster 053 3042693

TWO NOVEL HUMAN MYXOFIBROSARCOMA CELL LINES REPRESENT A CELLULAR MODEL FOR TUMOR HETEROGENEITY

Birgit Lohberger[1]*; Nicole Stuendl*[1]*; Andreas Leithner*[1]*; Beate Rinner*[2]*; Stefan Sauer*[3]*; Karl Kashofer*[3]*; Bernadette Liegl-Atzwanger*[3]

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Objective: Human cancers frequently display substantial intra-tumoural heterogeneity in virtually all distinguishable phenotypic features, such as cellular morphology, gene expression metabolism, and metastatic potential. Myxofibrosarcoma (MFS) comprises a spectrum of malignant neoplasms with prominent myxoid stromata, cellular pleomorphism, and distinct curvilinear vascular patterns. These neoplasms mainly affect patients in the sixth to eighth decades of life and the overall 5-year survival rate is 60-70%. Novel MFS cell lines, which enrich the bank of publicly available cell lines, are of extraordinary importance.

Methods: After the establishment of a novel MFS cell line with two well defined sub-clones called *MUG-Myx2a* and *MUG-Myx2b*, cells were characterized using short tandem repeat (STR), next generation sequencing (NGS) mutation analysis, and copy number variation (CNV). The growth behaviour and migration potential of the cells were analysed with the xCELLigence system and an MTS assay. The tumourigenicity of *MUG-Myx2a* and *MUG-Myx2b* were proved in female nu/nu Foxn1 mice.

Results: The frozen primary parental tumour tissue and both MUG-Myx2 cell lines showed the same STR profile. The facts that *MUG-Myx2a* showed higher proliferation activity, faster migration, and enhanced tumourigenicity were of particular interest. NGS mutation analysis revealed corresponding mutations in the FGFR3, KIT, KDR, and TP53 genes. In variation from this, the *MUG-Myx2a* cell lines had additionally a PTEN mutation. Analysis of copy number variation (CNV) revealed a highly aberrant karyotype with frequent losses and gains in the tumour sample. The two *MUG-Myx2* cell lines share several CNV features of the tumour tissue, some CNV are only present in both cell lines and each cell line also harbours private gains and losses.

Conclusion: The well-characterised novel MFS cell lines *MUG-Myx2a* and *MUG-Myx2b* will be a useful tool to gain further insights into the pathogenesis and tumour heterogeneity of MFS and explore new treatment options.

Poster 054 3042695

APOPTOTIC INDUCTION AND G1 CELL CYCLE ARREST OF MULTIDRUG RESISTANT SARCOMA CELL LINES BY THE HISTONE DEACETYLASE INHIBITORS VERINOSTAT AND PANOBINOSTAT

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Objective: Synovial sarcoma and high grade chondrosarcoma are characterized by their lack of response to conventional cytotoxic chemotherapy, the tendency to develop lung metastases, and low survival rates. Research within the field prioritizes the development and expansion of new treatment options for dealing with unresectable or metastatic diseases. Numerous clinical trials using histone deacetylases inhibitors (HDACi) have shown specific efficacy as an active antitumor agent for treating a variety of solid tumors. However, as of yet the effect of different HDACi on human synovial- and chondrosarcoma cells has not been investigated.

Methods: The effect of different HDACi on cell viability and proliferation was analyzed using MTS assay and the xCELLigence technology. FACS analysis was performed to determine the cell cycle profiles. The expression of class I HDACs, the phosphorylation of cell cycle regulator proteins, and PARP cleavage was examined using western blotting. The apoptotic induction was proved using Caspase-Glo® 3/7 assay and caspase-3 cleavage FACS analysis. To determine the synergistic effect of HDACi and doxorubicin the MTS assay has been applied.

Results: In this study, vorinostat (SAHA), panobinostat (LBH-589), and belinostat (PXD101) decreased cell viability of synovial sarcoma (SW-982) and chondrosarcoma (SW-1353) cells in a time- and dose dependent manner and arrested SW-982 cells in the G1/S phase. Western blot analysis determined the responsible cell cycle regulator proteins. In addition, we found apoptotic induction by caspase 3/7 activity, caspase 3 cleavage, and PARP cleavage. In SW-1353 cells only SAHA showed comparable effects. Noteworthy, all HDACi tested had synergistic effects with the topoisomerase II inhibitor doxorubicin in SW-1353 chondrosarcoma cells making the cells more sensitive to the chemotherapeutic drug.

Conclusion: Our results show for the first time that SAHA and LBH-589 reduced viability of sarcoma cells and arrested them at the G1/S checkpoint, while also inducing apoptosis and enhancing chemotherapeutic sensitivity, especially in chondrosarcoma cells. These data demonstrate the exciting potential of HDACi for use in sarcoma treatment.

Poster 055 3042709

THERAPEUTIC VULNERABILITIES IN UNDIFFERENTIATED SARCOMAS

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Objective: Undifferentiated sarcomas represent one of the most frequently diagnosed sarcoma subtypes and are categorized primarily based on morphological criteria (spindle cell, pleomorphic, round cell, epithelioid, not otherwise specified). Very few recurrent genomic events have yet been found and classical chemotherapeutic drugs remain the pillar of treatment. Nonetheless, the prognosis is poor in patients with metastatic disease. Given the paucity of cell line or animal models for this sarcoma subtype, we sought to use short-term cultures and patient-derived xenograft (PDX) models to identify druggable pathways in a drug-to-target approach.

Methods: Surgical specimens were digested by collagenase and dispase to generate PDX models and conduct drug screens in short-term cultures using 96-well flat-bottomed plates for sulforhodamine B assays. A panel of 20 compounds targeting key oncogenic pathways were used (Table 1) at two concentrations that were deemed therapeutically achievable. Genomic analysis was performed on an Illumina MiSeq system using a customized cancer gene panel. For validation purposes, the TCGA (The Cancer Genome Atlas; localized undifferentiated sarcoma, n=49) and DKTK MASTER (German Cancer Consortium Molecularly Aided Stratification for Tumor Eradication Research; metastatic undifferentiated sarcoma, n=24) datasets were queried for patients with undifferentiated soft-tissue sarcoma who had undergone whole-exome sequencing.

Results: The top three compounds identified in 10 short-term cultures were the PI3K inhibitor dactolisib, the histone deacetylase inhibitor panobinostat, and the conventional cytotoxic drug doxorubicin, which served as control. In four of nine samples, we found gene mutations affecting the PI3K signaling network (PTEN, NF1 [n=2], TSC1). The database queries revealed somatic mutations that may confer sensitivity to PI3K pathway inhibition in 17% (TCGA: PIK3CA [n=2], PTEN, TSC1, TSC2, RAS, NF1 [n=2]) and 12.5% (MASTER: TSC2 [n=2], AKT1) of cases. A novel, tumorigenic cell line (JUPS) representing high-grade myxofibrosarcoma was generated from one of the short-term cultures. JUPS exhibited strong phosphorylation of pAKT and pS6 and a high sensitivity to dactolisib (IC50: 35nM) even despite lacking activating mutations inside this pathway.

Conclusion: Short-term cultures represent a valuable tool to study drug sensitivity in undifferentiated sarcomas. Our drug-to-target screen revealed the PI3K/mTOR axis as a potentially druggable pathway. Mutational analyses provide evidence for genomic alterations in both localized and metastatic undifferentiated sarcomas that could sensitize cells to PI3K/mTOR inhibitors and serve as predictive biomarkers of response.

Pathway	Inhibitor	Company	Target	Concentration		Trial status
				low	high	
TGF-B	SB - 525334	Generic	TGF-B/ALK5	500nM	2µM	preclinical
WNT	XAV939	Cayman	Tankyrase	50nM	200nM	preclinical
Hedgehog	sonidegib	Novartis	Smoothend	500nM	1µM	phase II
HIF1a	topotecan	generic	Topoisomerase	2nM	10nM	approved
JAK/STAT	tasocitinib	Pfizer	JAK3	200nM	1µM	phase III
	S31-201	NCI	STAT3	100µM	500µM	preclinical
RAS/RAF	PD0325901	Pfizer	MEK	10µM	20µM	phase II
	SP600125	Celgene	JNK	500nM	2µM	phase II
	RAF265	Novartis	RAF wt, bRAF mutant	100nm	500nM	phase II
PI3K/PTEN	dactolisib	Novartis	PIK3K/MTOR	100nM	500nM	phase II
	MK-2206	Merck	AKT	2µM	10µl	phase II
	panobinostat	Novartis	HSP90 / pan-DAC	50nM	100nM	approved
	everolimus	Novartis	MTOR	200nM	400nM	approved
Apoptosis	navitoclax	Abbot	BCL-2	1µM	5µM	phase II
	nutlin-3	Roche	MDM2/p53	5µM	10µM	phase I
DNA Damage Control	veliparib	Abbot	PARP	2.5µM	5µM	phase II
	topotecan	Generic	Topoisomerase	2nM	10nM	approved
	cisplatin	Generic	DNA	1µM	5µM	approved
Control G1/S Transition	panobinostat	Novartis	Pan-DAC	50nM	100nM	phase II

Poster 056 3042722

SCREENING OF SYNERGISTIC REAGENT WITH PAZOPANIB AGAINST OSTEOSARCOMA USING COMPOUND LIBRARY.

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Objective: Osteosarcoma(OS) is the most common type of primary malignant bone tumor. The standard treatment of OS is surgical resection and chemotherapy. Furthermore, the regimen of MTX, CDDP, ADM and IFO have not changed over 10 years. Further prognostic improvement needs development of new strategy for OS treatment. Pazopanib(PZP) is an inhibitor of multi-tyrosine kinase including, PDGFR, and c-kit. PZP. PZP already demonstrated remarkable antitumor activity against soft tissue sarcoma. Additionally, PZP can be effective in treating patients with metastatic OS. The purpose of this study is to establish a new cocktail for OS treatment with PZP and to determine influential molecule for tumor cell proliferation.

Methods: Screening study: Human OS cells (MG63) were used. Cells were seeded on 96well plates (30000cells/well/100uL) with or without PZP (10uM). The candidate of synergetic effect with PZP was screened by compound library from Screening Committee of Anticancer Drugs (SCADS). Cell viability was assessed by MTS assay after a 24-hour treatment.
In vitro study of PZP and Crizotinib(CRZ): Human OS cells (MG63, 143B and HuO9) and mouse OS cells (LM8) were seeded on 96well plates (3.0×10^4cells/well/100uL). PZP and CRZ were treated for 24hours or 48hours. Cell viability was assessed by MTS assay.
Western blotting: MG63 were seeded on 6well plates (8.0×10^5cells/well/100uL) and divided into 4 groups: control group, PZP treated group, CRZ treated group, and PZP and CRZ treated group. These agents were treated for 30 minutes, 6hours, 12hours or 24hours. The concentration of PZP and CRZ was 10 μM. Proteins will be extracted from cell lysates and the samples will be analyzed by western blotting.
In vivo study: In vivo study was performed on 32 female BALB-C nu/nu mice, after permission from the committee of animal research of Mie University. OS cells(143B) were injected subcutaneously in mice (5.0×10^6cells/200uL). After tumor were engrafted, mice were administered PZP and CRZ orally (PZP:50mg/kg /day CRZ:25mg/kg/day). Groups were divided into next 4 groups: control group, PZP administered group, CRZ administered group, PZP and CRZ administered group. Tumor size was evaluated twice weekly.

Results: Screening study: Cell viability of MG63 was evaluated by MTS assay. Only 5 reagents indicated over 60% reduction of cell viability compared to control. In the 5 reagents, we excluded cytotoxic regents and narrowed down to CRZ among the 324 reagents.
In vitro study of PZP and CRZ : The cell viability were evaluated by MTS assay. Monotherapy of PZP or CRZ dose-dependently decreased tumor cell viability. The combination therapy of PZP and CRZ indicated remarkable synergistic effect against tumor cell proliferation (Fig.1) (Kruskal-Wallis Test: $P<0.01$). This synergistic effect was more evident at 48h than at 24h. The results of 143B, HuO9 and LM8 showed same results of MG63 (data not shown).
Western blotting: p-STAT-3 and p-Akt were decreased in PZP and CRZ treated group compared to control group 30 minutes after treatment (Fig.2). Cleaved caspase-3 was increased in PZP and CRZ treated group compared to control group at 6h and 12h after treatment (Fig.2). Cleaved PARP was increased in PZP and CRZ treated group compared to control group at 12h and 24h after treatment (Fig.2).
In vivo study: Tumor size was larger in control group than the other groups. There were tendency that tumor was slow growth especially in PZP and CRZ administered group compared to control group (Fig.3).

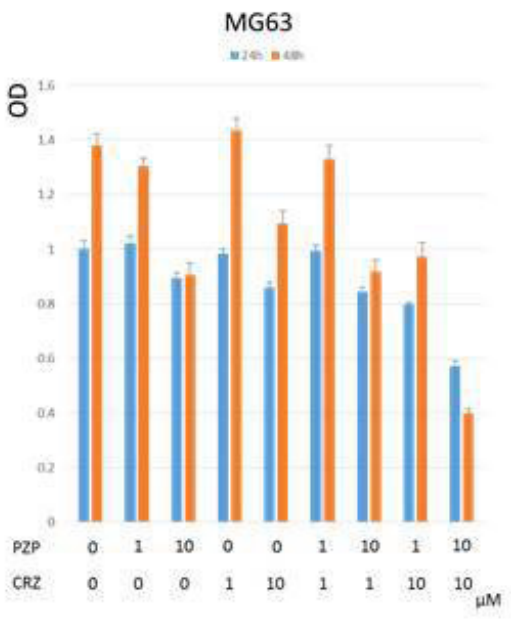

Figure 1

Conclusion: In this study, the combination therapy of PZP and CRZ showed a remarkable anti-proliferative effect against OS cells.From the western blot analysis, this combination therapy inhibited tumor growth by inducing apoptosis and interrupting cell cycle progression.
PZP and CRZ combination therapy may inhibit tumor progression in the clinical situation and to create a new inhibitor for c-kit, PDGFR, and ALK may have synergistic effect for OS treatment. This needs further study.

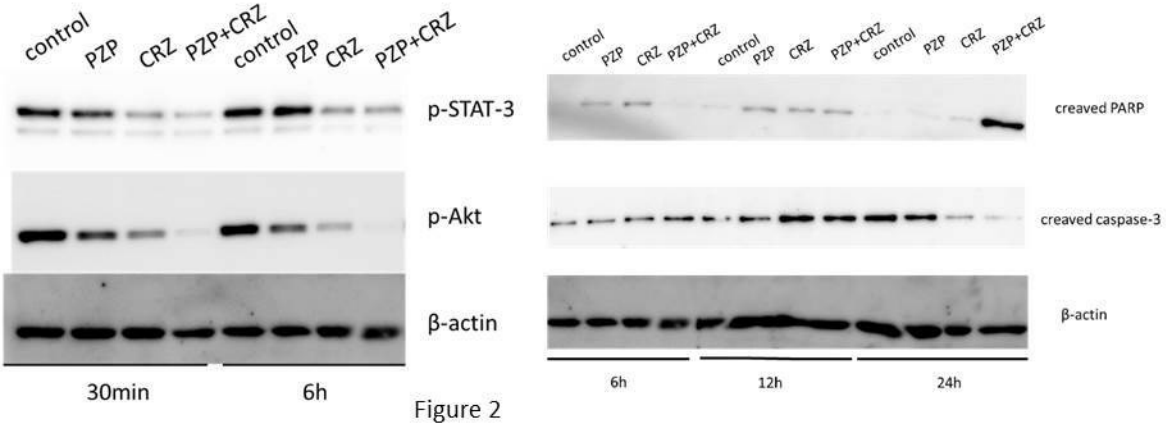

Figure 2

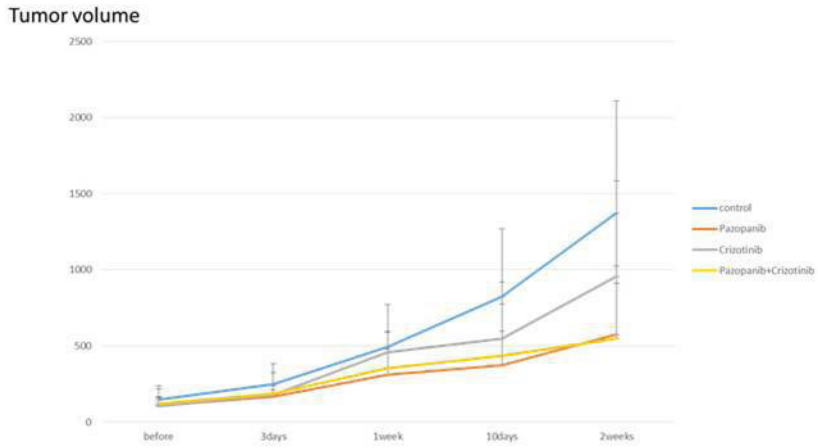

Figure 3

Poster 057 3042757

TARGETTING EPIDERMAL GROWTH FACTOR RECEPTORS AND UROKINASE-TYPE PLASMINOGEN ACTIVATOR RECEPTORS FOR SARCOMA THERAPY

Ashley J. Graef[1]*; Jong-Hyuk Kim*[1]*; Daniel A. Vallera*[1]*; Jaime F. Modiano*[1]
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Objective: eBAT is a bispecific angiotoxin consisting of truncated, deimmunized *Pseudomonas* exotoxin fused to epidermal growth factor (EGF) and the amino terminal fragment of urokinase. This drug was designed to use epidermal growth factor receptors (EGFR) and urokinase-type plasminogen receptors (uPAR) as baits to deliver the lethal toxin into the cells, rather than as a means to interrupt signaling by the receptors. We previously showed that eBAT is remarkably safe, and that it reduced tumor burden in mice with established human rhabdomyosarcoma xenografts. It also was safe and showed a strong efficacy signal when used in the adjuvant setting in a clinical trial for dogs with splenic hemangiosarcoma. Nevertheless, the therapeutic mechanism of action of eBAT remains to be elucidated. Our goal is to identify patterns of uPAR expression in sarcomas that promote sarcoma growth and that mediate sensitivity for therapeutic activity by eBAT.

Methods: We generated uPAR-knockout (KO) cells from MC1A-C1 mouse fibrosarcoma cell line using the CRISPR-Cas system to target exon 2 of the uPAR gene. We determined the effect of eBAT along with EGF- and uPA-monospecific toxins on proliferation of parental cells compared to uPAR KO cells using the MTS Cell Proliferation Assay. Engraftment efficiency was tested by limiting dilution of cells injected subcutaneously into syngeneic B6 mice.

Results: uPAR targeting by CRISPR-Cas resulted in cell lines D10 and H6, clonal uPAR knockouts, whereas, K02 and K06 represent mixtures where approximately 80% and 30% of the cells retain uPAR expression. uPAR expression in K02 and K06 has remained stable over numerous passages, indicating that loss of uPAR does not create selective pressure to enhance or inhibit cell growth in vitro. Furthermore, the growth kinetics of D10 and H6 are comparable to parental MC1A-C1

cells. eBAT treatment significantly inhibited proliferation of parental cells, but not of uPAR KO cells. In contrast, all of the cells were resistant to treatment with EGF- and uPA-monospecific toxins. The engraftment efficiency and tumor growth of uPAR KO cells in syngeneic hosts was substantially diminished when compared to K02 and K06 uPAR+ cells.

Conclusion: While uPAR-KO cells might be more resistant to eBAT therapy, uPAR expression appears to be necessary to create the tumor niche and/or to promote tumor growth in vivo. In our ongoing work, we are investigating how uPAR expression in stromal cells and in cells of the innate immune system influence sarcoma growth and the response to eBAT.

Poster 058 3042785

IMPROVING ONCOLYTIC VIROTHERAPY USING VANADIUM-BASED COMPOUNDS IN SARCOMAS

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Objective: Sarcomas are lethal cancers that stem from mesenchymal tissues. Survival rates of sarcoma patients with metastatic disease remain very low despite aggressive therapy. Immunotherapy is a robust treatment paradigm that has improved the prognosis of a broad range of malignancies such as melanoma, lung and renal cell cancers. However, it has not yet translated into meaningful outcomes in the clinic for sarcoma patients. Oncolytic virotherapy (OV) employs viruses with engineered oncotropism to selectively target and kill cancer cells as well as stimulate an antitumor immunity. Despite promising results achieved with OVs, some of which are approved (Imlygic) or in advanced stages of clinical development, heterogeneity of response and resistance to monotherapies remains a clinical challenge. Our group has discovered small molecule enhancers of OVs – these molecules, described as viral sensitizers (VSe), suppress the antiviral response thereby improving the efficacy of OVs. Most recently, our lab reported that vanadium-based protein tyrosine phosphatase (PTP) inhibitors improve viral oncolysis as well as long-term antitumor immunity and survival when used in conjunction with oncolytic virus VSVD51 in syngeneic glioma and carcinoma tumor models. Thus, we sought to evaluate the impact of the combination of VSVD51 and vanadate in the context of sarcoma.

Methods: The combination therapy was tested *in vitro* using a panel of canine, murine and human sarcoma cell lines where viral spreading as well as cytotoxicity were assessed. Viral infection was also measured by microscopy in *ex vivo*-treated human patients biopsies (liposarcoma and sarcoma) and human tumor xenografts. Murine intraperitoneal and subcutaneous syngeneic models of sarcoma were also used to monitor OV infection (quantified using an *in vivo imaging system*), survival and tumor progression.

Results: Upon infection, vanadate enhanced viral cell-to-cell spread in canine, murine and human sarcoma cell lines. Vanadate synergistically decreased cell viability upon VSVD51 infection. Furthermore, vanadate sensitized patient biopsies and human osteosarcoma xenografts (primary and metastatic tumors) to VSVD51 infection without causing infection of normal tissues. The combination therapy significantly improved tumor control and survival in murine models of sarcoma.

Conclusion: Overall, this project supports the translational potential of vanadium compounds paired with oncolytic virotherapy for the treatment of local and metastatic sarcomas. Future experiments will aim at testing alternative delivery approaches as well as delineating this VSe's mechanism of action.

Poster 059 3042828

SOMATIC TUMOR PASSENGER EVENTS ACT AS A FLIGHT RECORDER "BLACK BOX" TO PINPOINT THE CHROMATIN STATE OF THE TUMOR CELL OF ORIGIN

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Objective: Identifying the cell of origin has important implications in the treatment and prevention of cancer and in many tumors the cell of origin remains unidentified. Somatic events in tumor formation have been labeled as either "drivers" if they play a role in tumorigenesis or "passengers" if they occur as a result of mutational processes but are not significant to tumor clonal advantage. Theoretically, for a passenger event to be clonally present in a tumor it must have been present within the cell at the time the driver event(s) provide clonal advantage. If mutational processes are occurring based on chromatin accessibility, the universe of mutational events will mark the chromatin state of the cell of origin of the tumor.

Methods: We utilized a metaanalyses of a series of *Sleeping Beauty* mutagenesis mediated forward genetic screens where the cell of origin is defined by *Cre* mediated activation of *SB* transposase and compared the resulting transposon insertion sites with RNA-Seq transcriptional profiling as well as ATAC-Seq measurements of active chromatin states. We further utilized human mutation and RNA-Seq in an attempt to directly define the cell of origin for both sets of osteosarcoma tumors as well as individual osteosarcoma tumors.

Results: Generally, tissue specific activation of Cre recombinase to activate *SB* transposase to mobilize an activation/disruption gene trap cassette (*T2/Onc*) in murine forward genetic screens has identified genes that are also recurrently and specifically mutated in corresponding human cancers. Utilizing RNA-Seq transcriptional profiling, we report that *T2/Onc* transposon insertions, both drivers and passengers are highly significantly associated with genes found in transcriptional clusters associated with the osteoblast cell of origin in our OS mouse models. Because of 1) the similarity in genes mutated in human cancer and somatically modified with insertional mutagenesis forward genetic screens; 2) the strong and heretofore unrecognized preference for transposon insertion into specific transcriptional clusters indicative of the cell of origin; 3) the increased likelihood of transposon insertion to identify active transcription or chromatin state as exemplified by the success of ATAC-Seq based analyses, we make the following hypotheses. A) SB transposase mediated forward genetic screens may in reality be better described as in vivo ATAC-Seq screens followed by selection for tumor formation. B) If this is the case than the natural supposition is that mutational processes may also be at least partially occurring based on steric access to transcriptionally active DNA, which indicates that the universe of mutations present in a tumor may hold information regarding the chromatin state of the cell where the tumor originated from. Because passenger mutations become fixed as a result of clonal outgrowth, the passenger events act like a fight recorder or “black box” in a plane to record information regarding the initial chromatin states that a cell transforms from. We have termed this approach MUtation of Transcriptionally Active Chromatin (MUTAC-Seq) and will present the results of our analyses. Preliminarily as proof of principle in naturally occurring human tumors, we obtained mutation profiles from human osteosarcoma patients and were able to observe statistically significant enrichment within specific transcriptional components, including a cluster of genes which is specifically defined by osteoblast specific targets.

Conclusion: SB transposase mediated forward genetic screens as well as some normal mutation processes may in reality be better described as in vivo ATAC-Seq screens followed by selection for tumor formation. If this is the case, passenger somatic mutation events present in tumors may represent a “black box recorder” where the chromatin state of the tumor precursor cell of origin is locked into place by virtue of the set of passenger genes which are present at the initiation of driver events providing clonal advantage.

Poster 060 3042835

CANONICAL AND RECIPROCAL FUSION GENE EXPRESSION IN TRANSLOCATION ASSOCIATED SOFT TISSUE SARCOMA TUMORS IS ASSOCIATED WITH DISTINCT MOLECULAR SIGNATURES

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Objective: Soft tissue sarcomas (STS) encompass a heterogeneous collection of rare, but often aggressive tumors which disproportionately affect children and young adults. Many of these cancers express hallmark translocations that serve as both diagnostic tools and are believed to be driver mutations associated with tumorigenesis. Our objective is to characterize the expression of expected and novel fusion transcripts in STS and investigate the downstream signaling pathways associated with fusion expression.

Methods: In this study, we used the Illumina TruSight Fusion Panel to characterize the expression of expected and novel gene fusion transcripts in 38 soft tissue sarcoma tumors banked at Roswell Park Comprehensive Cancer Center. Tumor subtypes that are frequently characterized by translocations were included in this study: endometrial stromal sarcoma, mxyoid/round cell liposarcoma, clear cell sarcoma of the soft tissues (CCSST), Ewing’s sarcoma, extraskeletal mxyoid chondrosarcoma, and synovial sarcoma. Tumors also underwent RNA-sequencing and pathway analysis with the goal of identifying druggable targets and pathways disrupted in association with fusion transcript expression.

Results: Using the Illumina TruSight Panel, we were able to simply and efficiently identify both expected and novel fusion transcripts in STS tumor RNA. For endometrial stromal sarcomas, we identified both JAZF1/SUZ12 (4/11) and BCOR/ZC3H7B (2/11) fusion transcripts. For mxyoid liposarcoma, we identified tumor with either FUS/DDIT3 (6/15) or EWSR1/DDIT3 (1/15) transcripts. Additional expected fusions that were observed included EWSR1/ATF1 in 3/5 CCSST, EWSR1/NR4A3 in 2/2 EMC, and various SS18 fusions in 5/5 synovial sarcomas. A lack of fusion transcripts was observed in 8/28 tumors, while novel fusion transcripts involving multiple genes were identified in 7/38 samples. In those instances, the

majority of these fusions involved chromosomes 12, 9 and 17, and we are working to determine whether these transcripts are caused by complex rearrangements such as chromoplexy or post-transcription fusions/transsplicing. Interestingly, we also detected reciprocal fusion transcripts ZC3H7B/BCOR (2/2), ATF1/EWSR1 (3/3), and DDIT3/FUS (1/6) in some tumors where the canonical fusion was expressed, and are actively investigating the role that these reciprocal fusion transcripts play in tumorigenesis.

Conclusion: Unsupervised hierarchical clustering of RNA-seq data suggests that fusion gene expression is a primary driver of the transcriptome in these tumors, and we are currently working to identify the downstream signaling pathways associated with fusion expression with the ultimate goal of identifying novel therapeutic approaches to treat these rare cancers.

Poster 061 3042904

IDENTIFICATION OF SPLICING FACTOR-3B1 AS A PUTATIVE REGULATOR OF OSTEOSARCOMA METASTASIS

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Objective: Approximately 30-40% of patients with osteosarcoma (OS) develop pulmonary metastatic disease and five-year survival rate for such patients is dismal at 15-30%. This outcome has remained unchanged for over three decades. Therefore, to improve outcome of patients with OS, identification of factors associated with metastasis is critical.

Methods: We used bioinformatics analysis of publicly available OS gene expression datasets along with qPCR, immunofluorescence and immunohistochemistry to validate the expression of dysregulated genes and correlate to OS prognosis

Results: *In silico* analysis of 9 expression data sets with over 200 OS tumors vs. normal tissue for differentially expressed genes and pathways using Enrichr showed an enrichment of genes involved in ER protein folding machinery, proteosome and splicing machinery in OS tumors as compared to normal tissue. In agreement with these findings, we have previously demonstrated that activation of transcription factor ATF6-a, a regulator of ER protein folding machinery, is associated with poor prognosis and resistance to chemotherapy in OS. Herein, we found that the expression levels of splicing factor SF3B1, one of the most commonly mutated splicing factor in cancers, is significantly enriched in tumors from patients with OS when compared to normal tissue. Immunohisotochemical analysis of tumors from OS patients and age matched normal tissue validated our i*n silico* findings. Furthermore, patients who developed metastasis had increased expression of SF3B1 when compared to patients who did not. This suggests that SF3B1 might serve as a marker for metastasis.

Conclusion: Increased expression of splicing factor SF3B1 is a novel finding in OS and may hold promise as a potential prognostic or therapeutic biomarker.

Poster 062 3042916

IONIZING RADIATION CAUSES SARCOMAS THROUGH MECHANISMS INDEPENDENT OF INCREASING MUTATIONAL LOAD

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Objective: The cell-intrinsic mechanisms by which ionizing radiation causes sarcomas are not fully understood. Here, we performed whole-exome sequencing in murine sarcomas to compare the mutational load of radiation-induced sarcomas to the sarcomas induced by oncogenic alterations or the MCA chemical carcinogen.

Methods: We performed whole-exome sequencing to quantify non-synonymous mutations and somatic copy number alterations (SCNA) in primary soft-tissue sarcomas. Sarcomas were induced in mice treated with a single fraction of 30 or 40 Gy focal irradiation to the leg (n=6). The mutational load of radiation-induced sarcomas was compared to sarcomas that developed in unirradiated mice driven by mutations in Kras and p53 (KP) (n=13) as well as by a chemical carcinogen 3-methylcholanthrene (MCA) (n=18).

Results: Although the mutational load of MCA-induced sarcomas (mean=2268/ tumor) was about 70 times higher than the mutational load observed in KP sarcomas (mean=30/ tumor), there was no significant difference in the number of non-synonymous mutations between KP sarcomas and radiation-induced sarcomas (mean=28/ tumor). However, SCNA analyses showed that radiation-induced sarcomas had a higher frequency of deletions in known tumor suppressor genes

compared to KP sarcomas and MCA-induced sarcomas. Moreover, radiation-induced sarcomas showed amplifications in specific oncogenes, including Met, Birc3 and Yap1.

Conclusion: Our results reveal that radiation-induced sarcomas in mice do not harbor a higher number of non-synonymous mutations compared to the same tumor type driven by oncogenic alterations. These findings provide compelling evidence that ionizing radiation causes sarcomas through mechanisms independent of increasing non-synonymous mutations. The higher SCNA in radiation-induced sarcomas suggest that an increase in copy number variations could be an underlying mechanism of radiation-induced sarcomagenesis.

Poster 063 3042934

PRECLINICAL MODELING OF RESISTANT DISEASE USING AUTOPSY SAMPLES FROM PEDIATRIC PATIENTS WITH SOLID TUMORS

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Objective: Pediatric solid malignancies represent a vast landscape of tumor biology. This diversity, along with the rarity of many histologies, makes them difficult to study. Patients with disease recurrence have poor prognoses. Sampling tumors at time of disease recurrence and tumor progression can be valuable in identifying the mechanisms which have led to treatment failure. To support basic research of pediatric solid tumors, we established a biology protocol that allows patients to donate tumor tissue for molecular profiling and the creation of xenografts at any time point of their clinical course including autopsy performed at the time of death.

Methods: Consent was obtained from the patient when appropriate prior to death or from the patient family prior to tumor harvest and donation. After death, families were allowed to spend as much time as desired with their child prior to autopsy. Limited autopsy was performed and tumor was harvested from several sites when available. Tumor samples underwent pathology review for viability and confirmation of disease. Tumor tissue was processed and implanted into NOD scid gamma mice to create orthotopic patient derived xenografts (O-PDXs). Once engrafted, samples were extensively analyzed using histology, electron microscopy, whole genome sequencing, exome sequencing, RNA-sequencing and DNA methylation. High-throughput screening of primary cultures derived from O-PDXs was used to assess drug sensitivity and in vivo preclinical testing was performed to test drug combination efficacy. All data, samples, and animal models are shared freely with the research community through the Childhood Solid Tumor Network (CSTN) using an online request form (www.stjude.org/CSTN) without obligation to collaborate.

Results: Over the past 5 years, we collected tumor specimens from 23 pediatric patients with solid tumors at the time of autopsy. Samples represent 10 different histologies including: Ewing sarcoma (EWS), rhabdomyosarcoma, synovial sarcoma, osteosarcoma, and desmoplastic small round cell tumor. Tumor samples were processed and implanted orthotopically into mice 96% of the time (22/23), with the average time from patient death to implantation being 35 hours. To date, 45% of the samples have engrafted (10/22) with several newly implanted samples still awaiting growth. The median time to engraftment was 15 weeks (range 7 – 38 weeks). Preclinical testing of a EWS O-PDX created at autopsy from a patient previously treated with numerous chemotherapeutic regimens, including a PARP inhibitor, revealed a decrease in sensitivity to PARP inhibitor combinations (100% progressive disease, average survival on study 10 days) compared to other EWS O-PDXs created from non-progressive patients (88% complete response, average survival 77 days). To date, there have been no reported negative effects of tumor donation by patient families who consented to participate.

Conclusion: Collection of pediatric solid tumor samples for research purposes at the time of autopsy is feasible. Half of the tumor samples engrafted despite prolonged periods of time from patient death to implantation in O-PDXs. These samples include aggressive, multi-resistant phenotypes that are invaluable to the research community and may aid in distinguishing drivers of recurrent disease. Parents who donated their child's tumor have expressed benefit in knowing that the tumor is being used to drive research that may help future patients. By making these samples freely available through the CSTN, we hope to advance our understanding of the underlying biology of these devastating malignancies.

Poster 064 3043040

TARGETING STRESS GRANULES: A NOVEL APPROACH TO BLOCK SARCOMA METASTASIS

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Objective: To identify the critical roles of stress granules (SGs) in facilitating childhood sarcoma metastasis and to investigate the potential effects of targeting SGs on sarcoma cell behaviour.

Methods: We performed cell-based screen to identify novel and selective SG inhibitors. Further, we used extensive in vitro assays and in vivo experiments to detect the role of SGs in sarcoma metastasis and how SG inhibition impacts the metastatic phenotype of sarcoma cells.

Results: Small molecule screens for SG inhibitors, revealing several unexpected categories of SG inhibitors including class I HDACis. We find that SG formation can be virtually eliminated in sarcoma cells using several agents currently in clinical trials for different tumour types. These agents enhance acetylation of lysine 81 within the YB-1 RNA binding domain, blocking translational activation of *G3BP1,* a critical SG nucleating factor, and thereby inhibiting SG formation. Using EwS xenografts or PDX models, we found that class I HDACi such as MS-275 inhibits SG formation, and dramatically reduces metastasis *in vivo*. Mechanistically, SG inhibition enhances oxidative stress by reducing translation of NRF2, resulting in increased sensitivity to oxidative stress.

Conclusion: SGs facilitate sarcoma metastasis by bestowing malignant cells with increased cellular fitness and survival advantages. SG blockade therefore offers a promising strategy to reduce the burden of metastatic disease in childhood bone sarcomas.

Poster 065 2992803

INNATE IMMUNITY TOLL LIKE RECEPTORS TLR1/2; TLR6 AND MUCIN MUC5B ARE BINDING INTERACTION PARTNERS WITH ANTIPROLIFERATIVE PEPTIDE PRP-1 IN HUMAN CHONDROSARCOMA

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Objective: Metastatic chondrosarcoma is the second most common bone malignancy and does not respond either to chemotherapy or radiation; therefore the search for new therapies is urgent.Proline rich polypeptide 1, (PRP-1), also known as (galarmin) is produced by the brain neurosecretory cells ,it is mTOR kinase (mTORC1) inhibitor which causes 80-90% inhibition of chondrosarcoma cell growth, halting G1/S phase cell cycle progression in chondrosarcoma and other mesenchymal tumors . PRP-1 can also manifest cytotoxic effect dependent on cellular context. The receptors for PRP-1 were not known. The objective of the study was identification of the receptors for PRP-1 in human chondrosarcoma and their subcellular localization.

Methods: PRP-1 antiserum affinity chromatography purification; tissue culture of human JJ012 chondrosarcoma ;immunocytochemistry; TRICEPS technology (Dual Systems Biotech, Switzerland), mass spectrometry; RT2 qPCR primer assays; Discoverx platform of G protein coupled receptors and for nuclear receptors (USA), human MUC 5B Elisa ; electrophoresis and western blotting.

Results: Nuclear pathway receptor and GPCR assays indicated that PRP-1 receptors are not G protein coupled, neither nuclear or orphan receptors. In this work we have demonstrated that PRP-1 binding interacting partners belong to innate immunity pattern recognition toll like receptorsTLR1/2 and TLR6,(demonstrated by western blot and qRT PCR) and gel forming secreted mucin MUC5B applying TRICEPS Ligand Receptor Capture technology (Fig 1). Immunocytochemistry experiments confirmed the finding and indicated the predominant nuclear localization of PRP-1 as a ligand and its receptors. TLR1/2, TLR6 and MUC5B were downregulated in human chondrosarcoma and were upregulated in dose response manner upon PRP-1 treatment (Fig 2).PRP-1 upregulated TICAM2 (TRAM) adaptor protein in dose-response manner but did not have any effect on TICAM1 (TRIF) adaptor protein.TLR2, for example known to be TRAM dependent in addition to the MyD88-dependent pathway.TLR1/2, TLR6 and MUC5B as are recognized as potential markers of disease progression or inhibition. Our experiments indicated that in chondrosarcoma they have tumor suppressive effect.

Conclusion: (PRP-1) caused a significant upregulation of many tumor suppressors ,downregulation of oncoproteins and embryonic stem cell markers Nanog, c-Myc and Bmi-1 in human chondrosarcoma. To understand better the mechanism

of PRP-1 action it was very important to identify the receptors it binds to. Due to the importance of TLR signaling in tumorigenesis, TLR agonists have potential for antitumor therapy. Mucins are a class of major differentially expressed proteins between normal and cancer cells, which makes them a potential target for anticancer therapies From oncologic standpoint it is important that immune receptors play antitumorigenic role when bound to PRP-1 ligand.TLR and mucins (MUC)s have important role in host defense mechanism, however the link between two of them in noninfectious conditions and cancer pathology deserves attention. To our knowledge this is first work demonstrating the presence of toll like receptors and mucin MUC5B in human chondrosarcoma.

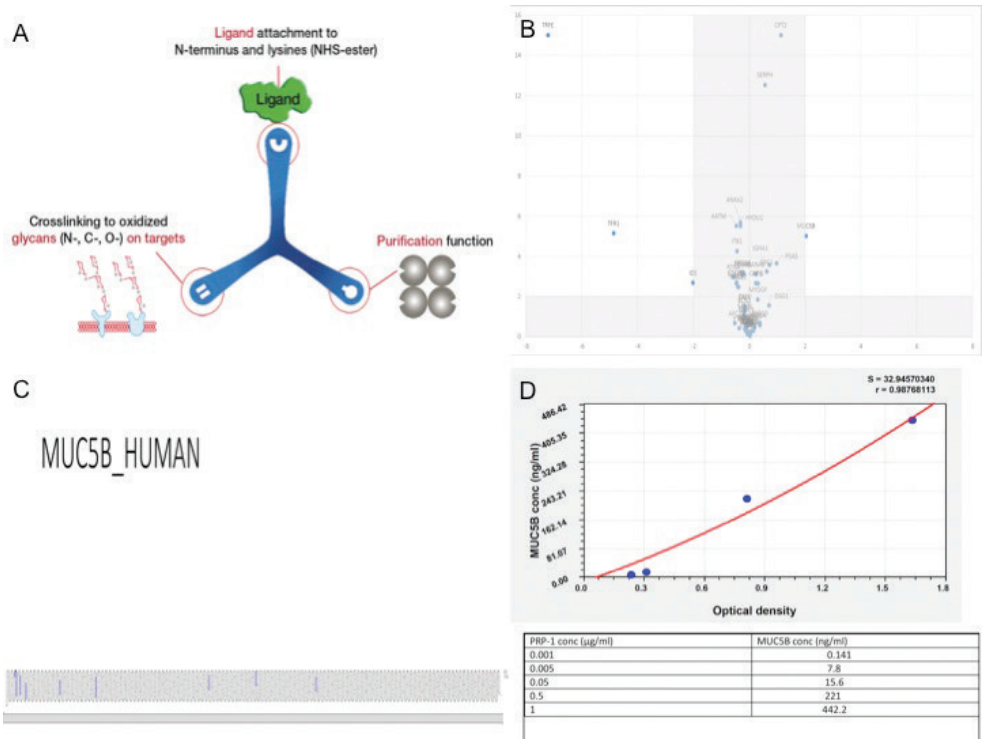

Figure 1. Identification of PRP-1 receptor binding protein MUC5B by Ligand-receptor capture technology (LRC) and human MUC5B ELISA in JJ012 chondrosarcoma cell line. (A) Ligand-receptor capture technology (LRC).(B) Volcano plot. LRC-TriCEPS volcano plot compares the proteins that are enriched. C) Protter. In the protter picture the tryptic peptides (highlighted) that are identified by LC-MS/MS measurement for MUC5B. (D) Human MUC5B
ELISA in the cell lysates of human JJ012 chondrosarcoma cells

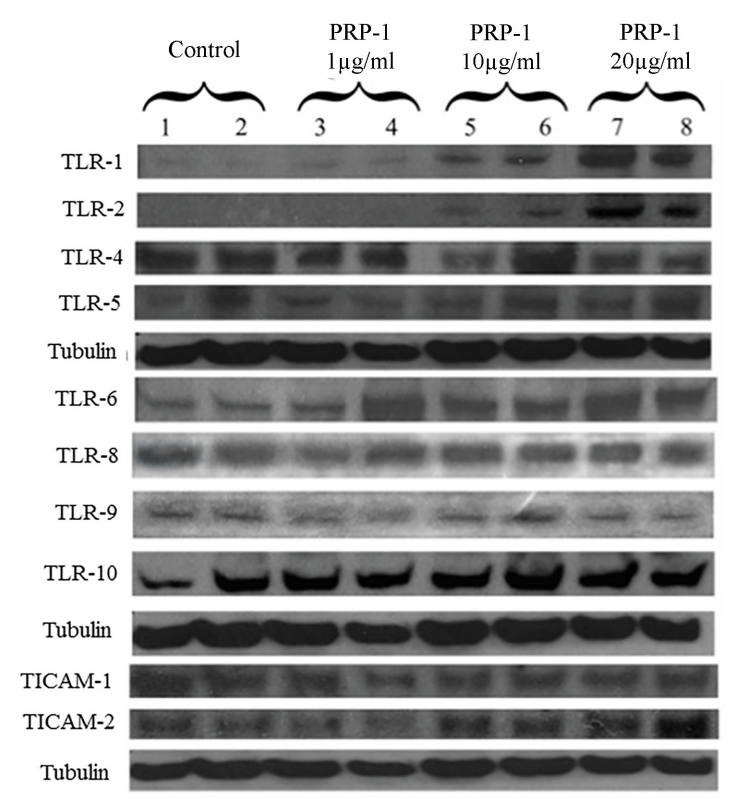

Figure 2. PRP-1 effect on TLR receptors and adaptor proteins in human chondrosarcoma JJ012 cell line. PRP-1 upregulated protein expression of TLR1, TLR2 and TLR6 in dose-dependent manner .

Poster 066 2993194

INHIBITION OF EMBRYONIC STEM CELL MARKERS EXPRESSION BY PRP-1 LEADS TO ELIMINATION OF CANCER STEM CELL POPULATION IN HUMAN CHONDROSARCOMA

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Objective: Chondrosarcoma, the second most common bone malignancy primarily affects the pelvis, long bones and spine as well as the larynx, head and neck. Metastatic chondrosarcoma of mesenchymal origin does not respond either to chemotherapy or radiation, therefore, the search for new therapies is relevant and urgent.We have demonstrated that stemness inducing miRNAs 302c* is upregulated in human chondrosarcoma cells and that cytostatic proline rich polypeptide , (PRP-1) downregulated it significantly along with its targets pcMyc, Bmi-1 (Fig 1) and Nanog .Based on this observation we proceeded with the the isolation of ALDH ^{high} cancer stem cell population, (CSC) in human chondrosarcoma JJ012 cells and whether PRP-1 had any effect on ALDH ^{high} cells.

Methods: Tissue culture of JJ012 human chondrosarcoma cells;Exiqon miRNA arrays, Aldefluor kit (cat# 01700) from StemCell technologies for isolation and identification of cancer stem cells, Fluorescence Activated Cell Sorting (FACS). Samples were sorted on a Becton Dickinson (BD) Biosciences (San Jose, CA) Special Order Research Product (SORP) FACSAria II, using BD FACSDiva software (version 6.1.3). Data analysis was performed using FlowJo Polyacrylamide gel electrophoresis and western blotting.

Results: Human JJ012 chondrosarcoma cells were examined for aldehyde dehydrogenase (ALDH) activity using the ALDEFLUOR™ Kit . The ALDH ^{high} (stem cell population) and ALDH ^{low} were successfully isolated.Panels (A) and (B) show control cells, stained with the Aldefluor™ reagent in either the presence (A) or absence (B) of the specific inhibitor DEAB. As seen in (C), a subset of JJ012 cells express ALDH ^{high}. (D) JJ012 cells were cultured in either the presence (+PRP) or absence (-PRP) of PRP-1) , then examined for ALDH activity . Cells cultured in the presence of PRP (+PRP, -DEAB graph) lost all ALDH activity, compared to those cultured without PRP (-PRP, -DEAB graph)(Fig2).

Conclusion: Accumulating evidence suggests that CSCs exist as a sub-population of quiescent cells within the dominant tumor bulk of heterogeneous tumor cells These typically dormant cells are considered resistant to standard anti-cancer therapies such as chemotherapy and radiation ,responsible for relapse and appea to be capable of self-renewal and differentiation These cells considered to be characteristic for ALDH ^{high}. PRP-1 proved to be antiproliferative agent.Inhibition of embryonic stem cell factors expression in chondrosarcoma cell line led to elimination of cancer stem cell population. It will be very important to proceed with in vivo studies and explore whether PRP-1 will prevent tumor formation or shrink the tumor irts role in spontaneous metastasis .

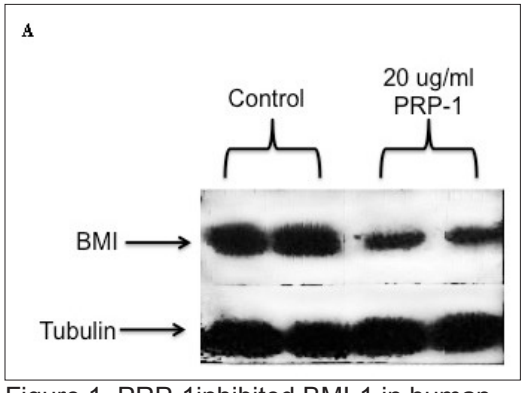

Figure 1. PRP-1inhibited BMI-1 in human chondrosarcoma JJ012 cell line.

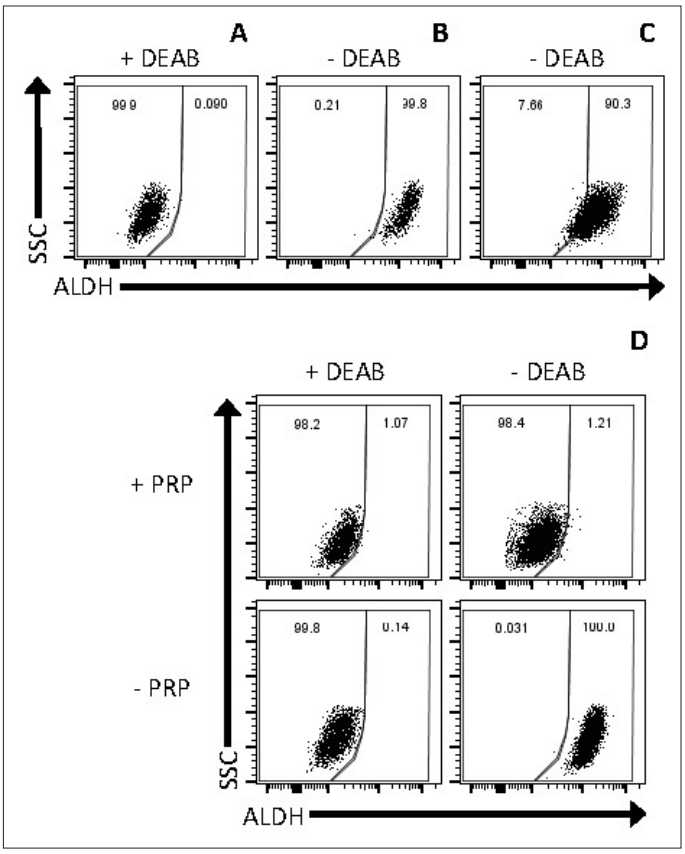

Figure 2. Human JJ012 chondrosarcoma cells were examined for aldehyde dehydrogenase (ALDH) activity using the ALDEFLUORTM Kit from StemCellTechnologies as described in Materials and Methods. Panels (A) and (B) show control cells, stained with the AldefluorTMreagent in either the presence (A) or absence (B) of the specific inhibitor DEAB. These control samples were used to establish negative and positive gates for (C). As seen in (C), a subset of JJ012 cells express ALDH, a marker for cells that have progenitor or stem cell properties. (D) JJ012 cells were cultured in either the presence (+PRP) or absence (-PRP) of Proline-rich polypeptide 1 (PRP) , then examined for ALDH activity as described in Materials and Methods. Cells cultured in the presence of PRP (+PRP, -DEAB graph) lost all ALDH activity, compared to those cultured without PRP (-PRP, -DEAB graph)

Poster 067 3042161

TUMOR SUPPRESSOR GENE MUTATION IN THE HEDGEHOG PATHWAY DEFINES A NEW SUBSET OF PLEXIFORM FIBROMYXOMA

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Objective: Plexiform fibromyxoma (PF) is a rare submucosal gastric tumor that can be confused with gastrointestinal stromal tumor (GIST). While slow growth and lack of metastases suggest an indolent natural history, these so-called benign tumors often present with upper GI bleeding and sometimes with gastric outlet obstruction. As there are no known drug therapies for PF, resection remains the only treatment. In 2016, the first insight into the molecular biology of 16 PFs demonstrated 4 tumors (25%) with activation of the *GLI1* oncogene, a transcription factor in the Hedgehog (Hh) signaling pathway. Despite this discovery, the underlying biology of most PFs remains unknown.

Methods: Following patient consent to an IRB-approved protocol, clinical data and tumor tissue were collected. After pathologic diagnosis, FoundationOne Heme next generation sequencing (NGS) of >400 genes was obtained. Real-time reverse transcription polymerase chain reaction (RT-PCR) for Hh pathway components was performed on mRNA extracted from resected tumor tissue. Additionally, primary tumor cells were dissociated, placed in culture, treated with Hh inhibitor [sonidegib (Novartis/Sun Pharma)], and assessed for cell viability using CellTiterGlo assay.

Results: We report a 65-year-old male that presented with acute upper GI bleeding from a 5.0 cm gastric mass. He underwent partial gastrectomy with R0 resection. The immunohistochemical profile (positive: SMA; negative: CD34, S-100, DOG-1, CD117) and histomorphology (transmural myxoid stroma, plexiform growth pattern with spindle cells, and prominent thin capillaries) were consistent with the diagnosis of PF. On NGS, an inactivating Patched 1 (*PTCH1*) deletion of exons 15-24 was detected on a single allele. Loss of *PTCH1,* a tumor suppressor gene in the Hh pathway, can induce downstream GLI1 activation and transcription of target genes. Single allele *PTCH1* alterations have been demonstrated to be sufficient for inducing in basal cell carcinoma, rhabdomyosarcoma, and medulloblastoma. To confirm that *PTCH1* haploinsufficiency was associated with activation of the Hh pathway in the PF, we performed quantitative RT-PCR analysis. This demonstrated high expression of *Gli1*, as well as downstream GLI1 transcriptional targets, including *Ccnd1* and *Hhip* (Fig. 1A). *In vitro*,

treatment of primary PF cells with a Hh pathway inhibitor, sonidegib, demonstrated cell killing after 48-hours (IC_{50} = 27 μM) (Fig. 1B).

Conclusion: For the first time, we report that a monoallelic inactivating *PTCH1* mutation is associated with the development of plexiform fibromyxoma. We show that tumor suppressor gene alterations, rather than oncogenic mutations, within the Hh pathway may also cause plexiform fibromyxoma. In turn, targeted Hh pathway inhibition may represent a viable approach for treating a subset of recurrent plexiform fibromyxomas. Further studies are warranted to investigate the clinical efficacy of these agents in appropriately selected patients.

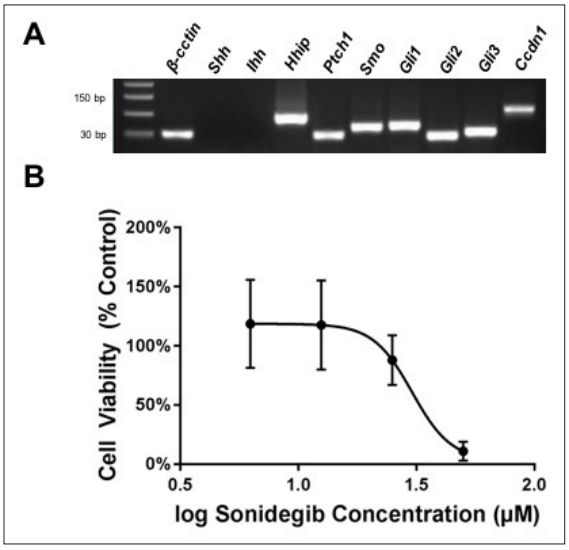

Figure 1: (A) qRT-PCR of primary PF demonstrates expression of Hh pathway components; (B) Dose-dependent cell killing of PF cells with SMO inhibitor.

Poster 068 3003854

THERAPEUTIC EFFECT OF SCLEROSTIN ON OSTEOSARCOMA

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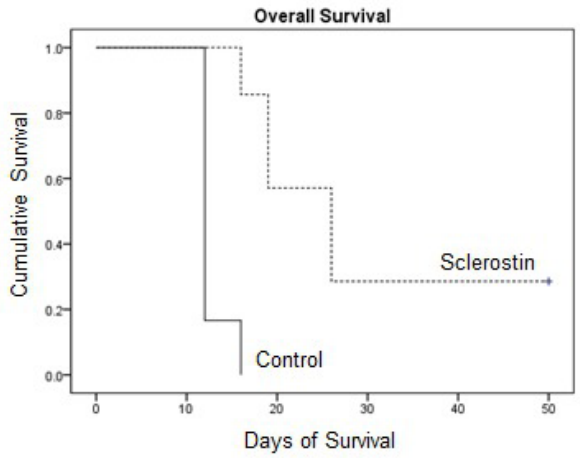
Objective: Wnt signaling controls a variety of cellular processes, including its involvement in regulating the development, growth, maintenance, and differentiation of stem cells. Canonical Wnt signaling regulates various gene expressions, in addition to cell proliferation and differentiation. Hyperactive Wnt signaling fosters tumorigenesis and metastasis of various cancers. Sclerostin is an extracellular soluble factor secreted by osteocyte and prevents bone formation by inhibiting the canonical Wnt signaling pathway. The objective of this study is to investigate the therapeutic effect of sclerostin on osteosarcoma, a malignant tumor derived from osteoblast lineage cells.

Methods: Osteosarcoma model mice were prepared by transplantation into the dorsal region of C3H/He and BALB/c-nu/nu mice using osteosarcoma cell lines LM8 (mouse) and 143B (human), respectively. Cell proliferation were evaluated by using AlamarBlue and scratch assays. The migratory ability of the cells were evaluated using a migration assay. Sclerostin was injected into the peritoneal cavity of mice once a day at 80 ng/g body weight for 7 days to examine the suppression of the increase in tumor diameter and extension of survival. mRNA was evaluated by RT-qPCT, and protein levels were evaluated by western blotting and immunostaining.

Results: Administration of sclerostin to osteosarcoma cells suppressed the expression of Wnt target genes, in addition to significantly inhibiting the growth and migratory ability of osteosarcoma cells. The Kaplan Meier curves and survival data (Figure) demonstrated that sclerostin significantly inhibited tumor growth and improved the survival of mice.

Conclusion: Sclerostin suppressed the proliferative capacity and migratory ability of osteosarcoma cells. The osteosarcoma model mice showed inhibited tumor growth and prolonged survival periods. Because sclerostin is not a cytocidal agent, the effect of its combined use with existing anticancer drugs such as doxorubicin should be investigated for future clinical applications.



Kaplan-Meier curve showing the cumulative survival of osteosarcoma model mice with or without administration of sclerostin. Survival was significantly better in sclerostin-administered mice (P = 0.001).

Poster 069 3011949

MACROPHAGES FACILITATE OCCURRENCE AND DEVELOPMENT OF HUMAN OSTEOSARCOMA CELLS MEDIATED BY NF-KB

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Objective: Osteosarcoma is the most common bone malignancy. Tumor-associated macrophages (TAMs) play an important role in the formation of inflammatory microenvironment that is associated with tumors. We sought to characterize the role of TAMs in initiation and development of human osteosarcoma cells and the underlying mechanisms.

Methods: Human osteosarcoma cells (MG63), macrophage-like THP-1 cells alone, and the mixture of MG63 and THP-1 cells (10:1) were injected into the back of nude mice (n=5/group), and the alternations of tumor xenograft growth and the weight of tumor were determined. Pathological changes (tumor nests and microvascular lesions) of HE-stained tumor tissues were evaluated. The expression of NF-κB p65 in tumors was determined using immunohistochemistry.

Results: Tumor size and weight in nude mice transplanted with the mixture of MG63 and THP-1 cells (10:1) were increased compared to those from the MG63 cells alone at the 10^{th}, 15^{th}, 20^{th} and 25^{th} day after cells transplantation. The number of tumor nests and microvascular lesions, and the protein expression of NF-κB p65 in tumors from the mixture of MG63 and THP-1 cells were increased apparently in contract to those in tumor from MG63 cells alone.

Conclusion: The presence of macrophages facilitates initiation and development of human osteosarcoma cells, which may be mediated by NF-κB.

Poster 070 3026538

CYCLIN-DEPENDENT PROTEIN KINAE 9 (CDK9) IS A NOVEL PROGNOSTIC MARKER AND THERAPEUTIC TARGET IN OSTEOSARCOMA

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Objective: Cyclin-dependent protein kinase 9 (CDK9) has been shown to play an important role in the pathogenesis of malignant tumors. However, the expression and function of CDK9 remains unknown in osteosarcomas. The purpose of this study is to assess the expression, function and clinical prognostic relationship of CDK9 in osteosarcomas, and therefore establish if it holds therapeutic potential for osteosarcoma treatment.

Methods: A tissue microarray of 70 patient specimens was analyzed by immunohistochemistry to measure CDK9 expression, which was further investigated for correlation with patient clinical characteristics. CDK9 expression in osteosarcoma cell lines and patient tissues was also evaluated by Western blotting. CDK9-specific siRNA and the CDK9 inhibitor were applied to determine the effect of CDK9 inhibition on osteosarcoma cell proliferation and anti-apoptotic activity. The effect of CDK9 inhibition on clonogenicity and migration activity was also examined using clonogenic and wound healing assays. A 3D cell

culture model was performed to mimic the *in vivo* osteosarcoma environment to further validate the effect of CDK9 inhibition on osteosarcoma cells.

Results: Immunohistochemistry demonstrated that higher CDK9-expression is associated with significantly shortened patient survival. Expression of CDK9 is inversely correlated to the percent of tumor necrosis post-neoadjuvant chemotherapy treatment in osteosarcoma tissues. Knockdown of CDK9 with siRNA and inhibition of CDK9 activity decreased cell proliferation and induced apoptosis in osteosarcoma both *in vitro* and mimic *in vivo*.

Conclusion: High expression of CDK9 is an independent predictor of poor prognosis in osteosarcoma patients. Our results suggest that CDK9 is a novel prognostic marker and a promising therapeutic target for osteosarcomas.

Poster 071 3030414

METHYLATION-SILENCING OF MULTIPLE TUMOR-SUPPRESSOR AND OSTEO/CHONDROGENESIS RELATED GENES IN OSTEOSARCOMA

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Objective: Prognosis of osteosarcoma (OS) patients with metastasis or those with recurrent tumors still remains poor. Recently, a few preclinical studies have revealed that OS had aberrant DNA methylation in several genes related to tumorigenesis, and, as for the novel therapeutic strategy, the efficacies of epigenetic drugs, e.g. DNA demethylating drugs, have been shown. However the precise mechanism of the therapeutic efficacy of DNA demethylating drugs for OS remains still unclear. In this study, we aimed to clarify the mechanism of how epigenetic therapy using a DNA demethylating drug has the therapeutic efficacy in OS.

Methods: The growth inhibitory effect of DNA demethylating drug, decitabine (DAC), was examined by treating four OS cell lines with various concentrations (0.1, 0.3, 1, 3, 10 μM), and using two OS xenografts treated with 0, 1 and 2 mg/kg body weight. The genome-wide DNA methylation profiles of 31 cases of OS and 11 cases of Ewing sarcoma (EWS) were obtained using Infinium Human Methylation 450 bead array (with 485,764 probes). We also utilized DNA methylation profiles of gastrointestinal cancers (stomach, esophagus, colon) previously obtained or obtained from a database. Methylation-silenced genes in OS were comprehensively searched for using two OS cell lines treated with DAC by microarray analysis.

Results: First, we analyzed growth inhibitory effect of DAC, on OS in vitro and in vivo. Cell proliferation of four OS cell lines was suppressed to a mean of 43% (4-81%) by treatment of 0.1 μM of DAC. The volume of xenografts was decreased to 29% by administration of 2 mg/kg of DAC. Next, DNA methylation profiles of 31 patients with OS and 11 patients with EWS were analyzed. The DNA methylation profiles were clearly distinct between the two cancer types. In OS, extensive hypomethylation was observed in the enhancer regions and normally-methylated CpG islands. In contrast, in EWS, DNA methylation changes were observed at only very limited number of genes. In primary OS, 10 of 28 cases showed methylation of multiple CpG islands, namely the CpG island methylator phenotype (CIMP). Notably, the number of hypermethylated genes (median 3.8%) in CIMP(+) OS was much smaller than those in other cancer types, such as CIMP(+) gastric cancers (median 11.8%) and colon cancers (median 6.4%). CIMP(+) OS patients tended to show shorter disease-free survival than CIMP(-) patients (5 years disease-free survival rate, CIMP(+) = 40.0%, CIMP(-) = 71.6%; P = 0.116). In contrast, in primary EWS, only 1 of 10 cases showed the CIMP. Gene ontology analysis revealed that genes involved in hormone metabolism, neurological function, skeletal system morphogenesis, and cell proliferation were aberrantly methylated in OS, and genes involved in apoptosis were methylated in EWS. Finaly, we found 31 and 13 genes in each OS cells were actually re-activated two-fold or more by DAC treatment and many of these genes function as tumor-supressors and bone or cartilage formation.

Conclusion: Our DNA methylation data showed that CIMP may be a poor prognostic factor in OS and methylation-silencing of tumor-suppressor and osteo/chondrogenesis-related genes is possibly involved in the development of OS. Reactivation of these genes were suggested to be the mechanism underlying therapeutic efficacy of DNA demethylating drugs in OS. These data indicated that targeting aberrant DNA methylation could be a rational therapeutic strategy for OS.

Poster 072 3042493

IL-6 MEDIATED SELECTIVE TOXICITY FOR TUMOR-INITIATING CELLS FUNCTIONS TO PREVENT OSTEOSARCOMA METASTASIS

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Objective: Osteosarcoma (OS) is the most common primary bone tumor, striking primarily adolescents. OS mortality occurs primarily as a consequence of metastatic spread to the lungs. With metastatic disease, chemoresistance develops to standard therapy and no adjuvant therapy has been effective in overcoming this resistance. Our lab has identified IL-6 and IL-8 as primary mediators of OS signaling as a part of a paracrine loop and has further investigated the use of inhibitors of these cytokines on proliferation and spread.

Methods: In a murine model of OS, mice bearing intra-tibial tumors were treated with standard chemotherapy (cyclophosphamide), with or without IL-6 and IL-8 inhibitors. Primary tumor growth was measured. In a second set of experiments, a panel of OS cells were suspended in soft agar and treated with IL-6 and IL-8 inhibitors. Colony formation was quantified over time.

Results: In a murine model, the combination of standard chemotherapy and cytokine inhibitors results in lower rates of recurrence compared with mice treated with chemotherapy alone. Soft agar assays demonstrate that IL-6 inhibition results in decreased colony formation across a panel of human, mouse and canine OS cell lines, while IL-8 inhibition has minimal effect.

Conclusion: The results in both the animal studies and colony formation assays suggest that cytokine inhibition exhibits selective toxicity for tumor initiating cells, which may be the cells that drive resistance and recurrence. Studies investigating the effect of combination treatment in a metastatic murine model are ongoing.

Poster 073 3042628

IDENTIFICATION OF INFLAMMATORY FACTORS AND THE NOTCH PATHWAY AS THERAPEUTIC TARGETS FOR SARCOMA-ASSOCIATED CACHEXIA

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Objective: We evaluate the expression of inflammatory factors and the Notch signaling pathway in cachectic and non-cachectic human sarcoma samples, hypothesizing that human sarcoma samples will display gene expression and protein production in a manner consistent with the clinical incidence of sarcoma-associated cachexia.

Methods: Patient weights were collected from 6 months pre and post surgery. Linear regression was performed to evaluate weight loss for 6 months. According to the definition of cachexia (weight loss / 6mo ≥ 5%), these sarcoma samples were classified into either the cachexia group or the non-cachexia group. At this time, 8 patient samples were tested. RM3 (rhabdomyosarcoma), SC10a (high grade sarcoma), MF9 (myxofibrosarcoma), PS5 (pleomorphic sarcoma) were classified into the cachexia group and RM4, OS15 (osteosarcoma), CS11a (chondrosarcoma), SC11 were classified into the non-cachexia group.
The sarcoma samples were minced and enzymatically digested at 37°C for 90 minutes. Primary cell populations were cultured until cells reached 80-90% confluence. Cells were then collected for extracting RNA.
RT-qPCR was performed to evaluate the expression of inflammatory factors (TNF-α, IL-1β, IL-6, IL-8) and Notch pathway factors (DLL1, JAG1, Notch1, Notch3, Hes1). Data were normalized by geometric mean of multiple internal control genes. Fold change of mRNA was normalized to the non-cachexia group.
Secretion levels of TNF-α, IL-1β and IL-8 in cell culture media were assayed in duplicate on multiplex U-Plex kits from Meso Scale Discovery.

Results: Increased gene expression levels of IL-1β and IL-8 were observed in RM3, SC10a, MF9 from the cachexia group. Gene expression levels of TNF-α and IL-6 did not show differences compared to the non-cachexia group. Gene expression levels of JAG1, Notch3 and Hes1 in Notch signaling pathway were decreased in the cachexia group. Protein secretion levels of TNF-α and IL-8 were higher in the cachectic cell population, RM3 compared to the non-cachectic cell population, CS11a. This is consistent with the increased gene expression levels of TNF-α and IL-8 in RM3. IL-1β was out of detection range, which indicated low translation of RNA into protein.

Conclusion: We identified IL-8 and IL-1β as potentially better biomarkers for sarcoma-associated cachexia compared to TNF-α and IL-6, which are traditional biomarkers of cancer-associated cachexia. We identified decreased gene expression of JAG1, Notch3 and Hes1 in the cachexia group, indicating impaired Notch signaling. The role of Notch pathway in sarcoma and muscle wasting needs further study.

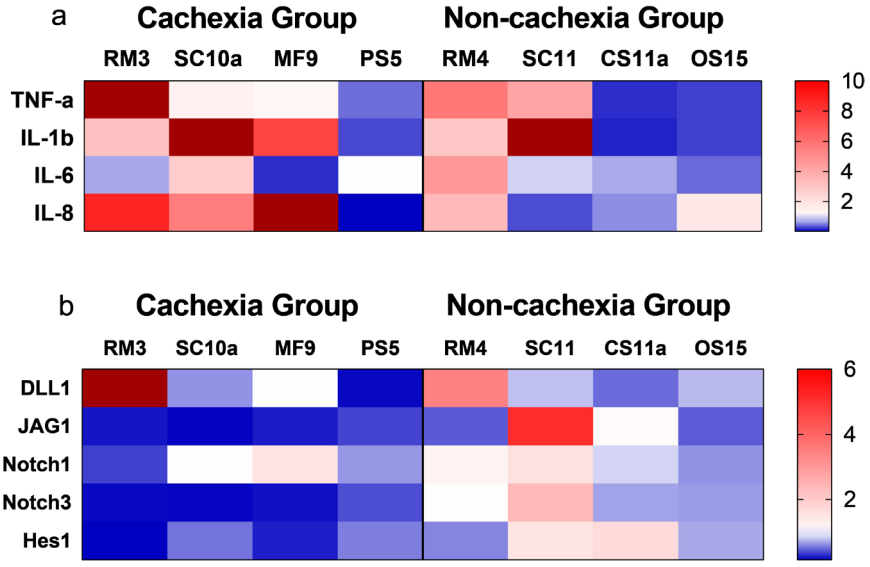

Figure 1. Gene expression levels of IL-1β and IL-8 were increased in RM3, SC10a, MF9 from the cachexia group. Gene expression levels of JAG1, Notch3 and Hes1 in Notch signaling pathway were decreased in the cachexia group.

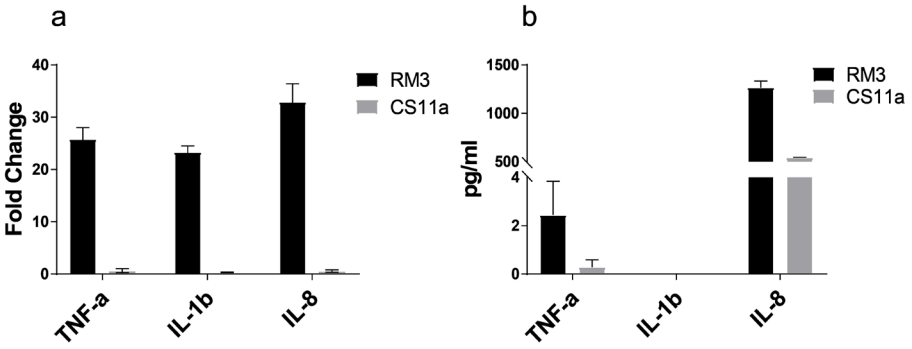

Figure 2. Both gene expression and protein secretion levels of TNF-α and Il-8 were increased in the cachectic cell population, RM3 compared to the non-cachectic cell population, CS11a.

Poster 074 3042650

ANTIPROLIFERATIVE EFFECT OF BUPIVACAINE ON PATIENT-DERIVED SARCOMA CELLS

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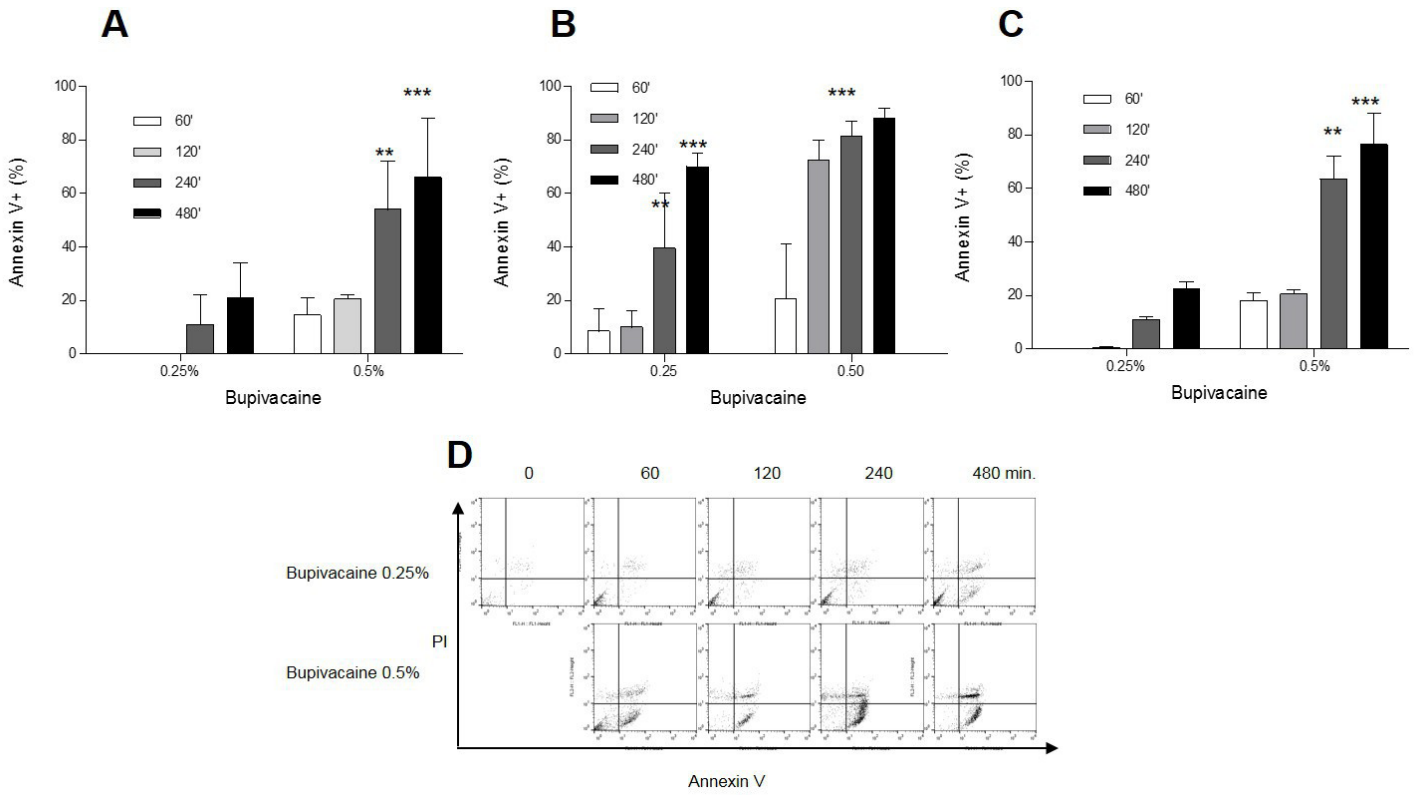
Objective: The purpose of this study is to investigate the cytotoxic potency of bupivacaine, a commonly used local anesthetic, on primary patient-derived sarcoma cells.

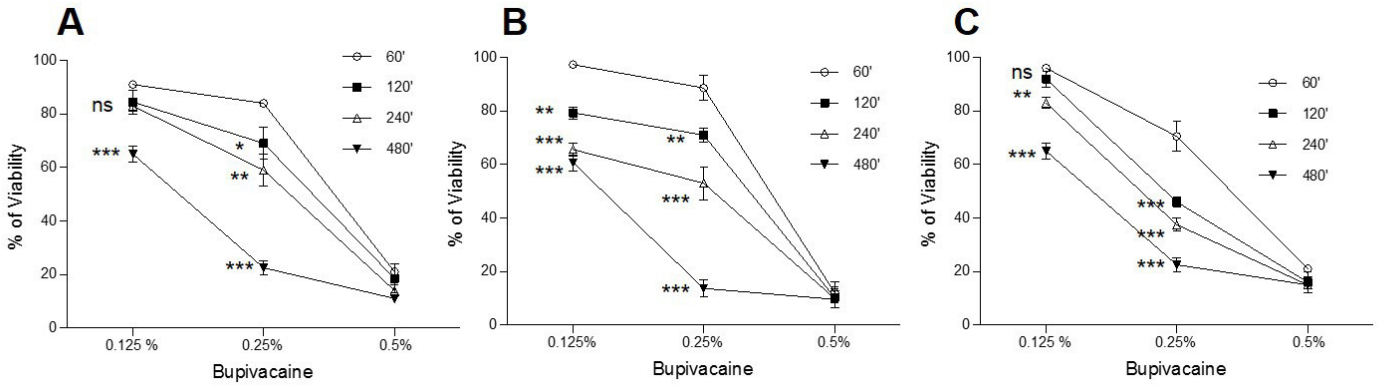
Methods: Multiple sarcoma subtypes were evaluated in this study including: a high-grade conventional osteosarcoma, a high-grade undifferentiated pleomorphic sarcoma of bone, and a high-grade synovial sarcoma. All tumor cells were harvested from patients prior to any neoadjuvant treatment. The tumor cells were exposed to various concentrations of bupivacaine for various durations. Tumor cell viability and apoptosis induction were evaluated by MTT assay and flow cytometry.

Results: Exposure to bupivacaine decreased cell viability and induced apoptosis which was confirmed by cell morphology and annexin+ cells in all sarcoma subtypes in a dose- and time-dependent manner. At clinically relevant doses, in vitro exposure to bupivacaine caused a decrease in cellular viability and an increase in the induction of apoptosis in a dose- and time-dependent manner in each of the tumor cells evaluated in this study.

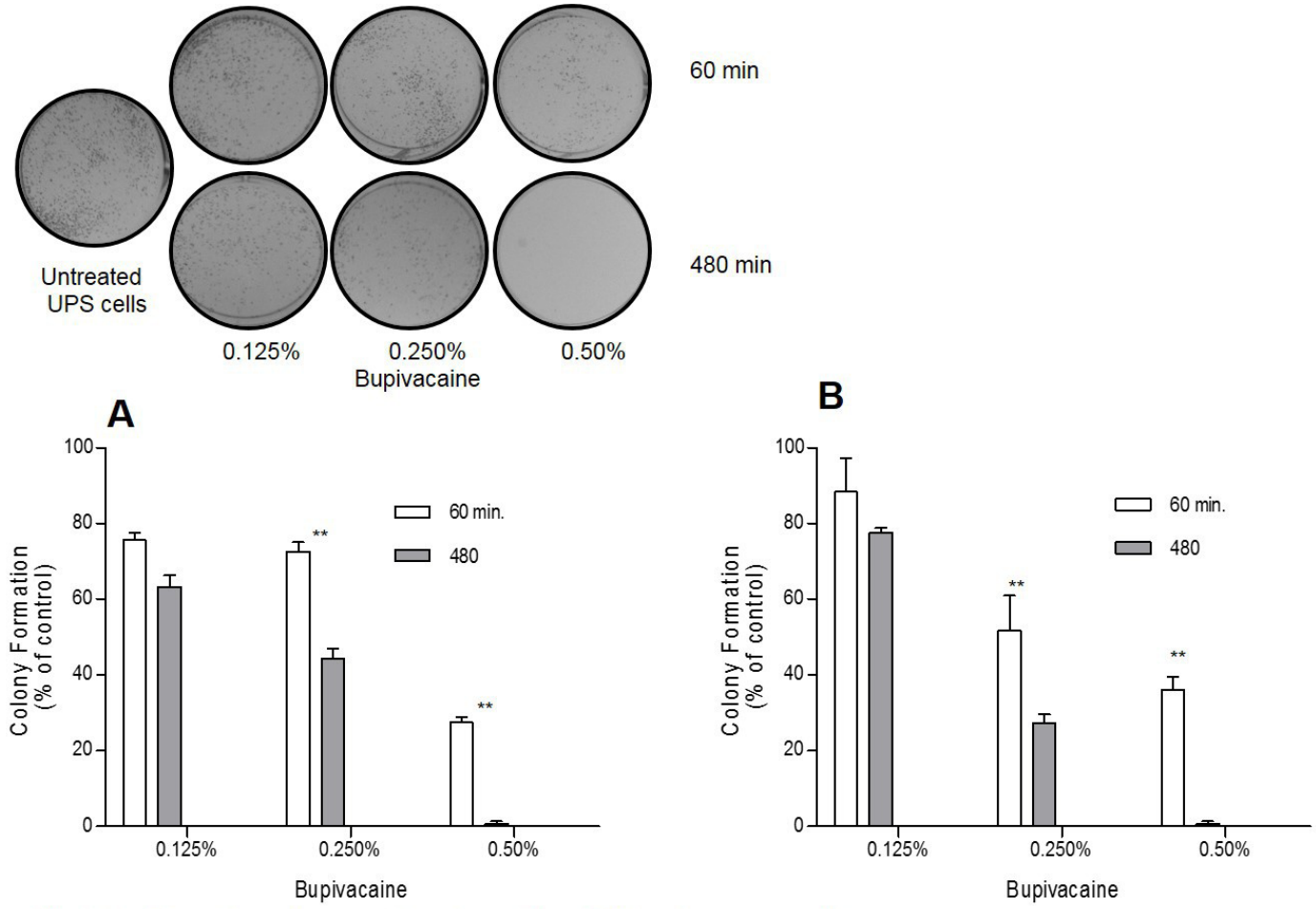
Conclusion: These findings have potential clinical relevance in the management of patients with sarcoma. Consideration should be given to using bupivacaine while performing biopsies to decrease the risk of biopsy tract contamination and as an adjuvant treatment after tumor resection.



Bupivacaine induces apoptosis in patient-derived sarcoma tumor cells.
Tumor cells (A:OS, B:UPS, C:SS) were treated with 0.25% and 0.5% bupivacaine (8.66 mM and 17.33 mM, respectively) for various time points (60, 120, 240 and 480 minutes). Cell death by apoptosis was analyzed using the Annexin V-fluorescein isothiocyanate (FITC) apoptosis kit after 24 hours. D) Dot plot graphs represent Annexin-V/propidium iodide double staining to assess the number of apoptotic cells from patient-derived synovial sarcoma tumor cells. Each experiment was done in triplicate (***pp< 0.01).



Bupivacaine reduces the viability of sarcoma tumor cells.
Patient-derived sarcoma tumor cells (A:OS, B:UPS, C:SS) were treated with 0.125%, %25 and 0.5% bupivacaine (4.33 mM, 8.66 mM and 17.33 mM, respectively) for various time points. MTT assay was performed after 48 hours. The bars represent the mean values of 3 independent experiments with standard error as error bars. Each experiment was done in triplicate (***pp< 0.01, *p< 0.05, ns p> 0.05).



Bupivacaine reduces colony formation ability of sarcoma cells.
Patient-derived sarcoma cells (A:UPS, B:SS) were treated with 0.125%, %25 and 0.5% bupivacaine (4.33 mM, 8.66 mM and 17.33 mM, respectively) for various time points. Colonies were stained with crystal violet after 12 to 14 days and the number of colonies was counted. The bars represent the mean values of 3 independent experiments with standard error as error bars. Each experiment was done in triplicate (**p< 0.01).

Poster 075 3042651

THE EFFECT OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS ON OSTEOSARCOMA CELLS

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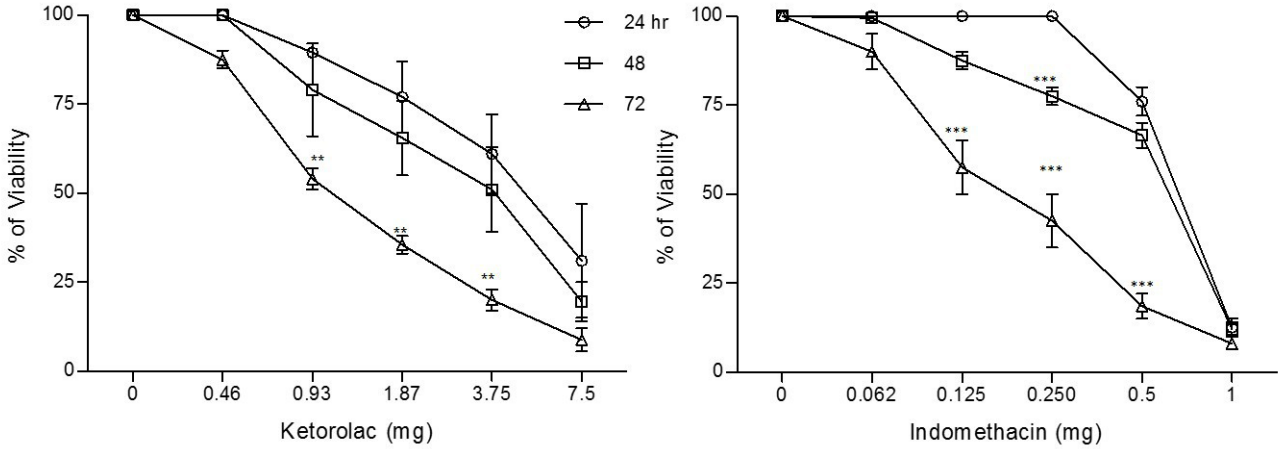
Objective: Osteosarcoma (OS) is an aggressive malignancy that is the most common primary bone tumor in children. Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used in orthopaedic surgery to reduce pain and inflammation. NSAIDs have been shown to be toxic to certain malignancies such as colorectal, breast, and pancreatic cancers as well as acute myeloid leukemia, but are not well-studied in OS. The purpose of this study is to assess whether ketorolac induces apoptosis in osteosarcoma cells and compare this to indomethacin, which has been shown to inhibit osteosarcoma proliferation, and explore the underlying mechanism.

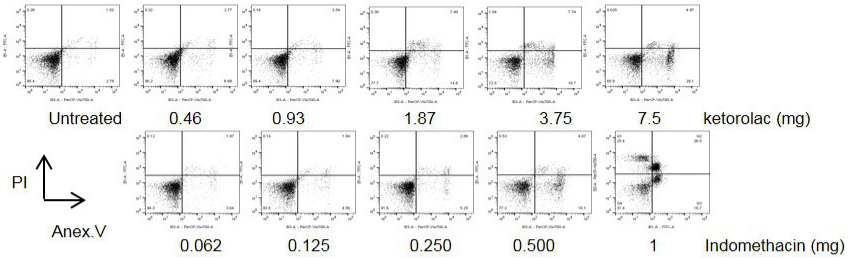
Methods: A rat osteosarcoma cell line (UMR-108) was exposed to various concentrations of both ketorolac and indomethacin. Cell viability, cytotoxicity, apoptosis induction, DNA fragmentation and the expression of apoptosis-related markers were examined by MTT assay, colony formation assay, flow cytometry, agarose gel electrophoresis, and western blot respectively.

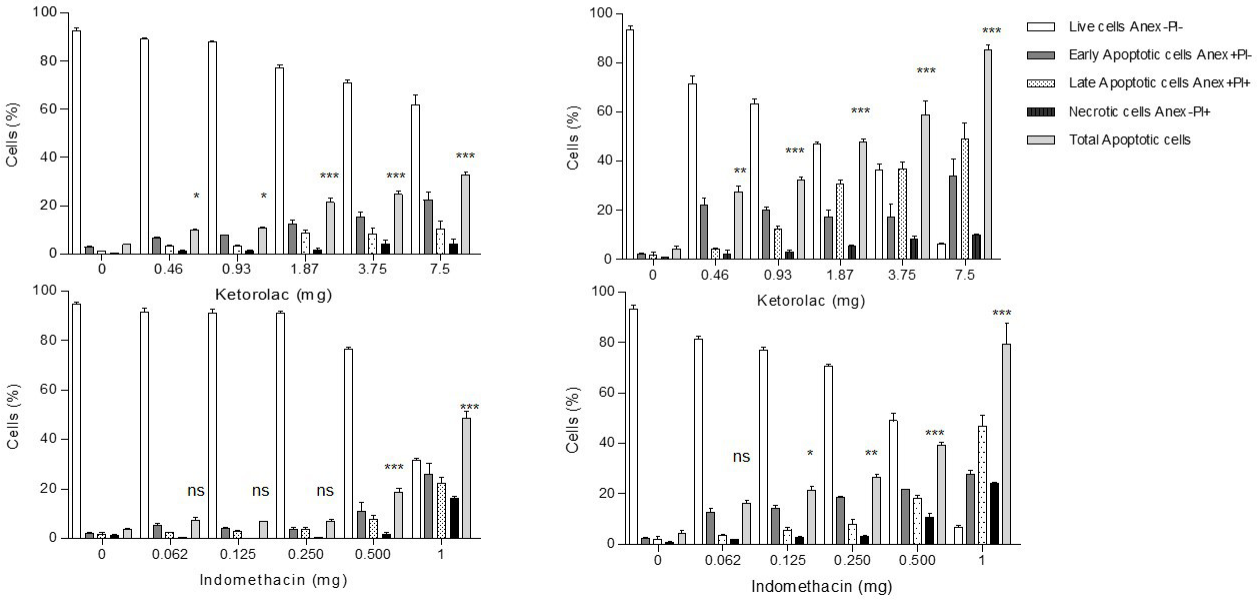
Results: The results indicated that ketorolac and indomethacin induced apoptosis of rat OS cells in a dose- and time-dependent manner. Apoptosis was confirmed by cell morphology and annexin positivity. Both NSAIDs induced morphological changes in OS cells and decreased their capacity to form colonies. The molecular data showed that NSAIDs affected expression of Bcl-2, survivin, and PARP.

Conclusion: These findings demonstrated that NSAIDs induced apoptosis in rat OS cells *in vitro*. Further reserach focusing on the potential cytotoxicity of NSAIDs *in vivo* are needed.

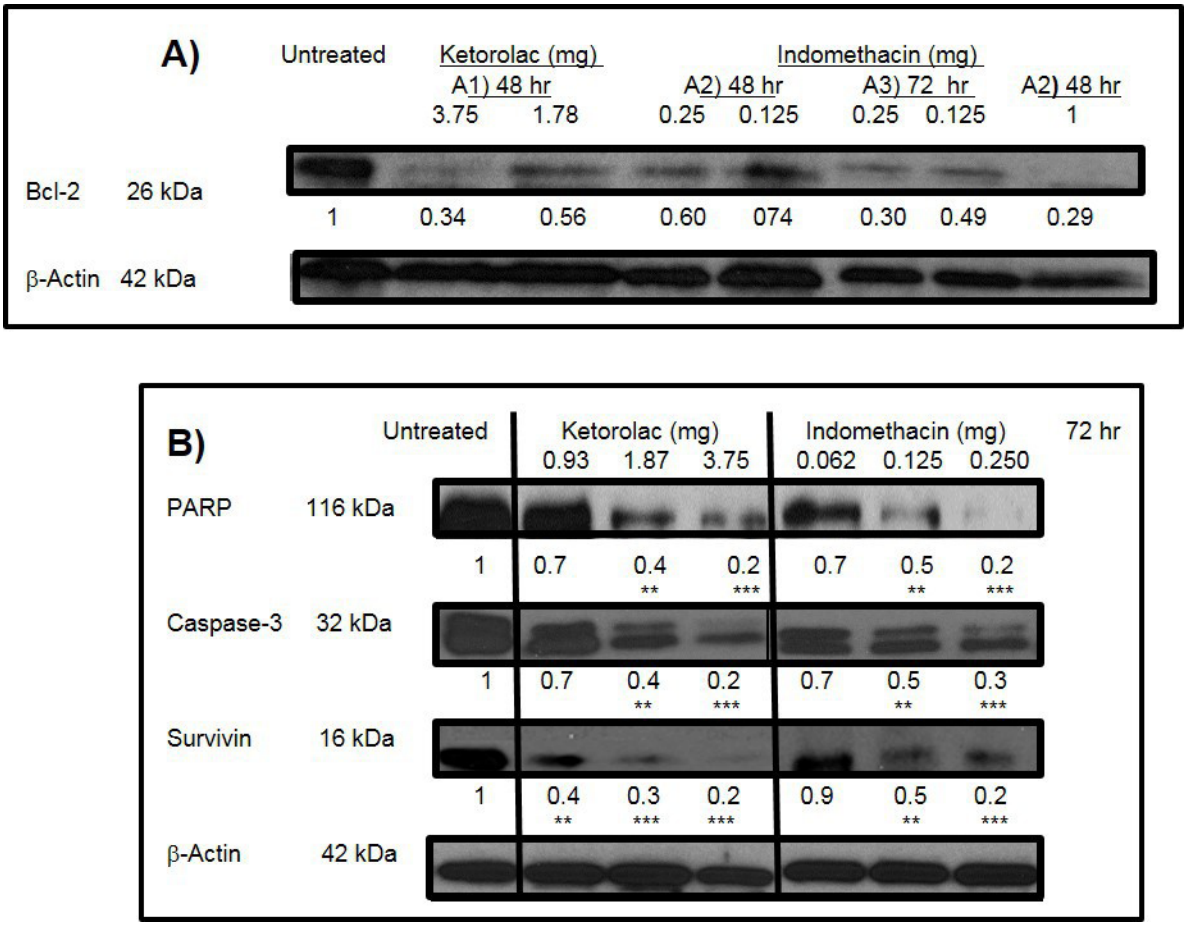


NSAIDs reduce the viability of OS cells. UMR-108 cells were treated with ketorolac and indomethacin at various concentrations for 24, 48 and 72 hours. MTT assay was performed at 24, 48 and 72 hours. Error bars indicate the standard deviation of the mean. Three independent experiments were performed in triplicate.(***p<0.01).





Flow cytometric analysis of NSAIDs on OS tumor cells. UMR-108 cells were exposed to ketorolac and indomethacin at various concentrations for 24 and 72 hours. Both floating and attached cells were harvested and washed. Flow cytometry with FITC-conjugated Annexin-V/propidium iodide (PI) double staining was used to assess the number of apoptotic cells and compared to the untreated group using the FlowJo software. Error bars indicate standard deviation of the mean of three independent experiments each performed in triplicate (***p



Expression of apoptotic proteins in OS tumor cells after being exposed to NSAIDs. UMR-108 cell were exposed to A1) 1.78 and 3.75 mg of ketorolac for 48 hours, A2) 0.125, 0.250 and 1 mg of indomethacin for 48 hours and A3) 0.125, 0.250 for 72 hours. B) Cells were exposed to 0.93, 1.78 and 3.75 mg of ketorolac and 0.062, 0.125 and 0.250 mg of indomethacin for 72 hours. Thetotal protein was then isolated. Equal amounts of protein from each sample were loaded and separated through 12% SDS-PAGE gels and then transferred to PVDF membranes. The following antibodies were used; PARP, caspase-3, Bcl-2, survivin, and b-actin. The bands were visualized by an enhanced chemiluminescence kit. Data were normalized to corresponding values of b-actin densitometry (***p< 0.01).

Poster 076 3042751

THE ATR INHIBITOR M4344 INDUCES TUMOR REGRESSION IN A PATIENT-DERIVED XENOGRAFT MODEL OF ALTERNATIVE LENGTHENING OF TELOMERS (ALT)- POSITIVE OSTEOSARCOMA.

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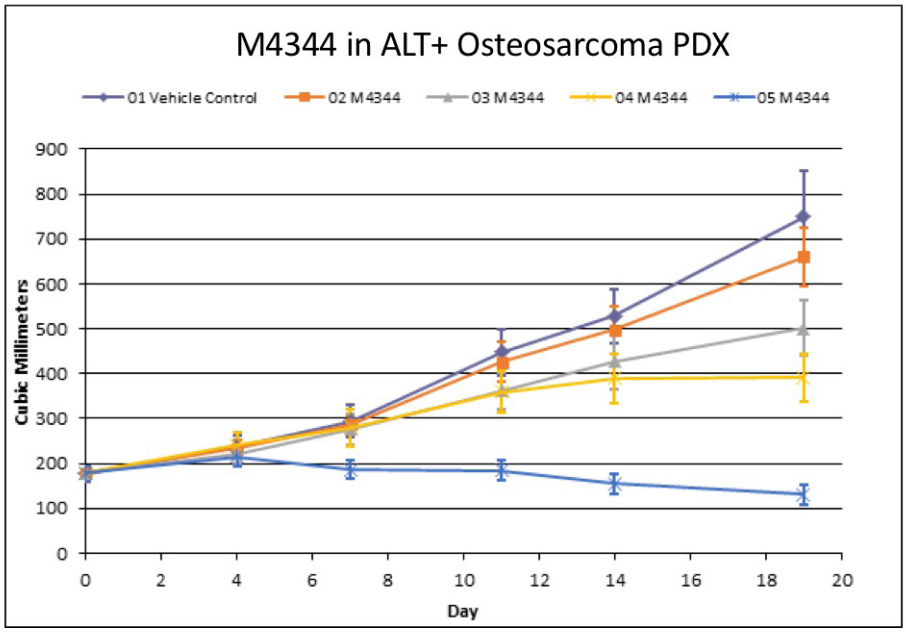
Objective: To evaluate the antitumor activity of M4344 in a low passage ALT+ human osteosarcoma model in immunocompromised mice.

Introduction: Cancers rely on either telomerase or the ALT pathway to extend telomeres and bypass senescence. ALT is a recombination-mediated mechanism, and it is estimated to be activated in 10–15% of cancers. It is now recognized that sarcomas have a high prevalence for ALT where, for example, it has been reported that up to >60% of osteosarcomas are ALT+. We have previously shown that loss or dysfunction of the ATRX-DAXX chromatin-remodeling complex generates a recombinogenic nucleoprotein structure (RPA-coated single-stranded DNA) at telomeres, which activates the ATR checkpoint kinase and promotes telomere recombination. Importantly, it was determined that ATR is a key regulator of ALT where ATR inhibitors disrupt the ALT pathway and selectively kill ALT+ cancer cells in a panel of osteosarcoma and glioblastoma cell lines. We sought to expand these data by exploring the activity of the ATRi M4344 in ALT+ osteosarcoma patient-derived xenografts (PDX).

Methods: We identified 11 candidate osteosarcoma mouse PDXs at the tumor modeling company Champions Oncology. Extracted DNA was analyzed by the c-circle assay to determine ALT status. Mouse PDX: stock tumors were implanted into the left flank of athymic nude-foxn1nu mice. When the tumors reached 150-300 mm^3 animals were matched by tumor volume into control and 4 cohorts of 10 mice each. Treatments were continued for 28 days (or until tumor volume reached 1500 mm^3) including 1. Vehicle 2. M4344 20 mg/kg once per week 3. M4344 20 mg/kg twice per week 4. M4344 20 mg/kg every other day 5. M4344 20 mg/kg every day. Tumor volume and mouse weights were obtained twice weekly. At day 30 the vehicle cohort was divided into two groups, 5 untreated and 5 treated with M4344, with samples obtained (serum PK and tumor) two hours after a single dose of M4344. At the conclusion of the treatment course mice were euthanized and tumor harvested for sample analysis.

Results: Of these models 4 of 11 were strongly ALT positive by the c-circle assay (telomere content post RCA > 1). One sample was borderline and the remaining <1, indicating non-ALT status. Model #4 was selected based on favorable tumor growth kinetics and ALT+ status. M4344 demonstrated robust tumor growth inhibition and modest tumor regression at the twice per day dosing. The agent was well-tolerated in this model. Experiments to determine the downstream endpoints of P-CHK1 and gH2AX are pending.

Conclusion: We analyzed a panel of human PDX osteosarcoma models to identify a mouse that was both ALT+ and which had favorable growth kinetics. We determined that in this model the optimal dosing of M4344 monotherapy is 20 mg/kg per day. Studies of ATRi in human ALT+ sarcomas are planned.



Group	-n-	Test Agent	Dose (mg/kg)	Dose Volume (mL/kg)	ROA	Schedule	Total Number of Doses
1	10	[1]VehicleControl	-	10	PO	QDx28	28
2	10	M4344	20	10	PO	1QWx4	4
3	10	M4344	20	10	PO	2QWx4	8
4	10	M4344	20	10	PO	Q2Dx28	14
5	10	M4344	20	10	PO	QDx28	28

[1]Vehicle Control: 15% Captisol in water

Poster 077 3042761

ROLE OF HSF1 IN OSTEOSARCOMA INITIATION AND DEVELOPMENT

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Objective: With 7 cases per million each year, osteosarcoma (OS) is the most common primary bone tumor, affecting mainly children and young adults. OS is characterized by an alteration of the bone remodeling process and metastastatic dissemination mainly to the lungs. The current treatment associates chemotherapy with surgical resection of the tumor. Unfortunately, the five years survival rate in case of metastases and for the bad responders stays low (30% at 5 years) despite the improvements. There is an urgent need to develop new therapeutic approaches. HSF1 (Heat Shock Factor I) is a member of the Heat Shock Factor family of proteins. This transcription factor is the major regulator of the Heat Shock Response (HSR), the cell's response to stress (heat shock, UV, hypoxia, oxidative stress, heavy metals…). It has been shown that HSF1 is overexpressed in several cancer types (lung, colon, breast…), but also in cancer associated fibroblasts, and its overexpression is a poor prognosis factor in breast cancer. For a long time, HSF1 role in cancer had been limited to HSR and the regulation of the chaperones, the guardian of proteostasis in the cell. But recently, several studies have shown that HSF1 regulates a large transcription network involved in the initiation and progression of the tumor. HSF1 deletion in mice reduces the number of apparition of sarcomas, after exposition to

carcinogenic compounds. In OS, it has been shown that HSF1 is involved in cell proliferation, migration and invasion. The goal of this study is to define the importance of HSF1 in OS.

Methods: HSF1 biological function will be studied, as well as its regulated genes. The study will also try to identify HSF1 partners and their impact on its action. And finally, the study will evaluate the impact of HSF1 inhibition on the biology of the tumor cell.

Results: We showed that HSF1 is overepressed in OS cell lines, and in biopsies from OS patients, compared to human mesenchymal stem cells. We also confirmed the involvement of HSF1 in OS cells proliferation and apoptosis. Chromatin Immunoprecipitation (ChIP) sequencing and RNA sequencing, after HSF1 inhibition by RNA interference, were performed in order to identify targets that are both bound and regulated by HSF1. This strategy produced hundreds of target genes, including known oncogenes and genes involved in bone physiology. These experiments also showed that HSF1 binds DNA in region identified as “super-enhancers” regions. Through Rapid immunoprecipitation mass spectrometry of endogenous proteins (RIME), we identified hundreds of interesting potential HSF1 partners on DNA, including proteins which involvement has been described in cancer and bone diseases.

Conclusion: These preliminary results indicate that HSF1 involvement in cancer is more important than previously described.

Poster 078 3042167

ERIBULIN SHOWS HIGH EFFICACY ON HIGLY CHEMOTHERAPY-RESISTANT OSTEOSARCOMA IN PATIENT-DERIVED ORTHOTOPIC XENOGRAFT MOUSE MODEL

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Objective: Osteosarcoma treatment includes surgery and intensive chemotherapy. MAP (methotrexate, doxorubicin, cisplatin) is the standard chemotherapy and improved cure rate significantly. However, five-year survival rate of relapsed and lung metastatic case is as low as 20%. We demonstrated efficacy of eribulin for relapsed and doxorubicin (DOX)-, cisplatin (CDDP)-resistant osteosarcoma using patient-derived orthotopic xenograft (PDOX) model.

Methods: A 16-year old patient developed left distal femoral high-grade osteosarcoma and underwent DOX-, CDDP-based neoadjuvant chemotherapy and surgery. However, the patient had a recurrence with pulmonary metastasis one year after surgery. PDOX model was established in nude mice from the original patient tumor and randomized into three groups including control (n=7), doxorubicin (3mg/kg, i.p., qw) (n=7), eribulin (1.5mg/kg, i.p., qw) (n=7). Tumor volumes and body weights were monitored. Significant differences for continuous variables were determined using the Steel-Dwass test for multiple comparison. A probability value of $P<0.05$ was considered statistically significant.

Results: After 14 days treatment, mice were sacrificed to harvest tumors. Doxorubicin could not suppress the tumor significantly. However, eribulin significantly regressed the relative tumor volume ratio (0.90±0.45) compared to control (6.41±2.98) and doxorubicin (5.99±2.09) group on day 14 ($p<0.01$, $p<0.01$, respectively).

Conclusion: We demonstrated high efficacy of eribulin with regression against DOCX-, CDDP-resistant osteosarcoma. Eribulin has potential to be the first- or second-line therapy for osteosarcoma.

Poster 079 3042622

DD LIPO CELL LINES AND PDX TO EXPLORE THE ACTIVITY OF ANTICANCER DRUGS AND COMBINATIONS

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Roberta Sanfilippo*[1]*; Silvia Stacchiotti*[1]*; Alessandro Gronchi*[1]*; Nadia Zaffaroni*[1]
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Objective: Well differentiated/dedifferentiated (WD/DD) liposarcoma (LPS) accounts for approximately 50% of all retroperitoneal sarcomas. Surgery remains the primary treatment for localized disease, but approximately 40% of newly diagnosed patients will eventually die from recurrences.

For advanced patients, few effective therapeutic options are available. Doxorubicin-based regimens, that are the most commonly used first-line treatment has only limited efficacy. High-dose ifosfamide, trabectedin and eribulin can be used from II line. Others (cabazitaxel; HDM2, CDK4/6 inhibitors, PPAR-gamma agonists) are under evaluation in clinical trials.

However, the rarity of DD lipo, their heterogeneity and the complexity of response assessment is a challenge in the development of new agents. In order to understand the biology of DD LPS, to assess and compare the anti-tumor activity of conventional and new therapeutic agents, we develop in vitro and in vivo models.

Methods: Tumor tissue was derived from patients with primary and naïve retroperitoneal MDM2 positive DD LPS surgically treated at INT from 2016.Fresh tissue was collected at the time of surgery, and an expert pathologist selected the DD component to be implanted into SCID mice to generate patient-derived xenograft (PDX) models.Cell lines were obtained directly from patient's tissue. Doxorubicin, ifosfamide, cabazitaxel, selinexor, eribulin, trabectedin alone and in combination were used for in vitro experiments. Drug activivity was determined by cell counting. Cell invasion was assessed by transwell invasion assay.

Results: Two established PDXs (≥ 3 passages in SCID mice) were obtained from patients with DD LPS with rhabdomyoblastic (R-DD1) and myogenic dedifferentiation (M-DD1), respectively. Two currently being developed PDXs (at first passage in SCID mice) were obtained from DD LPS with myogenic dedifferentiation (M-DD2) and with no heterologous dedifferentation (NR-NM-DD1), respectively. In vitro experiments were conducted using cell lines obtained from patients for whom PDXs were generated (R-DD1 and M-DD1). Type of drugs/combinations, drug concentrations and treatment times were presented in Table 1.

All tested drugs induced a dose-dependent antiproliferative activity in both cell lines. Doxo+Ifo combined treatment had an additive effect in inducing growth arrest in both cell lines, while Selinexor+Cabazitaxel had a synergistic effect, as detected by combination index < 1 in R-DD1 but not in M-DD1 cells. All drugs and combinations induced inhibition of cell invasion in both cell lines.

Conclusion: DD LPS cell lines can be used to test conventional therapies and new potentially effective combinations. The mechanism of actions can be further explored. In vivo experiments are ongoing to confirm the data obtained in cell lines.

Drug treatment schemes

Drug	Concentrations	Exposure time
Doxorubicin	from 0.01 to 10 (μM)	72h
Ifosfamide (4-hydroxyperoxy-ifosfamide)	from 0.01 to 10 (μM)	72h
Trabectedin	from 0.01 to 10 (nM)	72h
Eribulin	from 0.3 to 10 (nM)	72h
Cabazitaxel	from 1 to 1000 (nM)	72h
Selinexor	from 1 to 1000 (nM)	72h

Poster 080 3042654

CIRCULATING TUMOR CELL DETECTION FOR HEMANGIOSARCOMA DIAGNOSIS IN DOGS

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Objective: Hemangiosarcoma (HSA) is a common malignancy in dogs that is difficult to diagnose until late onset, resulting in emergency surgery. Once the disease is found, there is no cure for it and it is a rapidly fetal disease. To improve the outcome for this disease we have developed a test to detect HSA cells in blood using flow cytometry. Here, we sought to determine the utility of circulating tumor cell detection for early detection of HSA and to monitor disease relapse as prelude to developing this approach for early detection. The goal is to determine whether we can apply this test for early detection purposes, paired with a bispecific ligand targeted toxin (eBAT) therapeutic that eliminates the cells responsible for maintaining the disease.

Methods: We are using flow cytometry to detect circulating tumor cells from canine blood samples with an antibody panel designed to exclude normal leukocytes and identify HSA cells with a combination of progenitor and endothelial markers. A lower limit of detection was established by spiking cultured HSA cells into normal blood. Circulating tumor cells were enumerated in blood samples from dogs with HSA (n=13), splenic hematoma (n=12), cancer other than HSA (n=23), and no known disease (n=25). We are evaluating parameters to exclude monocytes, platelets, or all leukocytes, as well as to detect co-expression of the hyaluronic acid receptor (CD44).

Results: Using this test, we could identify as few as 5 HSA cells per µl of blood in normal dogs. Both canine platelets and HSA cells expressed alpha(v)beta(3) (aVb3)-integrin (CD51/CD61), alpha(2)beta(3) (a2b3)-integrin (CD41/CD61), and CD44. Cells co-expressing CD51/CD61 with CD34 and/or c-kit were detected in a small number of blood samples; however, CD51/CD61+ cells were more prevalent in dogs with HSA than in healthy dogs and in dogs with cancer other than HSA. When the CD51/CD61+ events were backgated onto light scatter plots, a SS-low population was apparent in samples from dogs that did not have HSA, whereas a SS-high was present in samples from dogs with HSA and in some samples from dogs with splenic hematoma, but not in samples from healthy dogs. Convalescent samples from dogs with HSA showed reduced numbers of CD51/CD61+ events during remission.

Conclusion: CD51/CD61+ cells are detectable in blood of dogs with HSA using flow cytometry. We favor the interpretation that these are CTCs, but they also might include activated endothelial cells or platelet-coated leukocytes. The addition of CD45 to the dump gate, and of CD44 to the analysis parameters, are expected to improve specificity of the test. RNA sequencing data are being used to guide additional refinements to the flow cytometry panel.

Poster 081 3011719

INCIDENCE OF CARDIOMYOPATHY WITH TRABECTEDIN USE IN SOFT TISSUE SARCOMAS

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Objective: Sarcomas are a rare group of solid tumors derived from mesenchymal tissue that collectively account for only 1% of all adult malignancies, of which soft tissue sarcomas (STS) are the most common subtype. Prognosis for patients with advanced or metastatic STS is poor, and systemic chemotherapy is largely palliative rather than curative. Treatment for patients with progressive disease despite first-line therapy is at least partially histology driven. Trabectedin, a novel marine-derived alkylating agent, was recently approved to treat advanced or unresectable leiomyosarcoma and liposarcoma that has failed anthracycline-based chemotherapy. Drug safety literature frequently discusses hepatic and hematologic toxicities of trabectedin, but real-world data is limited regarding cardiac toxicity. Initial trials indicated a relatively low frequency of grade 3 or 4 cardiotoxicity associated with trabectedin use, but our report highlights a substantially increased incidence of cardiomyopathy in patients treated with trabectedin.

Methods: A retrospective chart review was performed on 27 patients treated with trabectedin between November 2015 and November 2017. Patients with documented pre- and post-treatment ejection fraction (EF), obtained by either multi-gated acquisition scan (MUGA) or transthoracic echocardiogram (TTE) were included in our analysis. Patients with previously documented cardiomyopathy or pre-treatment EFs <50% were excluded from this study. We define cardiomyopathy as left ventricular systolic dysfunction evidenced by a decrease in the post-treatment EF to less than 50%, combined with a drop by more than 10% when compared to the pre-treatment EF. Using the Common Terminology Criteria for Adverse Events (CTCAE), grade 3 and 4 cardiomyopathies are defined as those with symptoms due to a drop in EF and poorly controlled heart failure due to drop in EF, respectively.

Results: We identified 18 patients treated with trabectedin that had documented pre- and post- therapy ejection fractions. Of these, 5 (27.8%) experienced a decreased ejection fraction to <50% with >10% decrease from their pre-treatment EF. Given their symptoms of dyspnea and/or lower extremity edema, all 5 met criteria as having developed grade 3 or 4 cardiomyopathy compared to only 15 (4%) of the 378 patients studied in the Phase 3, randomized, open-label, controlled YONDELIS trial (ET743-SAR-3007). The median time to develop grade 3 or 4 cardiotoxicity in our study was 2.35 months (ranging 8 days to 8.5 months) compared to 5.3 months (ranging 26 days to 15.3 months) in the YONDELIS trial, with 3 of our patients (16.7%) discontinued permanently from trabectedin compared to 4 (1.1%) in the YONDELIS trial.

Conclusion: The safety profile of trabectedin highlights myelosuppression and transient transaminitis as common grade 3 to 4 adverse effects, but real-world data regarding cardiotoxicity is scarce. Current guidelines recommend assessing LVEF prior to therapy and at 2- to 3-month intervals thereafter, however, our data suggest there may be some benefit to increased surveillance of cardiac function, particularly during the first 12 months of treatment. Given the high incidence of cardiomyopathy with trabectedin, whether a result of the prior anthracycline exposure, the trabectedin alone, or a combined effect, increased surveillance may prove significantly advantageous. If LVEF is assessed more frequently, cardiomyopathies may be detected earlier, allowing for preservation of cardiac function. This could serve to prevent early termination of a therapy that has otherwise shown to be effective in reducing the risk of disease progression or death in patients with soft tissue sarcomas that have progressed despite first-line agents.

Poster 082 3042939

A PHASE 1B/2 STUDY OF VORINOSTAT IN COMBINATION WITH GEMCITABINE AND DOCETAXEL IN ADVANCED SOFT TISSUE SARCOMAS (STS)

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[2]*MD Anderson Cancer Center, Houston, TX, USA*

Objective: Gemcitabine and docetaxel is an established active regimen for soft tissue sarcomas with modest response rate, significant improvements in progression-free survival, and overall survival. Chemotherapy resistance in solid tumors has been linked to epigenetic silencing of genes relevant to apoptosis and DNA repair, including histone deacetylation. Vorinostat is a histone deacetylase inhibitor that promotes potentiation of cytotoxic chemotherapy including gemcitabine and docetaxel. We propose a Phase Ib dose escalation trial to determine the safe dose of vorinostat in combination with gemcitabine and docetaxel in a novel dose and schedule, followed by an open-label Phase II dose expansion trial at the recommended phase II dose (RP2D) to determine the efficacy of the combination.

Methods: The primary objective of the phase Ib study was to determine the dose of vorinostat that can be safely combined with gemcitabine and docetaxel in patients with advanced STS and RP2D. Secondary objectives included pharmacokinetics (PK) and pharmacodynamics (PD) of vorinostat when combined with gemcitabine and docetaxel. Dose escalation was completed using the standard 3+3 design. The starting dose of vorinostat was 300mg orally daily (QD) along with gemcitabine 900 mg/m2 intravenously (IV) at fixed dose rate 10 mg/m2/min on days 1 and 8 and docetaxel IV 75 mg/m2 on day 8. Growth factor support was given on day 9 of each cycle. A cycle was 21 days. Dose limiting toxicities (DLTs) were evaluated for during the first cycle. Eligible patients (pts) were ≥18 years old with advanced metastatic or unresectable STS that have received up to 2 prior lines of systemic therapy and ECOG PS ≤2. Patients with Ewing sarcoma, osteosarcoma, GIST, low grade chondrosarcoma, and chordoma are excluded. Vorinostat (D-1 and 8) and gemcitabine+dFdU (D8) PK were evaluated with validated assays.

Results: Twelve pts (7 females, 5 males) are part of the evaluable population in phase Ib with a median age 53.5 (23 – 72) treated at doses of 300 mg QD (6) and 200 mg BID (6). STS subtypes included leiomyosarcoma (5), dedifferentiated liposarcoma (2), synovial sarcoma (2), alveolar rhabdomyosarcoma (1), clear cell sarcoma (1), and dedifferentiated solitary fibrous tumor (1). DLTs were G4 thrombocytopenia and G3 febrile neutropenia, which occurred in 1 pt at 200 mg BID, and G4 thrombocytopenia and G3 fatigue, occurring in 1 pt at 200mg BID. The most common adverse events related to study drug were thrombocytopenia (7.3%), anemia (6.7%), lymphopenia (5.5%), and fatigue (4.8%). Serious adverse events (SAEs) related to study drug were reported in 4 pts: febrile neutropenia (2 pts, 300mg QD; 1 pt, 200mg BID), pneumonitis (1 pt, 300mg QD), and diarrhea (1 pt, 300mg QD). The RP2D was 300 mg QD in combination with gemcitabine 900 mg/m2 on days 1 and 8 and docetaxel 75 mg/m2 on day 8. Gemcitabine and dFdU PK was largely as expected. Vorinostat PK on D8 displayed statistically significantly higher values for t1/2 (3.5-fold) and AUC0-inf (1.8 fold), likely due to polysorbate in the docetaxel infusion. Response rate will be presented.

Conclusion: Vorinostat in combination with gemcitabine and docetaxel is well-tolerated with a safety profile most consistent with gemcitabine and docetaxel alone. The maximum tolerated dose has been identified as 300 mg QD of vorinostat. A Phase 2 trial of gemcitabine, docetaxel and the RP2D of vorinostat 300mg QD is currently enrolling. Clinical trial information: NCT01879085.

Poster 083 3044509

EVALUATION OF LENVATINIB, EVEROLIMUS OR THE COMBINATION IN PEDIATRIC SARCOMA MODELS

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[1]*Pediatrics, MD Anderson Cancer Center, Houston, TX, USA;* [2]*Greehy Children's Cancer Research Institute, UT Health San Antonio, San Antonio, TX, USA;* [3]*Epidemiology and Biostatistics, UT Health Science Center San Antonio, San Antonio, TX, USA*

Objective: Lenvatinib is a potent multiple RTK inhibitor that selectively inhibits VEGF receptors, VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4), FGFR1-4, PDGFRα, KIT, and RET. Lenvatinib in combination with everolimus has achieved the higher rate of objective responses and the longer progression-free and overall survival in patients with advanced or metastatic renal cell carcinoma compared with everolimus following one prior antiangiogenic therapy. The objective this study was to evaluate the antitumor activity of single agent lenvatinib, single agent everolimus, and the combination in Ewing sarcoma, osteosarcoma, and rhadbomosarcoma *in vivo* models.

Methods: The antitumor activity of lenvatinib (7.5 mg/kg daily x 42, P.O) and everolimus (15 mg/kg, daily x 42, P.O) as single agents, or in combination was examined in two models of Ewing sarcoma (EWS-1, EW-5), five models of osteosarcoma (OS1, OS2, OS31, OS33, OS36) and six models of rhabdomyosarcoma (Rh10, Rh18, Rh28, Rh30, Rh36, Rh41). Efficacy was determined using tumor volume measurements to assess tumor regression and time to event (EFS). Inhibition of target kinase receptors was determined by immunoblotting at the end of treatment, and changes in tumor vascularity determined by immunohistochemistry.

Results: Single agent lenvatinib significantly inhibited growth of 10 of 13 tumor models (2/2 EWS, 3/5 OS, 5/6 Rh) and single agent everolimus also significantly inhibited growth of 9 of 13 tumor models (2/2 EWS, 4/5 OS, 3/6 Rh). The antitumor activity of the combination of lenvatinib with everolimus was significantly greater than either single agent in 4 of 8 models (1/2 EWS, 1/2 OS, 2/4 Rh). The combination was more active than lenvatinib in 8 of 13 evaluable models (1/2 EWS, 4/5 OS, 3/6 Rh) and more active than everolimus in 6 of 8 evaluable models (1/2 EWS, 1/2 OS, 4/4Rh). The predominant effect of single agents and the combination was slowing of tumor growth, without a high frequency of tumor regressions.

Conclusion: Lenvatinib and everolimus both have statistically significant antitumor activity in these sarcoma models. The combination was more effective than single agents in the majority of models, inducing almost complete stasis of tumor growth during the period of drug administration.

Treatment	EWS-1	EW5	Rh10	Rh18	Rh28	Rh30	Rh36	Rh41	OS1	OS2	OS31	OS33	OS36
Lenvatinib vs Control	**<0.001**	**0.018**	**<0.001**	0.051	**0.05**	**<0.001**	**<0.001**	**0.037**	**0.007**	0.183	**0.009**	**0.005**	0.065
Everolimus vs Control	**0.01**	**0.011**	**0.007**	0.924	**<0.001**	1	**<0.001**	0.245	**<0.001**	**<0.001**	**0.009**	**<0.001**	0.065
L+E vs Control	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.065
LE vs L	0.613	**0.002**	0.056	**0.039**	**0.001**	0.635	0.125	**0.003**	**0.027**	**<0.001**	**0.002**	**<0.001**	1
LE vs E	0.063	**0.001**	**0.019**	**<0.001**	---	**<0.001**	---	**<0.001**	---	0.235	**0.002**	---	---

Poster 084 3040916

RADIOTHERAPY (RT) COMBINED WITH TRABECTEDINE FOR LOCALLY ADVANCED OR METASTATIC, SOFT TISSUE SARCOMA (STS): AN UPDATE OF A SINGLE INSTITUTION EXPERIENCE

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[1]Radiation Oncology, National Cancer Institute CRO IRCCS , Aviano (PN), Italy; [2]Medical Oncology, National Cancer Institute CRO IRCCS, Aviano (PN), Italy; [3]Surgical Oncology, National Cancer Institute CRO IRCCS , Aviano (PN), Italy

Objective: Trabectedin (T) has demonstrated activity in Liposarcoma, Leiomysarcoma and in other histological subtypes, after failure of Anthracycline and Ifosfamide based Chemotherapy (CT), or for patients (pts) un-fit for these agents. Preclinical data showed a radiosensitizing activity of T nevertheless few data of feasibility and tolerance of combined T and radiation therapy (RT) are available. Aim of this study is to evaluate feasibility and safety of RT concurrent with T in a series of pts affected with extremity (ETS) and retroperitoneal sarcomas (RPS).

Methods: We retrospectively analyzed acute and late toxicity (according to CTCAE 4.0 scale) of a series of pts with primary, recurrent or metastastic STS, treated with concurrent RT 40.5Gy/18fxs/3.5wks and T 1.5mg/m^2 as 24 hours iv infusion, q3 weeks at our Institute.

Results: Data of 14 pts (F/M 10/5) with a median age of 51 yrs (range 34-66), treated between December 2012 and May 2018, were available. Median ECOG PS was 1 (0-2). The most common histologies were Leiomyosarcoma 5pts (36%) and Myxoid Liposarcoma 4pts (28.5%); other histological subtypes were Synovial Sarcoma, Fibrosarcoma and Epitheliod Sarcoma; 10 pts (71%) had high grade disease. Pts underwent RT combined with concurrent T on primary (2pts) or local recurrent tumors (8pts) or metastatic sites (4pts). Nine pts (64%) had received previous CT as primary treatment or for recurrence. Primary or recurrent tumors were retroperitonuem 3 (21%), extremity 7 (50%), superficial trunk 1 (7%); bone 2 (14%) and lung in 1 (7%) case, respectively.
Preoperative treatment intent was considered in 6pts (43%), 3 (50%) with RPS and 3 (50%) with ETS un-fit for Anthracycline based-CT . Palliative RT-T intent was consider in 8 pts (57%) at site of recurrent (50%) or metastatic disease (50%).

RT was given at the median dose of 40.5Gy (range 8-55.2 Gy) combined with T during 1st and 2ndcycles in 6 (42%), 2nd and 3rd in 4 (28.5%), 3rd and 4th in 4 (28.5%) cases respectively.
RT-T was stopped in only 1pts (7%), previously treated with 2 lines of CT, due to G3 anemia.
Grade 3 neutropenia was reported in 3 pts (21%) which required postponed T of few days and dose reduction. Grade 3 transaminitis occurred in only 1(7%) case. The most common non haematological toxicities were G1-2 radiodermatitis and G2 asthenia, reported in 7(50%) and 4 (36%) cases respectively. Most patients, 13/14 (93%) received the RT and T planned dose.
Major clinical response (RECIST) was reported in 7 pts (50%), 1 CR and 6 PR. All preoperative intent pts underwent surgery with intraoperative radiation therapy (IORT).
At a median follow up of 12.4 months (0-57 months) all operated pts are alive without disease, including RPS.

Conclusion: Combined RT at the dose of 40.5Gy (range 8-55.2Gy) and T 1.5mg/m^2 as 24 hours iv infusion, q3 weeks, appears feasible and safe, even in heavily pretreated pts. Despite grade 3 toxicity was reported, most patients completed the planned treatment. Also, combined RT and T appears feasible in RPS where larger RT volumes are required.

Poster 085 3042415

LEUCOENCEPHALOPATHY IS A COMMON COMPLICATION IN PATIENTS TREATED WITH HIGH DOSE METHOTREXTATE

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Objective: Methotrexate encephalopathy is a severe complication due to high dose methotrexate (MTX). Little information is available on the incidence and long term outcome of this event in patients treated for an osteosarcoma.

Methods: We studied the incidence of neurologic complications and leukoencephalopathy (LE) in osteosarcoma patients treated with methotrexate and etoposide-ifosfamide according to the M-EI arm of OS2006 protocol in the pediatric department of Gustave Roussy between 2007 and 2015. Brain MRI were proposed as a systematic procedure before surgery of the primary, during post-operative chemotherapy, at the end of treatment and during follow-up. Only patients having received a minimum of 3 courses of MTX and who could have at least one brain MRI during or after the treatment were included in the study. Most MRI were performed in a single center and reviewed by 2 trained neuroradiologists. LE was defined by the presence of hypersignal on sequence T2 and FLAIR of the periventricular white matter. Grading was based on Wilson staging system. Neurocognitive evaluations were proposed to all patients and performed by a licensed neuropsychologist a few weeks after the beginning of chemotherapy, at the end of the treatment and during follow-up.

Results: Overall 54/66 patients included in OS2006 trial met the eligibility criteria for the study. At least one episode of neurological complication due to MTX was reported in 40 (74%) patients including headaches in 27 patients (isolated in 13 and combined with other neurological symptoms in 14) and neuro-cognitive symptoms in 27 patients including moderate (N= 11) to severe (N=2) cognitive impairment, convulsions (n=4), severe depressive syndrome (n=10). Resolution of the acute symptomatology was complete in all patients within a few months except in one patient who keeps mild cognitive impairment and seizures more than 3 years after the event.
A total of 142 MRI were performed (median 3/ patients): 37 before surgery, 29 during post-operative chemotherapy, 42 at the end of treatment and 34 during follow-up. A LE was detected on at least one MRI in 52 patients (96%) with a maximum grade of 1 in 12 pts, 2 in 12 pts and 3 in 27. Methotrexate was withdrawn from the treatment because of LE in 16 patients (32%) with grade 2 or 3 LE with or without associated neurological symptoms.
The incidence of LE and the proportion of grade 2-3 increased with the number of courses of methotrexate: LE was detected in 23/37 pts (62%) with 6 grade 2-3 after 7 courses, 26/29 (89%) with 15 grade 2-3 after 12 courses and 41/42 (98%) including 34 grade 2-3 at the end of treatment. of which 12/12 (100%) including 9 grade 2-3 after 19 courses. Among 34 patients who had an MRI two years after the end of treatment, 32 (94%) still had signs of LE: 11grades 1, 11grades 2 and 10 grades 3.
38 patients underwent neurocognitive assessment at the end of treatment and the results were classified as slightly impaired (<85) in 10 (26%) patients including 7/16 (43%) patients with leucoencephalopathy grade 3. Compared with national norms, patients with abnormal cognitive evaluation demonstrated lower reading scores, more variability in sustained attention: poorer short-term memory and work memory, slower motor processing speed, slower motor processing, poor work memory and poor cognitive fluency. In the neuropsychological assessment monitoring performed in 33 patients at least one year after the end of treatment, results were improved for the majority of the tests. No aggravation of neuropsychological assessment is described.

Conclusion: In patients treated with Methotrexate and etoposide-ifosfamide, the presence of a LE is a common complication. Neurologic signs are not always present and may be limited to headache or severe depressive symptoms. The presence of LE is not obviously associated with neurocognitive impairment at short term but a longer follow-up is warranted.

Poster 086 3042845

TARGETING MICROENVIRONMENT AND CELLULAR IMMUNITY IN SARCOMAS WITH WEEKLY TRABECTEDIN COMBINED WITH METRONOMIC CYCLOPHOSPHAMIDE (TARMIC)

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Objective: Trabectedin is approved for the management of patients with advanced soft-tissue sarcoma (STS) refractory to anthracycline-containing regimen or who are unsuited to receive these agents. Recent pre-clinical data have suggested that the antitumor activity of trabectedin is not only related to their effects on tumor cells, but also on its ability to affect the tumor microenvironment (TME), in particular tumor associated macrophages and their pro-tumoral functions. We report results of the phase I part of the first study evaluating trabectedin in combination with metronomic chemotherapy on the TME of patients (pts) with advanced sarcomas.

Methods: TARMIC is an open-label multicenter phase I/II study of trabectedin in combination with low-dose cyclophosphamide in pts with advanced STS (NCT02805725). During the phase I part, all pts received trabectedin (4 dose levels: 0.3 mg/m2, 0.4 mg/m2, 0.5 mg/m2, 0.6 mg/m2) weekly for three consecutive weeks (days 1, 8 and 15) every 4 weeks and cyclophosphamide (CP) 50 mg BID 1week on, 1 week off. For the phase I part, the primary endpoint was the maximum tolerated dose (MTD) evaluated on the first cycle (D1 to D28) of trabectedin when coadministered with CP. Secondary endpoints included efficacy and evaluation of impact on TME through mandatory required tumor biopsies at baseline and after one cycle of treatment. D*ose escalation followed a conventional 3+3 design.*

Results: Overall 20 patients (10 males, 10 females) have been included between December 7 2015 and February 12 2018: 3 patients received trabectedin at dose level 1, 3 patients at dose level 2, 7 patients at dose level 3 and 7 patients at dose level 4. Patients had median age of 61 years (range: 27–73). The most frequent histological subtype was leiomyosarcoma (n=14, 70%). The median number of previous lines of systemic treatment for advanced disease was 2. No dose-limiting toxicity (DLT) was observed at dose level 1, 2 and 3. Two patients included at dose level 4 experienced at least one DLT including grade 4 creatine phosphokinase (CPK) increase and febrile pancytopenia. Therefore, the recommended phase 2 dose of weekly trabectedin in combination with metronomic CP is 0.5 mg/m2. Analysis of pre- and on-treatment tumor biopsies identified a favorable immunological outcome (increase in CD8+/Treg and/or decrease in M2/M1 macrophage ratios) in 6 out of 19 patients (31%). Moreover, a significant decrease in circulating kynurenine/tryptophan ratio, a marker of the immunosuppressive enzyme IDO activity was observed in 8 out of 18 (44.5%). The longest duration on study of more than 53 weeks was recorded in a patient included at dose level 3 who still remains on study. This patient has the best immunological outcome with a massive lymphocytic infiltration and a huge decrease in M2 macrophages in tumor tissue obtained after 4 weeks of treatment. Overall, increase in CD8/Treg ratio under treatment is significantly associated with improved progression-free survival (3.6 *vs*. 1.8 months, p=0.036).

Conclusion: We report the first demonstration of the immunological activity of trabectedin in patients with advanced STS. Modulation of TME under trabectedin appears to be correlated with outcome. Additional gene expression profiling data are still under evaluation. The phase II part of the study at the recommended weekly dose of 0.5 mg/m2 will start accrual soon.

Poster 087 2986862

THE IMPACT OF CHEMOTHERAPY ON PRIMARY BONE TUMORS OF THE VERTEBRAL COLUMN: A NATIONAL CANCER DATABASE REVIEW

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Objective: Chemotherapy has dramatically improved survival in many primary bone tumors. Bone tumors of the vertebral column (BTVCs) are rarer and the impact of chemotherapy on these tumors is not well established. We investigated the largest registry of primary bone tumors, the national cancer database (NCDB); our goal was to investigate whether chemotherapy is

associated with improved survival in patients with primary BTVCs. Specifically, our goal was to (1) investigate the differences in demographics and tumor characteristics in patients receiving chemotherapy (2) estimate the 5-year survival by use of chemotherapy; (3) examine the independent impact of chemotherapy on survival.

Methods: We retrospectively analyzed patients in the NCDB from 2004 through 2015. Patients were stratified based on chemotherapy use for primary BTVCs; these were further stratified by histologic subtype. Univariate and multivariate analyses were used to correlate specific outcome measures with these factors. Then, long-term survival between groups was evaluated using the Kaplan-Meier (KM) method with statistical comparisons based on the log-rank test. Multiple variables were analyzed between the two groups.

Results: We identified 941 patients presenting with primary BTVCs. 37 patients were treated with chemotherapy alone, 293 were treated with surgery alone, and 72 were treated with both surgery and chemotherapy; 78/ 127 patients with osteosarcoma (61.4%) and 146/164 patients with Ewing's Sarcoma (89%) underwent chemotherapy as compared to 16/243 patients with chondrosarcoma (6.6%) and 14/407 patients with chordoma (3.4%). Across the entire cohort of patients, patients who received chemotherapy were on average, younger (38 vs 56 years, p<0.0001) and lived closer to the facility (52 vs 110 miles, p=0.0062). Patients with osteosarcoma and Ewing's sarcoma had significantly improved survival when treated with chemotherapy (p=0.0156 and p<0.001, respectively); those patients with a chordoma demonstrated no significant difference in survival, and those with chondrosarcoma demonstrated decreased survival with chemotherapy treatment (p<0.001). Patients with osteosarcoma and Ewing's treated with the addition of chemotherapy had a lower risk of mortality overall than those treated without the addition of chemotherapy, with five-year survival rates that were superior in patients treated with chemotherapy as part of their treatment (44.1% five year survival) vs. without (22.5% five year survival, p<0.001). Survival for patients receiving treatment with surgery in addition to chemotherapy was far greater than for those receiving either chemotherapy or surgery alone (44.1% five year survival vs. 9.6% and 28.8% respectively, p<0.001 and p=0.021). When controlling for possible confounding factors, chemotherapy independently improved survival in patients with high-grade tumors as compared to those receiving treatment without chemotherapy (HR 0.43 (0.26-0.73), p=0.002).

Conclusion: This is the largest patient cohort to date examining the impact of chemotherapy on primary BTVCs. Chemotherapy use was far more likely for Ewing's sarcoma and osteosarcoma than chordoma and chondrosarcoma. Patients with either osteosarcoma or Ewing's sarcoma receiving surgery in addition to chemo had improved overall survival than those undergoing surgery or chemotherapy alone.

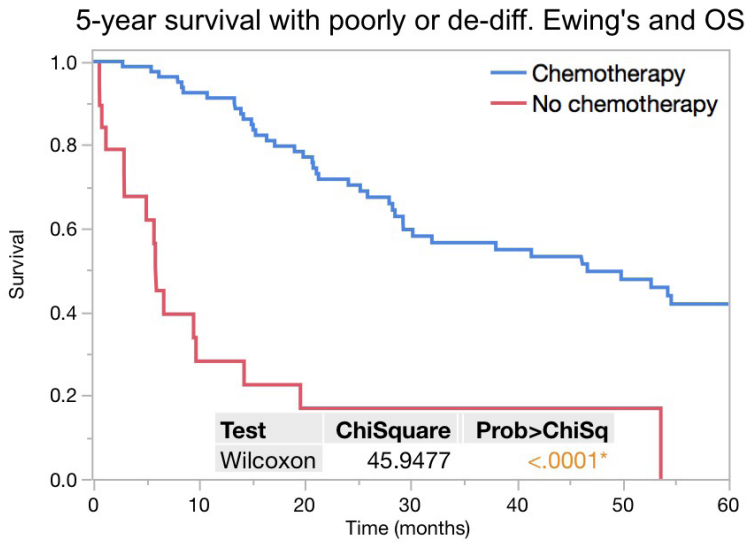

Figure 1. Kaplan Meier 5 year survival for patients with High Grade Ewing's Sarcoma and Osteosarcoma

Poster 088 3030645

NEOADJUVANT CHEMOTHERAPY IN LOCALLY ADVANCED SOFT-TISSUE SARCOMA: THE GUSTAVE ROUSSY EXPERIENCE

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Objective: Neoadjuvant chemotherapy (CT) with anthracyclines plus ifosfamide (AI) is a therapeutic option in patients (pts) with marginally locally advanced soft-tissue sarcoma (LASTS), aiming at a local benefit, facilitating surgery, in addition to the systemic one (ESMO guidelines 2017). The decision making process is done in multidisciplinary board and neoadjuvant chemotherapy is proposed when a R0 resection is not possible upfront. This study evaluates the results of this practice at our institution.

Methods: We retrospectively reviewed all consecutive pts with LASTS who received AI (doxorubicin 60 mg/m2 D1, plus ifosfamide 3g/m2 D1, D2 and D3) regimen treated from 1996 to 2015 in neo-adjuvant setting in our institution. Clinical, biological, imaging and pathology data were collected from patient files. Survival curves were calculated according to Kaplan-Meier and compared with the log-rank test or a Cox proportional hazard model, using R 3.4.3.

Results: The data of 161 pts (89 males, 72 females) was collected. The median age was 45 years and the median tumor size was 10 cm (range 3-27 cm). LASTS were located in the extremities (67%), trunk (17%) and retroperitoneal (8%). The main histotypes were UPS 73 (45%), L-sarcomas 36 (23%), and synovial sarcoma 26 (16%). According to the FNCLCC grading system, 58% of pts had a grade 3, 38% a grade 2 and 4% a grade 1 disease. The median number of cycles of CT administered was 3 (range 1-6). The clinical benefit rate was 87 % pts (partial response and stable disease according to RECIST). All patients were subsequently operated, including 5 amputations, 85% R0 and 15% R1 resections. Eighty percent of pts received adjuvant radiation therapy and 10% received adjuvant CT. Twenty-one pts experienced a local relapse and 48 developed distant metastases. After a median follow-up of 57 months, the 5-yr-DFS was 56% (CI 95% [47-65]) and the 5-yr OS was 70% (CI 95% [61-79]) . There was a quasi-linear significant relationship between the rate of residual identifiable cells (RIC) and both DFS and OS, with the most discriminating cut-off being 35% (respectively for OS and DFS, p= 0.012 and p=0.0054); each additional percent worsening the prognosis. Grade was strongly correlated to a good histologic response (p= 0.00019). A R0 resection was significantly related to a better DFS (p=0.025) with a trend on OS (p=0.058).

Conclusion: Neo-adjuvant CT with AI regimen in LASTS facilitates surgery, with a R0 resection achieved in 85% of these initially marginally resectable pts. DFS and OS were similar to the EI arm in the latest neoadjuvant Phase III trial and the rate of RIC correlated with outcome with a threshold of 35%. Prognostic and predictive factors are under investigation (biological, molecular, CINSARC signature).

Table 2. Chemotherapy efficacy

Median number of cycles	3 (range 1-6)
Clinical benefit rate	
Partial response and stable disease according to RECIST	87 %
Resection rate	100%
Amputation	3%
R0	85%
R1	15%
Adjuvant treatment	
Radiation therapy	80%
Chemotherapy	10%
Relapse Pattern	
Local relapse	13%
Distant metastases	29%

Table 1. Patient Characteristics

Number of pts collected	161
Median age	45 yrs (18-75 yrs)
Median tumor size	10 cm (3-27 cm)
Gender	
male	89 (55%)
female	72 (45%)
Site	
Extremities	109 (68%)
Trunk	28 (17%)
Retroperitoneal	13 (8%)
Head and neck	11 (7%)
Histotypes	
UPS	73 (45%)
L-sarcomas	36 (23%)
Synovial sarcoma	26 (16%)
Other	26 (16%)
FNCLCC grading system	
grade 3	69 (58%)
grade 2	45 (38%)
grade 1	5 (4%)

Figure 4. Pathologic response and relapse pattern

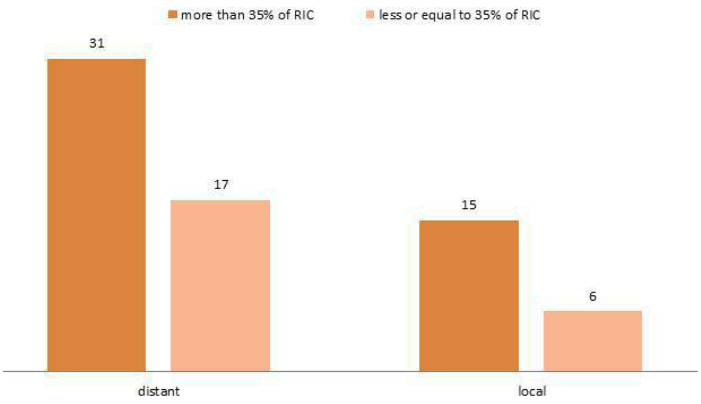


Figure 1. Survival analysis

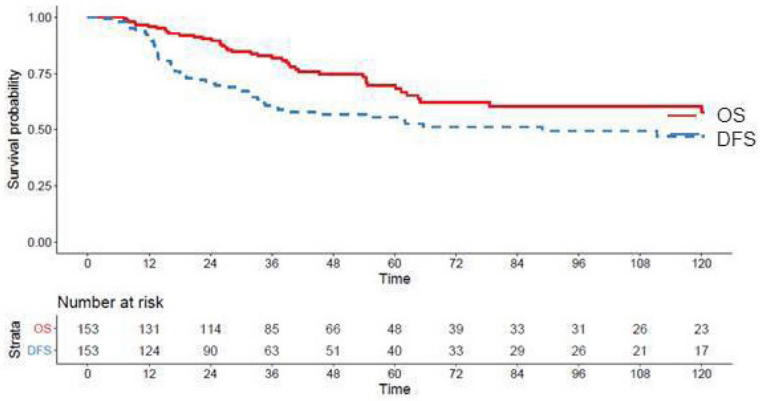
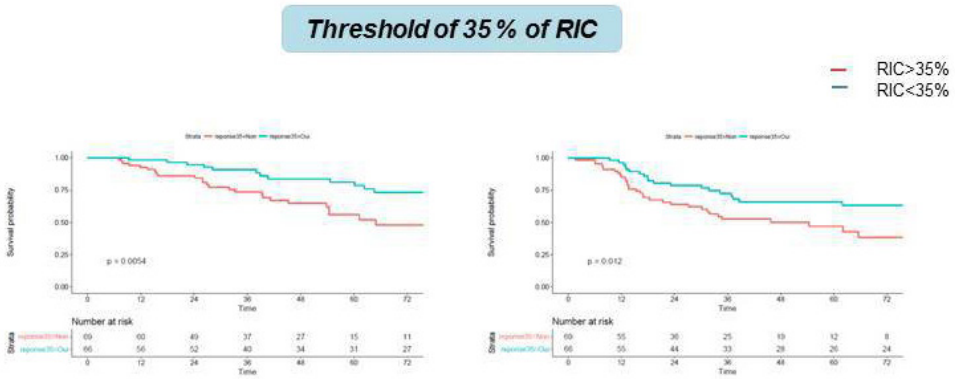


Figure 3. Survival according to histologic response



Poster 089 3035286

REAL-WORLD TREATMENT PATTERNS AMONG ADVANCED SOFT TISSUE SARCOMA PATIENTS RECEIVING SYSTEMIC THERAPY IN A COMMUNITY ONCOLOGY SETTING IN THE UNITED STATES

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Objective: Soft tissue sarcomas (STS) are very rare in the United States (U.S.), where they account for less than 1% of incident cancer diagnoses. Approximately 13,040 soft tissue sarcomas are expected to be diagnosed in the U.S. in 2018. About 40-50% of STS patients either present with metastatic or unresectable locally advanced disease, and over half of patients with early-stage disease will experience disease progression. Olaratumab is a monoclonal antibody that specifically binds PDGFRα. In October 2016, olaratumab was granted accelerated approval by the U.S. Food and Drug Administration (FDA) for the treatment of patients with STS not amenable for surgery and for whom an anthracycline-containing regimen is appropriate. Olaratumab is administered in combination with doxorubicin for up to 8 cycles; after doxorubicin discontinuation, patients continue on olaratumab monotherapy until disease progression or unacceptable toxicity. The purpose of this study was to describe current treatment patterns among patients with advanced STS who were treated in a U.S. community oncology setting since October 2016.

Methods: This retrospective observational study utilized The US Oncology Network's (USON) iKnowMed™ (iKM) EHR data. Eligible patients were age 18+ years of age at diagnosis of advanced STS and had to have initiated first (1L) or second-line (2L) systemic therapy between 10/19/2016 and 08/31/2017 in a USON clinic. Patients diagnosed with osteosarcoma, Kaposi sarcoma, or gastrointestinal stromal tumors were excluded. Demographic and treatment data were obtained from the iKM structured database. Demographics were examined overall, and compared between patients who received olaratumab versus those who did not using Chi-square for categorical and t-test for continuous variables by line of therapy. The most common regimens used in the first two lines of therapy were described, and the proportions of patients who progressed to the next LOT were calculated. All analyses were conducted using SAS 9.3.

Results: There were a total of 207 eligible patients identified in the iKM database. Of patients who initiated 1L therapy during the study period (n=148), the mean age was 59.8 years (SD=13.8) and 54.1% (n=80) were female. Approximately 76% (n=113) of patients were Caucasian. The most common 1L regimens were olaratumab+doxorubicin (n=39; 26.4%) and gemcitabine+docetaxel (n=34; 23.0%). The most common 2L regimens were olaratumab+doxorubicin (n=22; 37.3%) and trabectedin (n=6; 10.2%). In the 1L setting, there was a significantly lower proportion of female patients among those who received olaratumab compared to those who received other 1L regimens (39.5% vs 60.0%; p=0.02). Of note, a lower proportion of patients with uterine sarcoma (n=21) received olaratumab versus other therapies in the 1L setting (n=2, 9.5% versus n=21, 90.5%). All other clinical and demographic characteristics were similar between those who received olaratumab versus those who did not in both the 1L or 2L setting (all p>0.05). Of all patients receiving 1L therapy, 33 (22.3%) also received 2L therapy during the study period.

Conclusion: Current data representing the treatment patterns of patients with advanced sarcoma are limited. This study begins to fill this gap in knowledge by exploring the care of patients with advanced STS since the FDA accelerated approval of olaratumab in the U.S. During the first year since its approval, olaratumab+doxorubicin is the most common regimen used in both the 1L and 2L settings in the USON community of clinical practices. A study limitation is the small sample size. Further research is needed to examine treatment patterns by histology, patterns of disease progression, and survival outcomes of patients with advanced STS. These analyses are planned within the iKM database as data mature.

Poster 090 3035291

A RETROSPECTIVE STUDY TO ASSESS THE INCIDENCE OF EARLY AND LATE CARDIOTOXICITY EVALUATED BY MUGA IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC SARCOMA TREATED WITH DOXORUBICIN

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Objective: Doxorubicin, an anthracycline, is considered first line treatment in the metastatic setting of sarcoma. The use of Doxorubicin is often complicated by cardiotoxicity in 20% of patients. This study assessed the incidence of early and late cardiotoxicity in patients with locally advanced or metastatic sarcoma treated with Doxorubicin at Herlev and Gentofte University hospital.

Methods: A retrospective analysis was performed on all patients with sarcoma referred to Herlev and Gentofte University hospital between 2012 and 2016. Data included gender, start and end date of Doxorubicin, cumulative dose of Doxorubicin, other anticancer treatments, number and date of MUGA (at least 2 MUGAs were required), left ventricular ejection fraction (LVEF), height, weight, comorbidities, referral to cardiologist, initiation of anticongestive treatment and death. Cardiotoxicity was defined as a decline in LVEF of ≥ 10% to a LVEF < 50%. Early cardiotoxicity was defined as < 1 year and late ≥ 1 year.

Results: Between 2012 and 2016, 150 patients were referred. In total 76 patients were included in the study. The main reason for exclusion (65%) was that only one MUGA had been performed. Eighteen (24%) patients experienced cardiotoxicity, ten (56%) were female, median age was 57.1 years. Thirteen (72%) patients developed early cardiotoxicity and 5 developed late cardiotoxicity. Fourteen patients with cardiotoxicity were referred to a cardiologist and 11 patients commenced anticongestive medications. Seventeen patients with cardiotoxicity did not resume treatment with Doxorubicin as 13 had already received the maximum recommended dose. The remaining 4 patients had either progressive disease, excessive ventricular extra systoles, received treatment with liposomal-Doxorubicin or developed dehydration due to short bowel syndrome. One patient with cardiotoxicity resumed Doxorubicin but with a dose reduction.
In 9 patients with cardiotoxicity the LVEF remained low, in 7 patients the LVEF increased, and in 2 patients the LVEF increased but subsequently declined. In one patient cardiotoxicity was possibly due to subsequent treatment with Trabectedin. Only one patient received cardioprotective treatment with Dexrazoxane, since it was not considered standard treatment at that time. Median survival for patients with cardiotoxicity was 2.8 years 95 CI (1.8-3.9) and for patients without cardiotoxicity 1.8 years 95 CI (0.75-2.8). Hypertension and the use of tobacco was observed in 33% and 39% of patients with cardiotoxicity but was not found to be more frequent than in those without cardiotoxicity.

Conclusion: The incidence of cardiotoxicity in this cohort of patients treated with Doxorubicin was 24%. Early cardiotoxicity (72%) was more common than late. A later increase in LVEF was observed in 50% of patients with cardiotoxicity, which was lasting in 78%. Surprisingly, patients with cardiotoxicity had a longer median overall survival than patients without. This could possibly be due to intensified medical attention and anticongestive therapy. Further analysis is ongoing.

Poster 091 3041292

NEOADJUVANT CHEMORADIOTHERAPY IN ADVANCED SOFT TISSUE SARCOMA (ASTS)

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Objective: Patients with advanced sarcomas have a poor prognosis. Several studies attempt to analyze the role of neoadjuvant chemotherapy and radiotherapy (RT).

Methods: A prospective unicentric study in ASTS with neoadjuvant treatment based on epirubicin (60 mg/m2 day 1 and 2) and ifosfamide (1800 mg / m2 d1-5), every 3 weeks for 3 cycles, concurrently with radiotherapy (46-50 Gy) starting on day 22th. Adjuvant boost of RT may be administered after surgery. ASTS greater than 5 cm, high grade and deep localization, and those initially considered as unresectable were included. Patients were evaluated by radiology before and after of neoadjuvant treatment.

Results: Seven patients with a median age of 44 years (range, 30-61) were enrolled in the study. 5 of them were diagnosed of undifferentiated pleomorphic sarcoma, 1 of spindle cell and one more of pleomorphic liposarcoma. 5 tumours were located in the extremities, 1 in the scapula and the other in the pelvis. The average size was 9.6 cm (5-15 cm). The median number of cycles was 3 (range, 2-4). The dose of RT was completed in all patients. 4 patients received RT boost after surgery.

The clinical response was obtained in 29% (2/7) of the patients. According to RECIST criteria, 14% patients achieved a partial response (1/7), 57% a stabilization (4/7) and 29% a progression (2/7). According to CHOI criteria, 57% patients achieved a partial response (4/7), 14% a stabilization (1/7) and 29% a progression (2/7). Finally, diffusion magnetic resonance imaging (MRI) showed that 80% of the patients achieved response (4/5) and 20% did not achieve it (1/5).

The surgery was an en bloc resection, reaching complete resection in all patients. The histological response was equal to or greater than 90% of necrosis in 86% (6/7), with 29% of the patients with a complete response (2/7). The most frequent toxicity was delay in wound healing, requiring repair surgery in 2 patients. With an average follow-up of 16 months (5-24 months), 3 patients remain without disease and 4 have had pulmonary relapses. There was not local relapse in any of the patients. Two deaths were registered due to metastatic tumor progression.

Conclusion: Neoadjuvant treatment with chemotherapy based on anthracyclines and ifosfamide concurrent with radiotherapy achieves a very high rate of pathological responses and no local relapse. Nonetheless, systemic relapses remain.
CHOI criteria and diffusion by MRI have better correlation with necrosis than the RECIST criteria. The greatest toxicity is delay in wound healing.

Histology	Initial size (cm)	Clinical Response	RECIST	CHOI	Diffusion	Necrosis (%)	Toxicity	Degree	Relapse	DFI (m)	Follow-up (m)	Exitus
UPS	13	YES	PR	PR		100	Scar	2	NO		22	NO
UPS	5	NO	SD	PR	YES	99	Skin	2	NO		24	NO
PLPS	13	NO	SD	SD	YES	90	Skin	2	LUNG	3,8	22	YES
Spindle cell	8,5	NO	SD	PR	YES	100	No	0	LUNG	4,0	9	NO
UPS	15	NO	DP	DP	YES	90	Skin	2	LUNG	1,5	12	NO
UPS	6,6	YES	SD	PR	NO	99	Scar	3	NO		5	NO
UPS	6,3	NO	DP	DP		60	Scar	3	LUNG	5,7	16	YES

UPS = undifferentiated pleomorphic sarcoma; PLPS = pleomorphic liposarcoma; DFI = disease free interval. PR= partial response; SD= stabilization disease; DP= disease progression.

Poster 092 3041780

OLARATUMAB PLUS DOXORUBICIN FOLLOWED BY OLARATUMAB MONOTHERAPY FOR THE TREATMENT OF PATIENTS WITH ADVANCED/METASTATIC SOFT TISSUE SARCOMA: REAL-WORLD UTILIZATION AND OUTCOMES IN THE UNITED STATES

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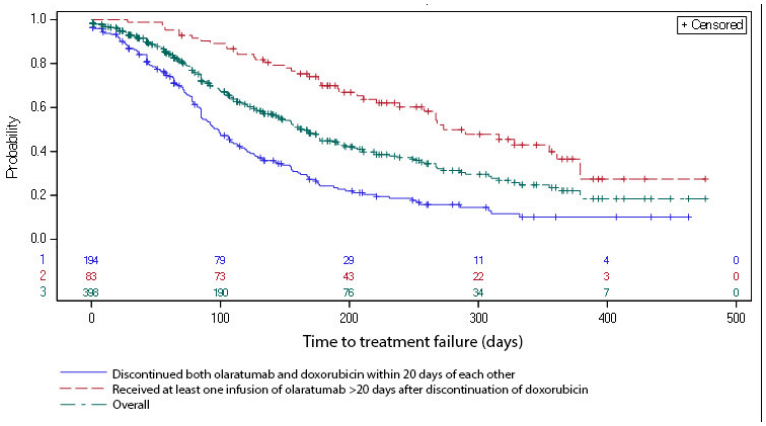
Objective: Olaratumab is a fully human platelet-derived growth factor receptor alpha (PDGFR-α) receptor antagonist that received U.S. Food and Drug Administration (FDA) accelerated approval October 2016 for use in combination with doxorubicin for the treatment of adult patients with soft tissue sarcoma who have disease not amenable for surgery and are candidates for anthracycline-based therapy. This approval was based on a randomized phase 2 study showing a statistically significant 11.8 months median overall survival benefit over doxorubicin monotherapy. In this retrospective, non-comparative observational cohort study we explore the use of olaratumab and its outcomes associated in a real-world setting using a multi-institutional electronic medical records database.

Methods: Data were obtained from the Flatiron database, a de-identified electronic medical records (EMR) database. This database acquires longitudinal data from patients treated at 265 cancer clinics by >2,500 oncologists in the U.S. that are updated monthly. Eligible patients for this study were all patients age 18+ who received at least one dose of olaratumab after its approval in Oct 2016. Descriptive, non-comparative analyses were conducted using SAS 9.3 to examine treatment patterns, sequences of care, duration of treatment (DOT) and time to treatment failure (TTF). For the purposes of this abstract, we defined TTF as time from first dose of olaratumab to death or initiation of subsequent therapy, whichever occurred first.

Results: There were 445 eligible patients [mean age 63.0 years (SD=12.7); 56.4% female] included in this analysis. 79.6% of patients were treated in community practices and 20.4% were treated in an academic setting. Most patients received an olaratumab-containing regimen in the first- (n=269, 60.4%) or second-line setting (n=106, 23.8%). 398 (89.4%) patients received olaratumab in combination with doxorubicin; 32 (7.2%) received olaratumab monotherapy, 9 (2.0%) received olaratumab with liposomal doxorubicin, and the remaining patients (n=6, 1.3%) received olaratumab in combination with other agents. Of those receiving olaratumab plus doxorubicin, 115 (28.9%) were still receiving this therapy at the last

timepoint available in the database and were censored from TTF analyses. 83 (20.9%) patients treated with doxorubicin + olaratumab received at least one dose of olaratumab monotherapy, with median DOT of 185 days (95% CI: 156-286) through last timepoint. 194 (48.7%) discontinued both agents, with a median DOT of 50 days (95% CI: 36-50). TTF is presented in the Figure. Overall median TTF in the olaratumab plus doxorubicin cohort was 167 days (95% CI: 144-191).

Conclusion: These early data show that within the first year of approval, olaratumab has been primarily used in combination with doxorubicin, and a subset of patients continue olaratumab monotherapy, with some continuing for long periods of time. The EMR database is limited in that the reason for discontinuing therapy is unknown and neither disease response nor progression data is recorded. Time to treatment failure was used to estimate outcomes, but may not be an accurate predictor of clinical outcomes, as patients may start new treatment for reasons other than progression. Additionally, many patients remained on therapy at the end of the available data. Despite the limitations of EMR data, this observational cohort study provides insight regarding the use and potential outcomes of olaratumab-based therapy in the U.S.



Poster 093 3042103

PHASE IB STUDY OF DECITABINE IN COMBINTATION WITH GEMCITABINE IN TREATMENT OF REFRACTORY ADVANCED SOFT TISSUE OR BONE SARCOMAS

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Objective: Sarcomas are a heterogeneous group of tumors originating from mesenchyme and are associated with high rates of local recurrence and metastases leading to poor prognosis. Numerous epigenetic changes including hypermethylation have been identified in several sarcoma subtypes. Restoration of normal methylation patterns is a potential therapeutic target for these tumors. In preclinical studies, use of DNA hypomethylating agent slowed tumor gorwth when combined with gemcitabine. Low continuous dosing of hypomethylating agents has shown to have epigenetic modulating effect with less toxicity in solid malignancies. Gemcitabine given as fixed dose infusion has shown activity in advanced sarcomas. Our primary objectives were to assess the safety and tolerability of decitabine in combination with gemcitabine in previously treated patients with advanced sarcomas, to identify the recommended phase 2 dose (RP2D) and describe the dose limiting toxicities (DLT).

Methods: Subjects with metastatic histologically or cytologically confirmed soft tissue or bone sarcoma after progression on at least one line of therapy were included. Prior decitabine or gemcitabine exposure was allowed. A modified 3+3 dose escalation design is employed for each diagnostic group. Two doses of decitabine, 0.1 and 0.2 mg/kg subcutaneously administered on a twice weekly schedule for three weeks of a 28-day cycle were tested. Gemcitabine was given as 900 mg/m2, IV over 90 min on Days 1, 8 and 15 of a 28-day cycle. Treatment was continued until disease progression or unacceptable toxicity. DLT is defined as any drug related non-hematological grade 3 or 4 toxicities per CTCAE v4.0. Disease assessment was performed every 8 weeks using RECIST v1.1. Additional subjects are being enrolled to each dose level to assess response in the expansion phase.

Results: To date, 12 sarcoma subjects have been accrued. Subjects received a median of 3 prior regimens and median of 2 cycles on this trial (range 2-6). 7 subjects had received prior gemcitabine. There were 2 serious adverse events attributed to tumor progression. No treatment related deaths noted. There were 1.6% grade 4 events out of 374 total AEs all of which were hematological.

Conclusion: Phase 1b results suggest that combination of gemcitabine with decitabine is safe and well tolerated. Both doses of decitabine were found to be safe and are being evaluated further in the expansion cohort with efficacy as the secondary endpoint. No DLTs were observed.

Poster 094 3042194

CHARACTERISTICS AND TREATMENT PATTERNS WITH ADVANCED SOFT TISSUE SARCOMA IN KOREA

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Objective: A soft tissue sarcoma (STS) is a rare type of cancer, accounting for 1% of adult solid cancers. The aim of the present study is to identify the incidence of localized and advanced STS in Korean patients, their treatment patterns, and the survival of patients by disease status

Methods: Medical data from the National Health Insurance Service (NHIS), which keeps the health claim data of the entire Korean population of around 50 million people, was used to extract the STS cohort. All individuals with a first STS diagnoses as main disease code or first sub-disease code from 2007 to 2014, who were 18 years of age or older at the time of diagnosis (STS Initial Cases) were included. Subgroups were defined using an algorithm based on treatment type (surgery, radiotherapy, chemotherapy), treatment period and survival. STS cohort was classified into mutually exclusive 5 subgroups: (1) patients who received only surgery (Surgery, OP); (2) only radiotherapy (Radiotherapy, RT); (3) patients who received surgery and pre/postoperative treatment (Pre-OP/Post-OP), (4) those who received only chemotherapy with or without radiotherapy (Systemic treatment, CTx/CCRT); (5) and those who died within a year after diagnosis (Clinical deterioration <1 year, CD). We defined localized STS as only local treatment (OP and RT) or surgery combined with pre/postoperative treatment followed by observation (Pre-Obs and Post-Obs). Advanced STS was defined as only systemic treatment after diagnosis (CTx/CCRT); rapid clinical deterioration within 1 year (CD), or patients who received treatment for longer than one year after diagnosis (Pre-Tx and Post-Tx). Descriptive analyses were conducted on patient demographics and clinical characteristics/medical resources, as well as treatment patterns. The STS incidence was calculated for 100,000 people using the mid-year population data from 2007-2014 of the Korean Statistical Information Service. The survival curve was estimated using Kaplan-Meier product-limit estimator method.

Results: A total of 7,813 patients were diagnosed with STS from 2007 to 2014, 4,307 were localized STS and 3,506 advanced STS cases. The STS patients showed an average initial diagnosis age of 54.5 (SD 16.2) years. The total incidence of STS was 2.49 per 100,000 person-years: 1.37 per 100,000 person-years for localized STS and 1.12 per 100,000 person-years for advanced STS. The main location for the total STS group was in “other connective and soft tissues” (C49xx, 67.26%), the second main location was in “retroperitoneum and peritoneum” (C48xx, 24.45%) and the rest of the locations (C47xx, C223, C224, C542) represented minor numbers (<10%). In total, 2,299 of the advanced STS patients received at least one chemotherapy treatment after diagnosis (65.57% of the STS advanced patient cohort); 657 were included in the CTx/CCRT group (28.58%), 1,096 in the “Pre-Tx or Post-Tx” group (47.67%), and 546 pertained to CD group (23.75%). Of the advanced STS patients who underwent chemotherapy, 1,149 were treated with anthracycline (49.98%). The largest fraction of patients used doxorubicin plus ifosfamide (458 patients, 19.92%), followed by paclitaxel (385 patients, 16.75%), others (372 patients, 16.18%), ifosfamide (336 patients, 14.62%). and gemcitabine and/or docetaxel (56 patients, 2.44%), and pazopanib (1 patient, 0.04%). The 5-year survival rate after diagnosis was 56.4% for all STS, 82.4% for localized STS, and 27.2% for advanced STS.

Conclusion: To our knowledge, this is the first study conducted in Korea that investigated epidemiological and clinical characteristics and treatment patterns of STS by analyzing the Korean National Health Insurance Service Database. This study provides insights into localized and advanced STS epidemiology, treatment patterns and outcomes in Korea, which could be used as fundamental data in improving clinical outcomes of STS patients in the future.

Poster 095 3042571

TRABECTEDIN-INDUCED MONOCYTES REDUCTION: A POTENTIAL SURROGATE PROGNOSTIC FACTOR?

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Objective: The antitumor activity of Trabectedin (T) is accompanied by direct effects on cancer cells, as well as changes to the tumour microenvironment. T has immune modulating effects, with cytotoxic properties against monocytes and tumour-associated macrophages. In this study, we assessed changes of circulating monocyte (M) levels during T administration in a large series of soft tissue sarcoma patients, and their potential relevance as a prognostic factor.

Methods: This retrospective analysis was conducted in three centers, based on clinical records or databases. Patients were treated with T at the approved dose of 1.5 mg/m^2, given as a 24-hour infusion every 3 weeks. Complete blood count was available in each patients before and after T administration of the first two T courses. All patients had metastatic or locally advanced inoperable disease and received at least one previous line of treatment containing anthracycline.

Results: 124 (63 females and 61 males, median age 54 yrs) patients were included in this analysis. The most frequent histotypes were: leiomyosarcoma (23 pts); dedifferentiated/well differentiated liposarcoma (24 pts); mixoid liposarcoma (18 pts). Median reduction of circulating M was 33% (95%CI: 21.7%-48.0%, P=0.02) and 39% (95%CI: 28.2%-60.7%; P=0.001) at day 7 and 14 respectively. The M modifications were similar in the second course of T. 59 patients showed a reduction of at least 40% in comparison to baseline. Interestingly, comparing patients with a reduction in M levels ≥ 40% with those showing a reduction in M levels < 40%, the first group had a statistically significant longer median PFS (4.5 vs 2.7 months, P=0.01) and OS (13.7 vs 6.2 months, P=0.004).

Conclusion: Our data confirm previous observations that T induces a significant and reproducible reduction of M along the first two courses. Patients with M reduction had a more pronounced benefit from T.

Poster 096 3042600

CLINICAL OUTCOME OF ERIBULIN IN PATIENTS WITH ADVANCED SOFT TISSUE SARCOMA: A COHORT STUDY INCLUDING NON-L-SARCOMAS

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Objective: Since only L-sarcomas (liposarcoma and leiomyosarcoma) were included in phase III clinical trial of eribulin, little is known about real-world clinical outcome of eribulin in non-L-sarcomas. Also, eribulin is a relatively new drug that has been approved for the treatment of soft tissue sarcoma (STS) for only a few years. The objective of this study is to be clarify the clinical outcome of eribulin in patients with advanced STS including non-L-sarcomas.

Methods: We surveyed patients with STS who was treated with eribulin between April 2016 and February 2018 in Kyushu University Hospital.

Results: A total of 18 STS patients ranged 21 to 82 years (median 67 years) of age were eligible for this study. The same number of men and women were included. The most common histology was leiomyosarcoma (n=5), followed by dedifferentiated liposarcoma (n=4), undifferentiated pleomorphic sarcoma (n=3), synovial sarcoma (n=3), myxoid liposarcoma (n=1), malignant peripheral nerve sheath tumor (n=1), and malignant solitary fibrous tumor (n=1). The most frequent primary site was retroperitoneum (n=5). Eribulin was administrated as the 1st-line treatment in 3 patients, followed by the 2nd-line in 3, the 3rd-line in 5, the 4th-line in 3, and the 5th-line in 4 patients, respectively. The regimens prior to eribulin included doxorubicin and ifosfamide (n=10), gemcitabine and decetaxel (n=6), pazopanib (n=6), and doxorubicin alone (n=5). Eribulin was generally given on days 1 and 8 of a 21-day cycle, and the number of cycles ranged 2 to 16 (median 4). The reason for discontinuation included progressive disease (PD) (n=12) and adverse events (n=2) such as peripheral neuropathy and myelosuppression. Dose reduction was necessary for 12 patients because of myelosuppression (n=12), liver dysfunction (n=2), and peripheral neuropathy (n=1). As the best response, 10 patients had stable disease, and 8 had PD. Progression-free survival (PFS) ranged 1 to 17 months (median 4 months), and overall survival reached 2 to 23 months (median 12 months). When divided into histology-based subgroups, median PFS was 10 months in dedifferentiated liposarcoma

subgroup, which showed the longest PFS. Median overall survival was 8, 18.5, and 12 months in leiomyosarcoma, UPS, and synovial sarcoma subgroups, respectively.

Conclusion: Eribulin was used for patients with several histological diagnoses of STS as a variety of treatment lines. It was speculated that eribulin showed effectiveness for not only liposarcoma but also other sarcomas including UPS and synovial sarcoma.

Poster 097 3042614

PAZOPANIB NEOADJUVANT TRIAL IN SOFT TISSUE SARCOMAS: A REPORT OF MAJOR WOUND COMPLICATIONS DURING DOSE-FINDING PHASE ON ARST 1321

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Objective: The care of soft tissue sarcomas (STS) is complex and multidisciplinary in nature. For intermediate to high risk STS, neoadjuvant radiation therapy (RT) +/- chemotherapy is one of the standard treatment options. Surgery alone for STS has a wound healing complication rate of 6-42%. Wound complication rates with neoadjuvant chemoradiation is 30-40% with neoadjuvant RT and doxorubicin/ifosfamide (ID)-based chemotherapy and 25% with neoadjuvant RT and bevacizumab. ARST1321 is a phase II/III study evaluating the multi-targeted tyrosine kinase inhibitor pazopanib +/- chemotherapy and RT in select high-grade STS. The dose-finding phase has been completed. We report the major wound complications among patients enrolled on the study's dose-finding phase.

Methods: Patients enrolled on regimens A (ID/RT + pazopanib) and C (RT + pazopanib) who completed the dose-finding phase were evaluated for Grade III wound complications. Patient demographics, tumor characteristics, and complication details were compiled and analyzed.

Results: 30 evaluable patients were enrolled (10 on regimen A [4 w age >18 years]and 20 on regimen C [14 > 18 years]). 9 patients experienced major wound complications during the dose-finding phase, including 20% (2/10 patients) on Regimen A and 35% (7/20 patients) on Regimen C. Most patients with wound complication has lower extremity primary site (78%, 7/9 patients) and > 18 years 7 (78%, 7/9 patients). Wound complications occured 3-12 weeks (median 6 weeks) post-operatively. Eight out of 9 patients with wound healing complications required re-operation with irrigation and debridement, all of whom were ultimately removed from the protocol due to grade 3 wound complications.

Conclusion: Neoadjuvant RT and pazopanib (+/- ID chemotherapy) had an overall rate of major wound complications of 30% (9/30), which was similar to the historical rate without a tyrosine kinase inhibitor. Also consistent with historic results was the predilection for wound complications with lower extremity primary site. The addition of pazopanib appears safe, with a wound complication toxicity profile similar to historic results with neoadjuvant RT +/- chemotherapy.

Poster 098 3042618

USE OF CARDIOPROTECTIVE DEXRAZOXANE AND MYELOTOXICITY IN ANTHRACYCLINE-TREATED SOFT-TISSUE SARCOMA PATIENTS

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Objective: Dexrazoxane (DEX) is indicated as a cardioprotective agent for patients receiving doxorubicin who are at increased risk for cardiotoxicity. Concerns have been raised on the use of dexrazoxane, particularly in the adjuvant setting, because of the risk of interference with the antitumor effect of doxorubicin. Two meta-analyses in metastatic breast cancer have rejected this hypothesis, but have shown an apparent increase in the severity of myelosuppression when DEX is used. No data in soft-tissue sarcoma (STS) patients is available, so far. Here, we retrospectively analyzed a cohort of our Institute database to assess whether the addition of DEX causes more bone marrow suppression in STS patients receiving Anthracycline-Ifosfamide (AI) combination in perioperative and advanced setting.

Methods: 113 patients who received AI between January 2006 and December 2017 were included. 36 of them received

DEX concurrently with the AI treatment. Hospital records were reviewed and available for all patients (the accessibility of all the data was an inclusion criteria). Compared to the non-DEX group, patients who received DEX were more frequently treated in the context of a perioperative setting (respectively 27.3 vs 38.8%). No other differences in terms basal patients features were recorded. Significantly, all patients received similar post-medication after each cycle.

Results: Compared with the non-DEX group, DEX treatment was associated with significantly higher rates of G3/4 hematological side effects: leukopenia (32.5 vs 61.1%, *P*=0.004); neutropenia (44.2 vs 75.0%, *P*=0.002); anemia (28.6 vs 44.5%, *P*=0.096); thrombocytopenia (32.5 vs 52.8%, *P*=0.039), Similarly, compared to the non-DEX group, there were more hospitalizations for febrile neutropenia (39.0 vs 69.4%, *P*=0.025) and dose reductions (19.5 vs 38.9%, *P*=0.027) in the DEX group, but no significant difference in the incidence of treatment delays or cancellations.

Conclusion: Adding DEX to Anthracycline-based chemotherapy in soft-tissue sarcoma patients leads to higher rates of bone marrow suppression in all blood components, as well as more febrile neutropenia events, and dose reductions.

Poster 099 3042688

COMBINATION OF ERIBULIN PLUS GEMCITABINE IN L-SARCOMAS

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Objective: Eribulin (Halaven®; Eisai Co., Tokyo, Japan) is a synthetic analogue of halichondrin B that was approved for advanced liposarcoma treatment. Eribulin, besides its well stablished cytotoxic activity, seems to ownexhibits particular chemical proprieties that may also contribute also to its the therapeutic effect. In fact, eribulin induces vascular remodelling and increased tumor perfusion, as well as inhibits pericyte- and endothelial-driven angiogenesis, which in *in vitro* studies. Therefore, these properties could facilitate the distribution of other drugs (e.g. gemcitabine) within the tumor. Altogether, we hypothesize that eribulin and gemcitabine, acting in different cell cycle phases and modulating distinctly tumor microenvironment, could be synergistic, without overlapping toxicity.

Methods: CP0024 human leiomyosarcoma primary cell line, SK-UT-1 human leiomyosarcoma cell line and, 93T449 and 94T778 human liposarcoma cell lines were treated with increased concentrations of eribulin ($1x10^{-7M}$ to $1x10^{-11}$M) and or gemcitabine ($1x10^{-9}$M to $1x10^{-13}$M) to determine IC50 values. Combination index values of eribulin plus gemcitabine were calculated, after treating L-sarcoma cell lines with both drugs using the following administration sequences: concomitant (E+G), eribulin followed by gemcitabine (E→G) and gemcitabine followed by eribulin (G→E). Cell viability, at 72 hours, was measured by MTS cell proliferation assay., 72 hours after the initial treatment.

Results: The IC50 values determined for eribulin ranged between 0.28nM (SK-UT-1) and 51.981nM (94T778CP0024), while IC50 values of gemcitabine ranged between 2.10nM (SKk-UT-1) and 7.02nM (94T778). The combination index values at ED50 (the effective doses at which 50% of cell killing occurred) ranged: between 0.27 (SK-UT-1) and 0.89 (94T778), when cell lines were treated with E+G; between <0.10 (SK-UT-1) and 0.33 (CP0024) when treated with G→E; and between <0.10 (SK-UT-1) and 0.20 (CP0024) when cells were treated with E→G. All the cell lines showed a higher synergism when treated using the E→G administration sequence.

Conclusion: Eribulin and gemcitabine combination is synergic in L-sarcoma cell lines. The administration of eribulin, followed by gemcitabine is the recommended administration sequence for further studies. The mechanisms underlying eribulin plus gemcitabine synergy, as well as predictive biomarkers of response to the combination, will be evaluated in *in vitro* and *in vivo* models of L-sarcoma.

Poster 100 3042696

PREDICTIVE ROLE OF HMG PROTEINS FOR RESPONSE TO TRABECTEDIN IN PATIENTS WITH ADVANCED SOFT TISSUE SARCOMA (STS): A SPANISH GROUP FOR RESEARCH ON SARCOMAS (GEIS-38 STUDY)

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Objective: High Mobility Group (HMG) proteins act as architectural transcription factors and can influence the expression of many genes. The role of promoting an undifferentiated pluripotent stem-like cell state makes HMGA proteins attractive for sarcoma research. Overexpression of HMGA1 and HMGA2 have been correlated with poor prognosis in some epithelial tumors but there is hardly any data on the prognostic role of HMGA in soft tissue sarcoma (STS). We present the analyses of protein expression of HMGA1/2 and B1 as prognostic factor in STS for response to trabectedin (Yondelis®).

Methods: Selection criteria were: patients with advanced STS (at diagnosis or at any time from then on), pretreated with at least 2 lines in the advanced setting (one line mandatory with trabectedin), with paraffin block available and ethic committee's approval. A tissue micro-arrays (TMA) was set up for nuclear expression of HMGA1 (Abcam), HMGA2 (Sigma-Aldrich) and HMGB1 (Abcam) with block taken at the time of diagnosis. An expert blinded pathologist reviewed and classified the intensity staining into negative, weak or strong and the extension as high (≥50% of stained cells) or low (<50%) for each protein. Kaplan–Meier was used for time-to-event variables and the log-rank test was used to compare groups.

Results: Among 387 registered patients samples from 301 patients were available for immunohistochemistry analyses. Patients had median age of 52 years (y), 53% were females and had a median follow-up from metastasis (M1) of 42 months. Strong and high expression were distributed as follows: HMGA1 24% and 18%, HMGA2 58% and 63%, HMGB1 69% and 75%, respectively. Strong expression of HMGA1 showed significant worse prognosis for OS from M1 time (31 *vs.* 22 months; *p*=0.007) and for PFS of trabectedin line (3.8 *vs*. 2.6 months; *p*=0.002) (Figure 1). Similar results were obtained with high HMGA1 expression. However, no statistically significant prognostic impact of HMGA2 y HMGB was found. In multivariate analyses, age (>60y; HR: 1.52, CI95%: 1.10-2.09, *p*=0.009); short lapse to metastases (<10 months; HR: 1.44, CI95%: 1.08-1.92, *p*=0.013); and strong expression of HMGA1 (HR: 1.45, CI95%: 1.06-1.48, *p*=0.018) showed to be independent prognostic factors for worse survival from M1.

Conclusion: Protein expression of HMGA1 exhibited a significant prognostic role in a series of advanced STS. Validation studies are ongoing to confirm its prognostic and potential predictive role, which possibly may open new targets in the treatment of STS.

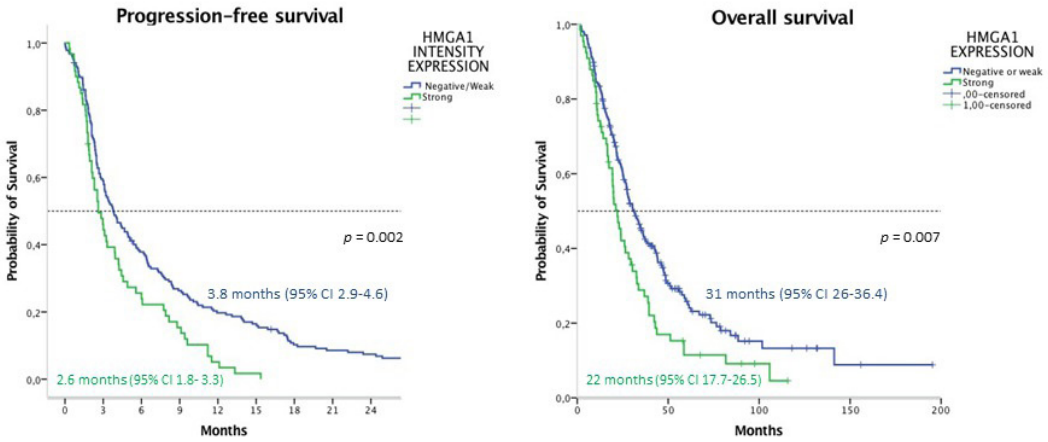

Figure 1. PFS and OS outcomes according to HMGA1 intensity.

Poster 101 3042141

REAL-WORLD EXPERIENCES WITH PAZOPANIB TREATMENT FOR PATIENTS WITH ADVANCED SOFT TISSUE AND BONE SARCOMA IN NORTHERN CALIFORNIA

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Objective: Pazopanib was approved for advanced soft tissue sarcoma after failing first or second line standard chemotherapy based on the Palette trial that excluded adipocytic tumors and bone sarcoma. We aimed to understand the real-world experiences with pazopanib treatment in patients with advanced soft tissue and bone sarcoma in Northern California through a retrospective case review.

Methods: We analyzed the response pattern of patients with advanced soft tissue and bone sarcoma from Northern California Kaiser Permanente who received pazopanib treatment from January 2014 to June 2018.

Results: We identified a total of 86 cases. Eighty-one of these patients have been assessed for response by the treating oncologist (not based on RECIST criteria), 8 patients obtained PR (partial response), 9 SD (stable disease), and 63 developed PD (progressive disease). For the 8 patients with PR, 3 were undifferentiated pleomorphic sarcoma (UPS), 1 synovial sarcoma, 1 pleomorphic rhabdomyosarcoma, 1 pleomorphic liposarcoma, 1 dedifferentiated liposarcoma, and 1 uterine leiomyosarcoma. Median duration of response was 9 months. Among 9 patients with SD, 1 Ewing's sarcoma, 1 osteosarcoma, 2 MPNST, 1 synovial sarcoma, 2 leiomyosarcoma, 1 malignant phyllodes tumor, and 1 UPS. Median duration of stable disease was 6 months. The patient with Ewing's sarcoma had SD for 13 months and the patient with osteosarcoma had SD for 9 months.

Conclusion: The response rate (9.3%) to pazopanib with our cohort of patients in Northern California is similar to that of the Palette trial, however, responses were observed in 2 patients with liposarcoma and prolonged SD was observed in two bone sarcoma patients indicating that pazopanib has activities in bone sarcoma.

Poster 102 3008065

NEUTROPHIL-TO-LYMPHOCYTE RATIO AFTER PAZOPANIB TREATMENT PREDICTS RESPONSE IN PATIENTS WITH ADVANCED SOFT TISSUE SARCOMA

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Objective: Pazopanib is a multi-tyrosine kinase inhibitor that is used to treat advanced soft tissue sarcoma, and its efficacy has been confirmed in several clinical trials, although no clinically useful biomarkers have been identified. In other cancers, the neutrophil-to-lymphocyte ratio (NLR), the platelet-to-lymphocyte ratio (PLR), and the lymphocyte-to-monocyte ratio (LMR) are associated with chemotherapy response and prognosis. Therefore, we aimed to evaluate the associations of pazopanib response with NLR, PLR, and LMR among patients with advanced soft tissue sarcoma.

Methods: Data regarding NLR, PLR, and LMR were obtained for 25 patients who received pazopanib for soft tissue sarcoma. The patients were categorized according to their values for NLR , PLR, and LMR, and we evaluated the associations of these markers with progression-free survival and overall survival using Kaplan-Meier curves and Cox proportional models.

Results: The median treatment duration was 6.7 months (range: 1–44 months), and the average pazopanib dose was 656 mg. The median follow-up duration was 5.5 months (range: 2.0–45.2 months), and 11 patients died within 6 months (median: 3.2 months, range: 2.0–5.9 months) after the initiation of pazopanib treatment. The median PFS for all patients was 3.8 months (95% CI: 2.9–5.8 months), and the median OS was 13.5 months (95% CI: 3.8–24.9 months). The median NLR was 3.77 (interquartile range [IQR]: 3.19–5.87), the median PLR was 228 (IQR: 181–398), and the median LMR was 2.42 (IQR: 1.54–3). Thus, the cut-off values were defined as 3.8 for NLR, 230 for PLR, and 2.4 for LMR, respectively. There were no significant differences in PFS or OS based on the patients' pre-treatment NLR, PLR, and LMR values We also considered the changes in these variables at 1 month after the pazopanib treatment, and observed that decreased PLR values and increased LMR values (vs. the pre-treatment values) were non-significantly associated with prolonged PFS and OS. Only decreased NLR values were significantly associated with prolonged PFS ($p = 0.0003$) and OS ($p = 0.006$).

A Cox proportional hazards model was used to evaluate the potential predictors, and the univariate analyses revealed that decreased NLR values were associated with PFS (HR = 0.15, p = 0.0004). We also performed multivariate analyses using increased LMR values and Glasgow prognostic score as covariates, which confirmed that decreased NLR values were independently associated with better PFS (HR = 0.07, p = 0.001). Similarly, decreased NLR values were significantly associated with better OS in the univariate analyses (HR = 0.14, p = 0.0007). We also performed multivariate analyses using the Karnofsky performance status as a covariate, and confirmed that decreased NLR values were independently associated with better OS (HR = 0.17, p = 0.006).

Conclusion: Decreased NLR values after pazopanib treatment may predict the chemotherapeutic response and prognosis of patients with advanced STS. Based on the high morbidity rate of advanced STS, the selection of STS treatments would be greatly enhanced by access to non-invasive, convenient, and inexpensive biomarkers

Poster 103 3026226

THE SIGNIFICANT EFFECTS OF PAZOPANIB ON ADVANCED SOFT TISSUE SARCOMA: A RETROSPECTIVE ANALYSIS IN CHINA

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Objective: Pazopanib, a multi-targeted tyrosine kinase inhibitor, has been approved for the treatment of patients with selective subtypes of advanced soft tissue sarcoma (STS) following the previous standard chemotherapy. We noticed the lack of evidence on the efficacy of pazopanib for Chinese sarcoma patients. In addition, there is also a lack of validated prognostic markers that could be used to stratify patients to pazopanib therapy. We aimed to investigate the activity of pazopanib and clinical characteristics for Chinese patients with sarcomas among multiple subtypes, and hoping to discover prognostic biomarkers contributing to STS treatment.

Methods: A retrospective study of patients, diagnosed as advanced sarcomas of multiple subtypes excluding liposarcoma, treated with pazopanib therapy at Sun Yat-sen University Cancer Center. Patient and tumor characteristics were collected. CT or MRI re-examination was regularly performed once every 2 months. Response was assessed according to RECIST 1.1. and survival analysis was performed using SPSS standard version 16.0 (SPSS Inc., Chicago, USA) and GraphPad Prism version 6.0. The whole-exon genome sequencing was accomplished on Illumina platform and differential analysis was based on two-sample t-test at *p* value of 0.05.

Results: Thirty-five patients were identified, including multiple histological subtypes of sarcomas except liposarcoma. The objective response rate(ORR) was 25.7%(9/35) among all the subtypes, and the disease control rate(DCR) was 74.1%(25/35). According to the statistical analysis, the responses might highly correlate to various factors including age, pathological patterns, site of primary tumor, degree of differentiation, level of lactate dehydrogenase, etc. Moreover, the adverse events were observed and we indicated that the occurrence of liver damage might be associated with age. Above all, the median progression-free survival (PFS) was 4.6 months (95%CI 3.6–5.6). In order to explore valuable prognostic biomarkers, 22 patients were equally seperated as good reponders and bad responders, whose tissue and peripheral DNA was extracted for the whole-exon genome sequencing. Further, we distinguished 86 amplified and 113 deleted genes by differential analysis of copy number alterations.

Conclusion: The activity of pazopanib in Chinese STS patients is comparable to its reported activity in America or European STS patients. Although, in this study, specific characteristics were still demonstrated among Chinese patients, in terms of the risk factors and adverse effects. Importantly, the genomic alterations revealed potential prognostic markers of STS.

Results of pazopanib in sarcomas

Study	Results
Schedule	Pazopanib 600mg daily
Treatment Interval	2 months
Population	35 patients
State	Metastatic or unresectable sarcomas, stage III or IV
Pathological Type	All Types, except liposarcoma
Prior Treatment	Surgery, chemotherapy or others but no target therapy
ORR	9(25.7%)
SD	16(45.7%)
DCR	25(71.4%)
mPFS	138 days

Poster 104 3031108

SHOULD NEOADJUVANT CHEMOTHERAPY BECOME STANDARD TREATMENT FOR HIGH-RISK SOFT TISSUE SARCOMAS? A SINGLE CENTRE RETROSPECTIVE ANALYSIS.

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Objective: High risk soft tissue sarcoma (STS) of the trunk and extremities is defined as grade 3, deep site, > 5 cm tumours. Despite correct local treatment, half of these patients will experience local or distant recurrence within the first 5 years. Treatment algorithm includes radical surgery and radiotherapy. Neo/adjuvant chemotherapy has been widely discussed. Recently, preliminary results of ISG-STS-1001 GEIS25 have been published, suggesting a benefit from anthracycline plus ifosfamide neoadjuvant treatment. Here, we present the outcome results for patients treated with neoadjuvant chemo/chemorradiation at our institution for the past 10 years.

Methods: We retrospectively analysed 67 patients with STS of extremities or trunk who underwent neoadjuvant chemo/chemorradiation at Sant Pau Hospital form January 2006 to August 2016. The aim of the study was to find relapse patterns and prognostic factors. Pathologic response after neoadjuvant treatment was classified as high (>90% necrosis), intermediate (90-30% necrosis) or low (<30% necrosis). Overall survival (OS) and recurrence-free survival (RFS) estimation were calculated using Kaplan-Meier curves and were compared using log-rank test. For the comparative analysis, we used X^2 test or Fisher's exact test in categorical variables, and the t-test in quantitative variables.

Results: Patient characteristics are shown in Table 1. With a median follow up of 50.6 months, there were 5 local relapses (7%), 24 distant metastases (35.8%) and 10 patients (14.9%) experienced local and distant relapse. There were 29 deaths (43.3%) due to disease progression. The median RFS of this series was 27.4 months and the median OS was 66.4 months. A total 53 patients (79.1%) received treatment within clinical trials (GEIS 8, 15, 20, 25), and those patients had a trend towards better overall survival (73.8 vs 51.5 m) (p=0.181). Patients treated within a clinical trial (GEIS-8, GEIS-25) with high-dose ifosfamide plus radiotherapy (HD-Ifos-RT) achieved a high pathological response in 62.5%. Local recurrence rate was also low for the patients treated with HD-Ifos-RT (4.2%). However, 66.7% of these patients had a distant relapse. Patients treated with anthracycline plus ifosfamide (AI) were less likely to relapse than those treated with other chemotherapy regimens (36.4 % *vs* 41%), p=0.008. The median OS for patients treated with AI was 114 months (9.5 years) compared to 51.5 months for patients treated with other chemotherapy regimens (p= 0.105). R0 surgery correlated with a lower probability of relapse (51.1% for R0 surgeries compared to 20% for R1 and R2, p=0.001), but it was not associated with survival. There were no differences regarding the

Table 1

	n= 67
Age	53.2 (20-78)
Sex	
- Male	44 (65.7%)
- Female	23 (34.3%)
Site	
- Lower limb	51 (76.1%)
- Upper limb	12 (17.9%)
- Trunk	4 (6%)
Stage	
- II	2 (3%)
- III	65 (97%)
Histology	
- Synovial sarcoma	14 (20.9%)
- Leiomyosarcoma	6 (9.0%)
- Myxofibrosarcoma	5 (7.5%)
- Liposarcoma (pleomorphic and myxoid)	3 (4.5%)
- Undifferentiated pleomorphic sarcoma	15 (22.4%)
- Malignant peripheral nerve sheath tumour	2 (3%)
- Others	4 (6%)
Clinical trial	
- Yes	53 (79.1%)
- No	14 (20.9%)
First treatment	
- Chemotherapy (CT)	29 (43.3%)
- Chemorradiation (CT-RT)	38 (56.7%)
Scheme QT	
- Adriamycin	2 (3%)
- Anthracyclines + Ifosfamide	24 (35.8%)
- Ifosfamide	34 (50.7%)
- Histotype-tailored CT (GEIS25)	7 (10.4%)
RT	
- Neoadjuvant (+/- boost)	40 (44.8%)
- Adjuvant	22 (32.8%)
- No	5 (14.9%)
Surgery	
- R0	47 (70.1%)
- R1	18 (26.9%)
- R2	2 (3%)
Pathologic response	
- ≥90	30 (44.8%)
- 30-89%	22 (32.8%)
- <30%	7 (10.4%)
- Unknown	8 (11.9%)

administration of radiotherapy pre or postoperatively in terms of risk of relapse, OS or RFS. No differences were found either with regard to RECIST or pathological response based on the different neoadjuvant treatments. Additionally, in this series, patients who underwent surgery for metastases had longer survival, 49.4 months, compared to 21 months for patients who were not treated with surgery (p=0.013).

Conclusion: Patients treated with neoadjuvant AI have a lower risk of relapse and longer overall survival than those treated with other chemotherapy regimens. HD-Ifosfamide plus radiotherapy provides a high local control although this does not translate into longer survival. Patients undergoing pulmonary metastasectomy achieved long survival in our series.

Poster 105 3033961

GEMCITABINE AND DOCETAXEL AS TREATMENT OPTION FOR ADVANCED ANGIOSARCOMA

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Objective: Angiosarcoma is rare malignant sarcoma derived from vascular endothelial cells, and accounting for 1–2% of all soft-tissue sarcomas. Angiosarcoma is usually regarded as a high-grade tumor, aside from morphology, being marked by one of the highest metastatic potentials among sarcomas, with an overall median survival of <4 years and a cure rate of <40% at 5 years. The combination of gemcitabine and docetaxel for soft tissue sarcoma (STS) has been widely adopted over the last decade. This regimen was first examined in a phase 2 study in leiomyosarcoma and showed a high RECIST response rate of 53%. Very few data are available on gemcitabine and docetaxel in advanced angiosarcoma.

Methods: We reviewed all cases of advanced angiosarcoma treated with gemcitabine in combination with docetaxel (gemcitabine 900 mg/m2 over 90 minutes on days 1 and 8 and docetaxel 100 mg/m2 over 60 minutes on day 8 with granulocyte-colony-stimulating factor 300 microgram/m2 support on days 9 through 18, every 3 weeks), at N.N. Blokhin Russian Cancer Research Center from 2009 till 2018. Disease was histologically confirmed by a sarcoma pathologist. CT/MRI were repeated every 2 cycles of treatment and then every 2–3 months of follow up period. Treatment response was assessed by RECIST criteria. Progression-free survival (PFS) and overall survival (OS) were estimated with Kaplan-Meier method.

Results: Twenty-five patients were enrolled (72% women; median age 51 years old). The most commonly affected sites were breast (24%), extremities (16%), trunk (12%) and heart (12%), and retroperitoneal space (8%), brain (8%), uterus (4%) and neck (4%) were less commonly involved. Only 8% of patients were locally advanced. Median follow-up was 15.2 months, minimum 2.9 months and maximum 90. Best tumor response by RECIST was as follows: complete response 2 (8%), partial response 5 (20%), stable disease 14 (56%), progressive disease 4(16%) cases, for an overall response rate (CR+PR) of 28% and overall control rate (CR+PR+SD) of 84%. Median overall survival (OS) was 16.6 months (95% CI: 9.8-23.3). Median progression-free survival (PFS) was 7.3 months (95% CI: 3.5-11.2). One patient with a locally advanced breast angiosarcoma became resectable after 8 cycles of treatment, with partial tumor response by RECIST. Overall, gemcitabine/docetaxel combo was well tolerated.

Conclusion: In this study we achieved overall disease control rate of 84% for advanced angiosarcomas (CR+PR+SD). Combination of gemcitabine and docetaxel is an active regimen for the treatment of patients with advanced angiosarcomas. Further investigation and direct comparison with antracycline and paclitaxel based regimens are awaited.

Patients characteristics

Patient ID	Gender	Age	Tumor grade	Site of primary	Previous treatment	Disease extension	Best respons, RECIST	PFS	OS
1	F	22	Low grade	Breast	No	Metastatic	SD	16.89	30.52
2	M	51	N/A	Lung	No	Metastatic	SD	7.03	11.07
3	F	59	High grade	Brain	No	Metastatic	SD	4.60	4.9
4	M	32	High grade	Heart	No	Metastatic	PR	6.60	7.46
5	F	51	High grade	Retroperitoneum	No	Metastatic	SD	90.28	90.28
6	M	53	High grade	Adrenal	No	Metastatic	SD	6.54	16.62
7	F	48	High grade	Neck	No	Metastatic	PR	7.39	10.74
8	M	57	High grade	Retroperitoneum	No	Metastatic	SD	4.01	14.78
9	F	31	High grade	Breast	Yes	Metastatic	CR	11.73	55.75
10	F	36	N/A	Heart	No	Metastatic	PR	9.82	15.41
11	F	31	High grade	Breast	No	Metastatic	SD	18.50	26.38
12	F	22	High grade	Breast	Yes	Locally advanced	PR	72.38	72.38
13	F	24	High grade	Trunk	No	Metastatic	PR	3.68	39.75
14	M	18	High grade	Spleen	No	Metastatic	PD	1.22	2.92
15	F	48	High grade	Brain	Yes	Metastatic	SD	9.20	12.58
16	F	59	N/A	Breast	Yes	Metastatic	PR	82.99	82.99
17	M	60	High grade	Trunk	No	Metastatic	PD	1.81	4.99
18	F	51	High grade	Breast	Yes	Metastatic	SD	7.36	16.07
19	F	62	High grade	Trunk	Yes	Metastatic	SD	11.37	11.37
20	F	56	High grade	Extremity	No	Metastatic	SD	6.77	6.77
21	F	62	High grade	Uterus	No	Metastatic	CR	20.44	20.44
22	F	29	High grade	Extremity	Yes	Metastatic	PD	3.48	16.36
23	M	52	High grade	Extremity	No	Locally advanced	SD	5.39	20.63
24	F	59	High grade	Extremity	No	Metastatic	SD	5.78	11.01
25	F	48	High grade	Heart	No	Metastatic	PD	3.48	7.59

CR, complete response; F, female; M, male; N/A, not assessable; OS, overall survival; PR, partial response; PD, progressive disease; PFS, progression free survival; SD, stable disease;

Figure 1. Overall survival.

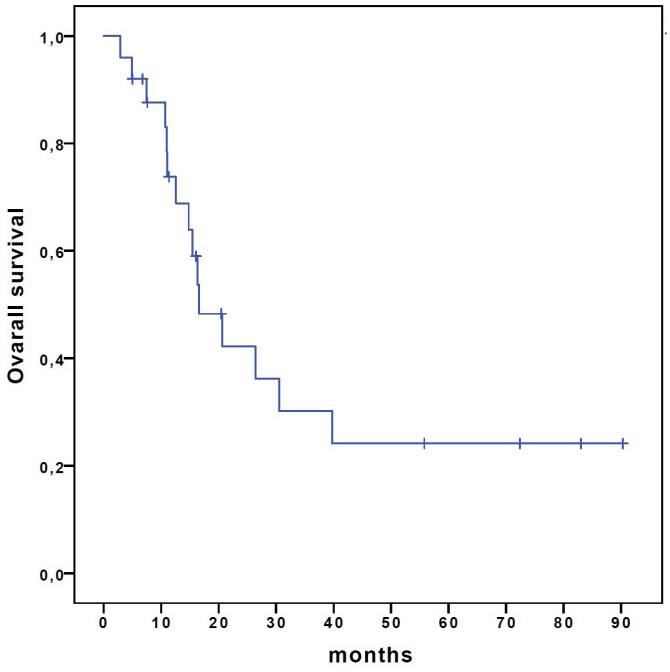
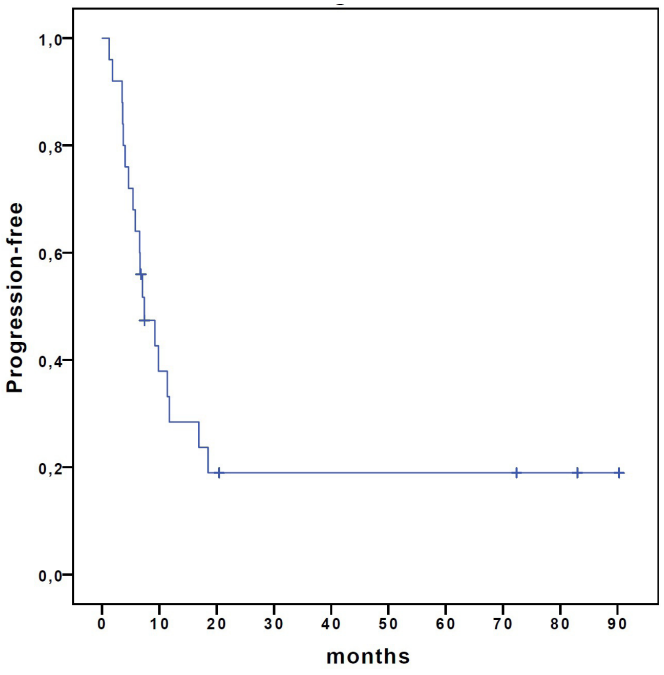


Figure 2. Progression-free survival.



Poster 106 3041672

TROFOSFAMID AND ETOPOSID – AN EFFECTIVE PALLIATIVE CHEMOTHERAPY FOR RECURRENT MENINGEAL SARCOMA

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Objective: Meningeal sarcoma is a rare disease which may arise *de novo* or from a meningioma. It is primarily treated by neurosurgery, but has a strong tendency to recur and the final outcome is poor in almost all cases. Recurrences are treated by further surgery, radiotherapy or radiosurgery. There are no effects of medical treatment, e.g., chemotherapy, to be found in the literature. At our institution we have since many years used a per oral combination of trofosfamide and etoposide as a palliative treatment in soft tissue sarcoma, and we presented a series of 69 patients at CTOS 2015, now published (J Sarcoma Res 2017;1(1):1006). We have noted positive effects with this treatment also in meningeal sarcoma.

Methods: We searched both our above mentioned case series encompassing patients initiating this treatment between May 2002 and September 2015 and patients treated after that with this regimen for cases of meningeal sarcomas. The cases found have been histopathologically reviewed by experienced sarcoma and neuro pathologists. The medical records of the patients have been scrutinized for effect and tolerance of the treatment.

Results: Two cases where the diagnosis of meningeal sarcoma could be verified were found. They received our schedule of trofosfamide 100 mg bid in total dose combined with etoposide 50 mg bid in total dose during 10 days with a cycle length of 21 days, with some dose modifications as needed. The first patient had a long history since 2003 when first operated followed by postoperative radiotherapy, with re-surgery five times between 2007 and 2011, the last surgery focused on growth behind and inferior of the left orbita and into the maxilla. This was also followed by radiotherapy to the same region. The same year also lung metastases were noted. After a strong progression of multiple meningeal manifestations between May and November 2011, trofosfamide and etoposide was started. After that, no further progression was seen up to June 2012 i.e., during 7 months. Within the coming months, however, a clinical progression was noted which was verified in September when the treatment was ended. The other patient went through surgery for her meningeal sarcoma in 2012 followed by postoperative radiotherapy. In 2015 recurrence treated by radiosurgery, but only 3 months later a new rapidly growing recurrence, which was too large for a new radiosurgery. Started on trofosfamide and etoposide in April 2016, and is still on treatment (June 2018) without further progression, in spite of a decreased dose intensity to a cycle length of 4 weeks.

Conclusion: We present the first effective chemotherapy for meningeal sarcoma in two patients. Trofosfamide and etoposide may be offered to patients with this disease if otherwise untreatable. The tolerance was fairly good in our two patients.

Poster 107 3042807

TEMOZOLOMOMID MONOTHERAPY AS AN OPTION IN LOCALLY ADVENCED AND METASTATIC SOLITARY FIBROUS TUMOR: A GUSTAVE ROUSSY SERIES

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Objective: Solitary fibrous tumors (SFT) are rare mesenchymal tumors, with an unpredictable behavior. Complete surgery is the treatment of choice for localized disease, while the optimal systemic treatment in metastatic setting is emulated from sarcoma guidelines. Temozolomide (TMZ) is a prodrug of the same imidazole alkylating agent than dacarbazine which is an active drug in SFT. TMZ is a well-tolerated, orally available drug, which offers a better quality of life in this patient population with chronic disease. Efficacy of TMZ has been observed but no clinical trial has been reported so far. Among these observations, a retrospective series of Dr M. Park from MD Anderson Cancer Center showed evidence efficacy of bevacizumab plus TMZ combination with a prolonged clinical benefit in 14 patients. Likewise, this work presents a serie of patients with locally advanced or metastatic SFT treated by TMZ monotherapy at our institution.

Methods: Between 2013 and 2017, we analyzed retrospectively the clinical, biological and radiological data from files of patients presenting locally advanced or metastatic SFT who progressed after one or several lines of standard chemotherapy. TMZ was administered at the dose of 140 mg dayly, from day 1 to day 14, over a 28 day-cycle. Patients who received concomitant bevacizumab were excluded. Statistical analysis was performed through SPSS program.

Results: Fourteen patients were treated by TMZ monotherapy. Median age was 65 [56 – 70] and two third were female patients. The majority of patients had a performans status of 0 or 1 (86%). The median follow up was 10.5 months [3,75 – 20,25] . Nine patients had clinical response based on physician assessment. The best radiologic response according to RECIST criteria were 2 patients had partial response (14.3%), 8 had stable disease (57.1%) and 5 experienced progression (35.7%). Five patients (35%) were long responders for more than 6 months. The estimated progression free survival was 4 months [2 – 9,25]. Median number of cycle was 3 [2 – 8]. Five patients died and 4 patients are still under TMZ at the time of the analysis. Five patients had previously received adriamycin, 7 patients endoxan, 4 dacarbazine and 7 pazopanib. Some had several lines among them. Lymphopenia was the main side effect found in 42.9% of patients. One patient stopped treatment because of pneumocystis. No other toxicity related interruption of treatment was observed.

Conclusion: Based on our experience, TMZ may be a relevant therapeutic option in locally advanced and metastatic SFT with an acceptable toxicity profile. The investigation of an underlying biological mechanism predictive of response such as MGMT methylation is ongoing.

Poster 108 3042842

HEPATOTOXICITY AS A PREDICTIVE FACTOR FOR SOFT TISSUE SARCOMA TREATED WITH TRABECTEDIN

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Objective: Trabectedin is currently approved as second line treatment on soft tissue sarcomas (STS) on patients after first line progression or unfit for anthracyclines. On several clinical trials it has been described a transient non-cumulative hepatotoxicity on chemotherapy onset, which can be dose-limiting. As trabectedin is mainly metabolized in the liver, specially by CYP3A, it also results in higher plasma exposures on patients presenting with hepatotoxicity. The authors' objective was to evaluate if trabectedin treatment hepatotoxicity could be related to progression free survival (PFS).

Methods: The authors identified retrospectively all patients with the histological diagnosis of soft tissue sarcoma who started treatment with trabectedin between January 2010 and January 2018. Primary endpoint was the evaluation of hepatotoxicity impact on PFS. Toxicity grading was defined according to the National Cancer Institute Common Terminology Criteria for Adverse events (NCI CTCAE). Survival analysis was performed using the Kaplan-Meier method and Cox regression.

Results: 39 patients were identified, with a median age of 57 years old (min.18- max.79). The median follow-up was 44.6 months. Most patients were female (n=21; 53.8%) and the most frequent histologic type was leiomyosarcoma (n=24; 61.5%), followed by liposarcoma (n=11; 28.2%). The retroperitoneum was the most frequent primary location (n=16; 41%) and almost all were high grade tumors (n=30; 76.9%). 30.8% were metastasized on diagnosis (n=12). Trabectedin was used

at 1.5 mg/m2 on a 24h infusion, q3w, after failure of first or more therapy lines with anthracycline-based protocols. Four patients were unfit for anthracyclines and received trabectedin as a first line therapy. The median of cycles of trabectedin was 6. Six patients (15.4%) had stable disease and nine patients obtained partial response (23%). Sixteen patients had mild hepatic toxicity (G1/G2). The overall survival (OS) from the beginning of palliative chemotherapy was 18.6 months and PFS under trabectedin treatment was 4.9 months. There was a significant difference of PFS between the group who presented with mild hepatic toxicity on the beginning of the treatment and those who did not (13 *versus* 4 months, respectively; p=0.027). Hepatic toxicity was still predictive of PFS in multivariate analysis when adjusted for the number of previous chemotherapy lines, histology, and presence of liver metastasis.

Conclusion: Our results show that the development of mild hepatotoxicity during the first cycles of trabectedin treatment predicts a better response to trabectedin and a longer PFS and that may allow us to select patients who would benefit more from this treatment. However, prospective studies are needed as well as further molecular analysis to understand which patients would benefit more from trabectedin.

Poster 109 2990389

THE RESULTS OF TREATMENT WITH TRABECTEDIN FOR ADVANCED SOFT TISSUE SARCOMAS: A JAPANESE SINGLE-CENTER EXPERIENCE

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Objective: In recent years, new drugs such as trabectedin were developed for advanced soft tissue sarcomas. Therefore, we examined the results of treatment with trabectedin for advanced soft tissue sarcomas in our hospital.

Methods: In our hospital, 16 patients with advanced soft tissue sarcoma were treated with trabectedin. There were 8 male patients and 8 female patients. Their age ranged from 51 to 67 years (mean 59.5 years). The pathological diagnosis was leiomyosarcoma in 4 patients, myxoid liposarcoma in 3, dedifferentiated liposarcoma in 3, synovial sarcoma in 2, dermatofibrosarcoma protuberans in 1, malignant peripheral nerve sheath tumor in 1, myxofibrosarcoma in 1, and angiosarcoma in 1. We examined the outcome and the adverse events of these 16 patients.

Results: The number of the regimens before trabectedin ranged from 1 to 4 (mean 1.9). Doxorubicin alone, ifosfamide-doxorubicin and/or gemcitabine-docetaxel etc. were performed before trabectedin. The number of the regimens after trabectedin ranged from 0 to 3 (mean 1.1). Pazopanib and/or eribulin etc. were performed after trabectedin. The course number of trabectedin ranged from 1 to 20 courses (mean 6.0 courses). As for the reason of trabectedin cancellation, 14 patients were cancelled by progression disease (PD), and 2 patients were cancelled by complications. The progression free survival (PFS) ranged from 0.4 to 22.1 months (mean 6.3 months, and median 3.0 months). The progression free rate of 12 weeks (12w-PFR) was 50% (8/16), and the partial response (PR) was found in 2 patients (12.5%). The histological type of 2 patients with PR was myxoid liposarcoma. The PR was obtained after 3 courses, 4 courses of trabectedin, respectively. The histological type of 4 patients who were given trabectedin more than 10 courses was myxoid liposarcoma in 3 patients and leiomyosarcoma in 1. As for the outcome, died of disease (DOD) was 9 patients, and alive with disease (AWD) was 7. Overall survival (OS) ranged from 0.4 to 39.4 months (mean 16.0 months, and median 12.4 months). As for the adverse events of grade 3 or higher, neutropenia was found in 9 patients, liver dysfunction was found in 4, CPK increase was found in 2, and fatigue was found in 1. The CPK increase was found after 3 courses, 12 courses of trabectedin, respectively. As for the adverse events of grade 2, fatigue was found in 2 patients, anorexia was found in 2, CPK increase was found in 2, edema was found in 1, and cough was found in 1. [Case presentation] A case was 58 years old female patient with myxoid/round liposarcoma of neck. The several surgery, radiotherapy and chemotherapy (doxorubicin alone, and ifosfamide etc.) were performed, but recurred in abdomen (Figure 1). The PR was obtained after 3 courses of trabectedin (Figure 2). We were able to perform 20 courses of trabectedin (for 21 months) until the PD.

Conclusion: In our hospital, the PFS of 16 patients with advanced soft tissue sarcoma treated with trabectedin was median 3.0 months, the 12w-PFR was 50%, and the OS was median 12.4 months. These were more moderately poor than the result of phase II study in Japan. The known adverse events were found, but all were tolerable and the treatments with trabectedin were performed safely.

Figure 1. Before trabectedin administration

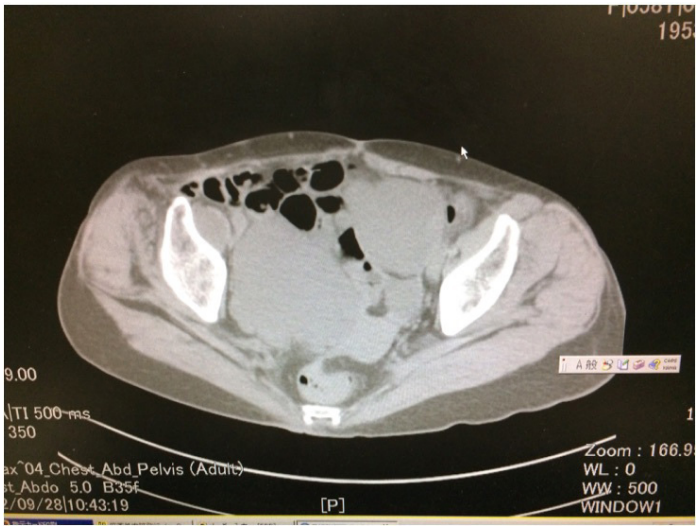
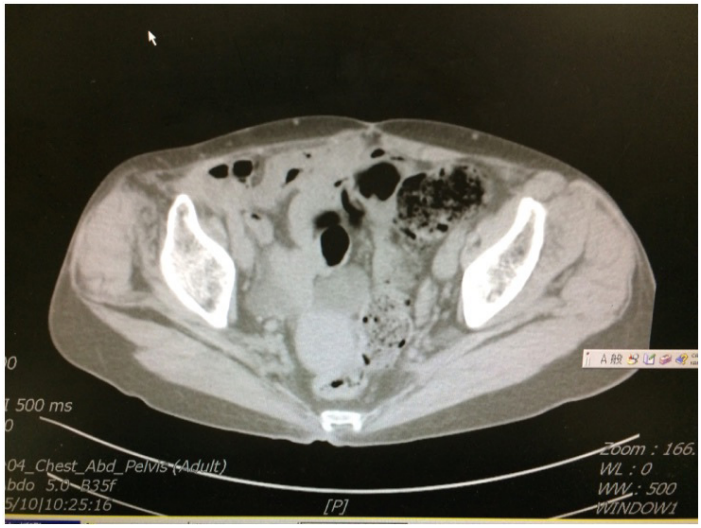


Figure 2. After 3 courses of trabectedin



Poster 110 3042740

SAFETY AND EFFICACY OF OLARATUMAB ADDED TO DOXORUBICIN-BASED COMBINATION CHEMOTHERAPY IN THE TREATMENT OF ADVANCED SOFT-TISSUE SARCOMA (STS).

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Objective: Patients with metastatic STS treated with doxorubicin-based chemotherapy have a median overall survival of 12-16 months and a 2-year survival of approximately 30%. Adding olaratumab (olara) to single agent doxorubicin showed an increase in median survival by 12-months. Olara did added minimal toxicity when added to doxorubicin. However, the combination of doxorubicin plus ifosfamide (AI) is an active and accepted therapy for patients with advanced STS. The combination of AI appears to be superior to single agent doxorubicin in overall response rates, progression free survival, with a trend toward overall survival benefit. Moreover, the combination AI is also active in the adjuvant treatment of primary STS after surgery and radiation. Whether adding olara to a doxorubicin-based doublet regimen (AI or other) is effective in patients with good performance status without adding toxicity is still unknown. This study aims to describe the safety profile of such regimen and describe the initial response to treatment.

Methods: We conducted a retrospective cohort study of patients with advanced STS treated at our institution. Between January 1, 2017 and February 1, 2018, we identified 12 consecutive patients treated with olara plus a doxorubicin-based doublet regimen and 24 consecutive patients treated with a doxorubicin-based doublet regimen without olara. We reviewed office progress notes and laboratory results after every cycle of chemotherapy to obtain clinical and hematologic adverse events (AE) data. AE difference between the olara-exposed and olara-unexposed group was analyzed using logistic regression to calculate the odds ratio (OR) and the corresponding 95% confidence interval (CI). We assessed initial responses by RECIST and CHOI criteria and described the results by frequencies.

Results: All patients had ECOG performance status 0-1, and stage III or IV STS. Median age was 64 (range, 21-80) and 58% were women. Histologies were leiomyosarcoma 25%, liposarcoma 22%, myxofibrosarcoma 16%, rhabdomyosarcoma 14%, synovial sarcoma 5%, and one case each of Ewing sarcoma, desmoid tumor, MPNST, carcinosarcoma, and osteosarcoma. Mean number of cycles received in the olara group was 3.4 vs. 4.6 in the controls. Doxorubicin was paired with either ifosfamide, cyclophosphamide, vincristine or dacarbazine. Total AE and clinical AE were lower in the olara group, OR 0.64 (95% CI 0.46–0.89, p = 0.0081) and 0.51 (95% CI 0.32-0.81) respectively. There was no difference in total hematologic AE, OR 0.4918 (95% CI 0.1925-1.2563). However, when stratifying by severity, OR for hematologic grade 3-4 AE was 0.34 (95% CI 0.16-0.71, p =0.0043) and for 1-2 hematologic AE was 1.19 (95% CI 0.37-3.81, p=0.7673). Initial responses to treatment while on therapy were similar between both groups. By RECIST, 67% of olara cases had stable disease (SD) vs. 71% of controls; 17% of olara cases had partial response (PR) vs. 13% of controls; 8% (1 olara case) had progression of

disease (PD) vs. 0 in the controls. By CHOI, 42% of olara cases had SD vs. 21% of controls; 33% of olara cases had PR vs. 54% of controls; 17% of olara cases PD vs 8% of controls. One olara case and 4 controls had non-measurable disease for assessment.

Conclusion: In this retrospective cohort, the addition of olara to a doxorubicin-based doublet appears safe and effective. Although possibly due to small sample size, olara plus a doxorubicin-based doublet was associated with fewer clinical and grade 3-4 hematologic adverse events than patients treated with a doxorubicin-based doublet without olara. This finding may be in part due to the small sample size or the fewer number of cycles received in the olara group. This data supports the feasibility of adding olara to doxorubicin-based combination chemotherapy for patients with advanced sarcoma and good performance status. Further prospective clinical trials are ongoing to help determine whether this translates into better outcomes.

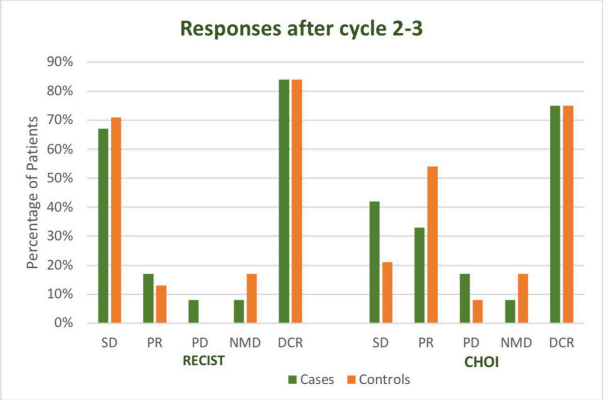

Figure 1. Comparison of responses to treatment after 2-3 cycles by RECIST and CHOI criteria. SD: Stable Disease, PR: Partial Response, PD: Progression of Disease, NMD: Non-Measurable Disease, DCR: Disease Control Rate (SD+PR)

Poster 111 3003237

PREDICTING SURVIVAL IN LOCALIZED CHONDROSARCOMA

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Objective: Chondrosarcoma is the second most common primary malignant bone tumor. Surgery remains the mainstay of treatment for most subtypes, and the utility of adjunctive therapies remains poorly defined. In addition, although established prognostic factors for survival in chondrosarcoma are suggested to include age, size, grade, margin status, and tumor site, most studies remain limited by low sample sizes, and the degree of impact on survival has been difficult to quantify. Our goal was to identify the factors most prognostic of survival in adults. Specifically, we sought to identify the A) demographic B) tumor and C) treatment characteristics most correlated with survival.

Methods: We retrospectively analyzed patients in the National Cancer Database (NCDB) from 2004 through 2015. Patients were included who had localized chondrosarcoma. All patients with metastatic disease, or under the age of 18, were excluded. Unadjusted overall survival (OS) was estimated using the Kaplan Meier method, with statistical comparisons based on the log-rank test. Cox proportional hazard model was used to estimate the association between demographic, pathologic, and treatment variables and OS after adjustment for known covariates.

Results: We identified 5,013 patients presenting with primary chondrosarcoma. The patient cohort had a median age of 52 (range 18-90); 2615 (52%) of the patients were males. Of the 5,013 patients with chondrosarcoma, 4,366 had a tumor grade reported, of which 1,912 (44%) were low-grade, 1,654 (38%) were intermediate-grade, and 800 (18%) were high-grade. In a multivariate analysis, the factors that most significantly correlated with survival in chondrosarcoma included lower tumor grade, younger age, and type of surgery. Amongst the demographic variables, younger age and female sex were the factors that had the most favorable prognostic impact (Age >60 vs. <40 years hazard ratio [HR] 3.06 (2.43-3.87), p<0.001; Male vs. Female HR 1.22 (1.08-1.38), p=0.002)). Amongst tumor characteristics, lower tumor grade, tumor site and smaller size had the largest positive prognostic impact on survival (High grade vs. Low grade HR 4.30 (3.57-5.18), p<0.001; Size >5cm vs. <5cm HR 1.81 (1.51-2.16), p<0.001). Amongst treatment characteristics, factors that were most associated with greater overall survival were surgery type and surgical margins (No surgery vs. Surgery HR 2.70 (2.14-3.42), p<0.001; Amputation

vs. Radical resection 1.23 (1.01-1.49), p=0.035; Positive vs. Negative margins HR 1.76 (1.46-2.13), p<0.001). Factors that were not independently associated with survival included race, income and education.

Conclusion: This is the largest patient cohort to date examining factors prognostic for survival in chondrosarcoma. The most important factors prognostic of survival were lower tumor grade and younger age. Surgery with a positive margin was significantly associated with death from disease. Further investigation is necessary to help define interventions that can improve survival in chondrosarcoma.

Table 1. Independent predictors of mortality in multivariate proportional hazards analysis

Variable	HR	Lower 95%	Upper 95%	P value
Patient variables				
Age (years) (Ref=0-40)	Ref			
40-60	1.65	1.33	2.04	<0.001*
>60	3.06	2.43	3.87	<0.001*
Male sex (Ref=Female)	1.22	1.08	1.38	0.002*
Hispanic (Ref=Non-Hispanic)	0.80	0.61	1.04	0.091
Race (Ref=Caucasian)				
African-American	0.93	0.71	1.21	0.578
Asian	0.88	0.55	1.40	0.586
Comorbidity Score >1 (Ref=0-1)	1.85	1.47	2.34	<0.001*
Insurance (Ref=Private Insurance)				
Medicare	1.85	1.56	2.20	<0.001*
Medicaid	1.85	1.45	2.37	<0.001*
No insurance	1.22	0.85	1.74	0.274
Income below median ($48,000)	1.11	0.96	1.29	0.155
Education below median (87% HSD)	0.93	0.80	1.07	0.304
Tumor and treatment variables				
Size >5cm	1.81	1.51	2.16	<0.001*
Grade (Ref=Low grade)				
Intermediate grade	1.71	1.43	2.04	<0.001*
High grade	4.30	3.57	5.18	<0.001*
Location (Ref=Limb)				
Spine	1.29	0.97	1.72	0.075
Pelvis	1.05	0.89	1.24	0.537
Surgery (Ref=No surgery)				
All types	0.37	0.29	0.47	<0.001*
Amputation	0.51	0.38	0.69	<0.001*
Radical resection	0.42	0.32	0.54	<0.001*
Local resection	0.32	0.25	0.41	<0.001*
Surgical margins positive	1.76	1.46	2.13	<0.001*
Radiation use	1.35	1.14	1.59	0.001*
Chemotherapy use	1.63	1.35	1.98	<0.001*

HR = hazard ratio; * indicates statistical significance (at alpha of 0.05)

Poster 112 3042422

PARP INHIBITORS; A NOVEL THERAPEUTIC STRATEGY FOR CHONDROSARCOMA?

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Objective: Chondrosarcoma is the second most common bone malignancy and accounts for 20% of all bone tumors. Fifty to seventy percent of these tumors have specific isocitrate dehydrogenase *(IDH)1* or *IDH2* point mutations, leading to the conversion of α-ketoglutarate (αKG) into the oncometabolite (D)-2-hydroxyglutarate (D2HG). This oncometabolite inhibits αKG-dependent enzymes such as histone and DNA demethylases causing epigenetic changes (e.g. hypermethylation phenotype). Currently, the only treatment option for chondrosarcoma patients is surgery which underlines the need for novel targeted therapies for patients with unresectable chondrosarcoma. Recently, a study was published on the synthetic lethal interaction between *IDH1/*2 mutations and poly (ADP-ribose) polymerase (PARP) inhibitors in primary glioma and acute myeloid leukemia with endogenous *IDH* mutations. In engineered *IDH* mutant cell lines, this study determined that D2HG inhibits KDM4A and KDM4B, resulting in a DNA double strand break repair defect and thereby a BRCAness phenotype (Sulkowski et al. 2017). We here explore if PARP inhibitors are synthetic lethal with *IDH* mutations in chondrosarcoma cell lines and if PARP inhibition alone or in combination with radio- or chemotherapy could be a potential novel therapeutic strategy for chondrosarcoma patients.

Methods: Dose-response curves (DRCs) were performed with the PARP inhibitor Talazoparib (BMN 673) in our chondrosarcoma cell line panel, existing of five *IDH1/2* wildtype and five *IDH1/2* mutant cell lines representing central conventional, dedifferentiated and mesenchymal chondrosarcoma. Additionally, a PARP inhibitor DRC was performed in one *IDH1* mutant cell line treated for >20 passages with the *IDH1* mutant inhibitor AGI-5198 to assess whether long-term mutant inhibition rescues the effect of PARP inhibition. To determine the underlying cell death mechanism, cell cycle analysis and apoptosis induction were determined after 24h and 48h treatment with ~IC75 concentrations of Talazoparib. To assess homologous recombination efficiency, a RAD51 foci assay was performed in chondrosarcoma cell lines and a BRCA signature analysis was performed on sequencing data from five *IDH1* mutant chondrosarcoma tumors. To determine synergy with chemotherapy, Talazoparib was combined with Doxorubicin, Cisplatin and Temozolomide in DRCs.

Results: All chondrosarcoma cell lines were sensitive to PARP inhibition, although IC50s after 72h of treatment varied from 18nM to 1300nM. Sensitivity was not correlated to *IDH* mutation status and treatment with the *IDH1* mutant inhibitor AGI-5198 did not rescue the PARP inhibition effect. Treatment with 500nM Talazoparib for 24h or 48h induced a G2 cell cycle arrest in both tested cell lines. Apoptosis was detected after 48h treatment with 500nM Talazoparib in one of the most sensitive cell lines. The RAD51 foci assay showed that all tested chondrosarcoma cell lines were homologous recombination proficient, independent of their sensitivity to PARP inhibition (i.e. IC50s ranging from 18nM to 520nM) and *IDH* mutation status. Furthermore, no BRCA signature was identified in the sequencing data from five *IDH1* mutant chondrosarcoma tumors. Combination of Talazoparib with Doxorubicin or Cisplatin did not induce a synergistic effect in three cell lines. However, combination treatment with Temozolomide resulted in synergy.

Conclusion: To conclude, PARP inhibition alone or in combination with Temozolomide is a promising therapeutic strategy in chondrosarcoma. However, no synthetic lethal interaction between *IDH* mutations and PARP inhibition was determined. Chondrosarcoma cell lines seem to be homologous recombination proficient, indicating that further investigation is needed to explain PARP inhibitor sensitivity. Ultimately, this could lead to *in vivo* testing of Talazoparib alone or in combination with chemo- or radiotherapy in our established chondrosarcoma mouse model and to clinical trials in chondrosarcoma patients.

Poster 113 3026463

CLINICAL UTILITY OF 2-HG AS A BIOMARKER IN IDH MUTATED CHONDROSARCOMA

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Objective: Chondrosarcoma is the second most common malignant bone tumors and resistant to both chemotherapy and radiotherapy due to low vascularity and abundant extracellular matrix. New targeted therapy has been needed because there are no effective treatment choices for relapsed or metastasized chondrosarcoma. Mutations in isocitrate dehydrogenase (IDH) genes are observed in various malignant tumors including chondrosarcoma. IDH mutations have been reported

to contribute to the malignant transformation of the tumors through the production of 2-hydroxyglutarate (2-HG) and the competitive inhibition of α-KG-dependent dioxygenases. Therefore, we have presumed that IDH mutant inhibitors can be novel anticancer drugs for IDH mutated tumors and proceeded to develop a novel, orally bioavailable, selective IDH1 mutant inhibitor, DS-1001b. Indeed, this drug impairs proliferation of IDH1 mutated chondrosarcoma cells *in vitro* and *in vivo* in accompany with decreasing 2-HG levels. However, it remains unclear whether IDH mutation status is associated with prognosis of chondrosarcoma patients and 2-HG can be a useful biomarker of IDH mutated specimens. In this study, we investigated the relationship between IDH gene status and clinicopathological data of chondrosarcoma patients, and clinical utility of 2-HG as a surrogate biomarker using clinical samples.

Methods: To determine IDH mutation status in chondrosarcoma, 38 frozen samples obtained from chondrosarcoma patients were analyzed with sanger sequencing. We investigated the relationship between IDH gene status and clinicopathological data of these patients extracted from clinical records including age, sex, location, histological grade, tumor volume, treatment, recurrence and clinical outcome. Additionally, to evaluate the usefulness of 2-HG as a biomarker in chondrosarcoma, we measured intratumoral 2-HG of 38 frozen tissues and serum 2-HG levels obtained from 22 patients using LC-MS/MS.

Results: We detected 15 cases (40%) of IDH1 mutations and 5 cases (13%) of IDH2 mutations and the rest 18 cases were IDH wild-type tumors. Consistent with the previous reports, IDH1R132C was the most frequent mutation in chondrosarcoma (n=10). Histological type and grade (FNCLCC) were consisted of 32 cases of conventional chondrosarcoma (Grade 1: 13 cases, Grade 2: 17 cases, Grade 3, 2cases) and 6 cases of dedifferentiated chondrosarcoma. Histological grade was relatively high in the IDH mutated tumors, resulting in the significant worse clinical outcomes compared to the IDH wild-type chondrosarcomas ($P = 0.015$). The intratumoral 2-HG levels of IDH mutated specimens were significantly higher than those of IDH wild-type specimens (1,546 ± 2,479 vs 9 ± 8 pmol/mg; $P < 0.001$). Although 12 IDH mutated samples were associated with higher serum 2-HG levels, difference of the levels between IDH mutated and wild-type samples was not clear as that of acute myeloid leukemia (364.7 ± 66.9 vs 288.3 ± 80.3 ng/ml; $P = 0.029$).

Conclusion: In this study, IDH mutations were not only identified with approximately 50% of chondrosarcoma patients but also associated with shorter survival. Additionally, intratumoral 2-HG could be a good surrogate biomarker of IDH status and treatment. Our study has provided proof of concept for inhibition of mutant IDH as a novel therapeutic approach with a useful biomarker, 2-HG, in unresectable and metastatic chondrosarcoma. For the next step, we are planning to perform deep sequencing of these clinical samples to analyze additional mutations or signaling activation related to poor prognosis of IDH mutated chondrosarcoma patients.

Poster 114 3027412

IMMUNE LANDSCAPE OF HIGH GRADE CHONDROSARCOMAS: IDENTIFICATION OF KEY PLAYERS CREATING AN IMMUNOSUPPRESSIVE TUMOR ENVIRONMENT

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Objective: CHS is a heterogeneous group of tumors characterized by their capacity to synthetize cartilage and their highly chemo- and radio-resistance. CHS's 10-y survival rate - ranging from 29% to 83% depending on CHS subtype and grade- hasn't changed over the last 4 decades and innovative therapeutic approaches are therefore urgently needed. If recent exciting developments of immunotherapies raised hopes for cancer therapy; these approaches are less advanced for people with bone sarcomas. Knowledge of chondrosarcoma immune landscape still remains poor; thus, in order to evaluate whether chondrosarcoma patients could benefit from immunotherapy, we deciphered high grade chondrosarcomas (Grade II and III conventional CHS and Dedifferentiated CHS) immune landscape and its correlation with tumor agressivity -by using immunohistochemistry and molecular analyses.

Methods: From a chondrosarcoma cohort comprising 26 conventional grades 2 and 3 CHS and 44 DD CHS, immunohistochemistry was performed to characterize major immune cells subsets (CD3, CD8, CD163). Markers were quantified by counting positive-staining lymphocytes and macrophages.
Expression of targetable immune checkpoints and immunomodulatory molecules (OX40/OX40L; B7H3, TIM3, LAG3, CTLA4, PD1/PDL1, CSF1/CSF1R) was quantified by RT-qPCR and compared to cell lines known to express or not the targets (cell line database). In addition, PDL1 and CSF1R expression were confirmed by immunohistochemistry. The expression of PDL1 was scored by percentage of tumor cells exhibiting positive membranous staining (cutoff 1%); CSF1R was quantified by counting positive-staining macrophages.

Results: Localization of the immune infiltrates varied amongst conventional and DD CHS being limited to peritumoral area for the first ones while immune cells were encountered in the peritumoral and in the intratumoral dedifferentiated part of DD CHS. Amongst conventional and DD CHS, the composition of immune infiltrate was similar and composed of CD8+ and CD163+ cells; the latter population being the most present. When patients were allocated according to the CD163+ cells proportion (cut off value: 40%), a correlation between CD163+ cells count and patients survival was found: a CD163+ percentage above the median value being associated with worse survival ($p = 0.04$). Moreover, in DD CHS, CD163+ cells density in primary tumor was correlated with metastatic potential: 10 out of 12 metastatic DD CHS patients (83%) had a tumoral infiltrate with high CD163+ cells density (>40% positive cells) while 12 out of 20 non metastatic patients had a tumor infiltrate with low CD163+ cells (<40%). Transcriptomic analyses of targetable ICP revealed a great heterogeneity of expression between checkpoints, CHS subtypes and patients. Amongst the panel of targetable ICP evaluated, PDL1 expression - confirmed at the transcriptomic and immunohistologic level - was limited to dedifferentiated part of DD CHS and was found of high level (cutoff: >5% positive cells) for some patients (27.3% of patients). CSF1R expression was high for both CHS subtypes in a majority of patients (>50% of patients).

Conclusion: The high infiltrate in CD163+ cells and the expression of CSF1R by high grade CHS tend to indicate that these tumors maintain an immunosuppressive environment. Further studies are pending to determine the significance of these findings for immunotherapy response.

Poster 115 3027640

CLEAR CELL CHONDROSARCOMA: CLINICAL CHARACTERISTICS AND TREATMENT OUTCOMES IN 19 PATIENTS

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Objective: Clear cell chondrosarcomas (CCC) represent less than 6% of all chondrosarcomas. Analyzing clinical characteristics and treatment patterns, thus increasing our knowledge, may improve outcomes. We review our institutional experience with 19 patients, including one case with dedifferentiation.

Methods: A retrospective review was conducted of all CCC patients treated at MD Anderson Cancer Center from 1996 to 2015. Descriptive statistics, survival analysis, and Cox proportional hazards regression models were performed.

Results: 19 patients were identified. Median age at diagnosis was 43 years. 68% were male. The most common presenting signs were pain (13 patients; 68%) and fracture (4 patients; 21%). The most common site was proximal femur (10 patients; 53%). All patients had MSTS Stage I disease. Primary treatment included wide resection in 13 patients (68%), and intra-lesional or marginal resection in 6 (32%).
Five patients died during the study period, 1 with dedifferentiation of recurrent CCC. The median time to death was 14.2 years [95% CI: (12.8; NA)]. The median survival time for patients who had intralesional/marginal resection was 12.8 years, and for patients who had wide resection it was 15.3 years [95% CI: (14.2; NA); $p=0.52$]. The median time to either recurrence or death was 4.49 years for patients who had intra-lesional/marginal resection, and 16.44 years for patients with wide resection ($p=0.06$). The median time to recurrence or death was 16.4 years for patients treated at MD Anderson first, and 5 years [95% CI: (4.49; NA)] for patients treated at other facilities first ($p=0.02$).

Conclusion: CCC is a rare entity, and our understanding of it is still evolving. We observed a higher recurrence rate for intra-lesional or marginal resection, and wide resection alone remains the mainstay of treatment. Better outcomes were observed in patients initially treated by trained orthopedic oncologists. Due to the propensity of CCC to recur decades after initial resection, lifelong surveillance is recommended.

Poster 116 3042912

IMPACT OF NODAL INVOLVEMENT ON DISEASE SPECIFIC SURVIVAL IN CHONDROSARCOMA: ANALYSIS OF THE SURVEILLANCE, EPIDEMIOLOGY, AND END RESULTS (SEER) DATABASE (2004 – 2015)

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Objective: Chondrosarcoma is the second most common primary solid malignancy of bone, comprising 25% of all bone sarcomas. Chondrosarcomas, like other sarcomas, are viewed as having a hematogenous route of dissemination; pulmonary metastasis typify its metastatic behavior and surveillance protocols. Therefore, there is a paucity of data to guide the treatment of chondrosarcoma patients presenting with the uncommon finding of lymph node (LN) involvement at primary diagnosis. To address this, we analyzed the SEER database, a population-based cancer registry covering ~28% of the U.S. population to assess demographic, clinical and histologic factors associated with LN involvement in chondrosarcoma and outcomes based on treatment modality.

Methods: A total of 2600 unique chondrosarcoma cases involving the axial and appendicular parts of the body were identified in the SEER database for the 2004-2015 date range. Cases involving the head and neck were excluded. Demographic, clinical, pathologic and treatment parameters were summarized with respect to LN status (LN+ vs LN-) at the time of initial diagnosis. These were compared by Fisher's exact test or t-test, using a Bonferroni correction to account for multiple comparisons. Disease-specific survival (DSS) was evaluated by Kaplan-Meier analyses and log-rank test. Hazard ratios (HR) for DSS were estimated using univariable Cox proportional hazards analyses; multivariable analyses were not conducted due to the limited number of LN+ cases.

Results: Synchronous regional LN metastases were present in 35 (1.4%) of the study population. Those with LN metastases were more likely to have an extraskeletal location, and a different primary site distribution, with the pelvis being especially overrepresented among LN+ (37% LN+ vs. 17% LN-) **[Table 1]**. LN+ patients were also more likely to present with distant metastases at diagnosis (34% vs. 4.5%, p<0.001). LN are more commonly involved with tumors that are larger (p<0.001) and more poorly differentiated (p<0.001). In LN+ or LN- patients, "chondrosarcoma" and "myxoid chondrosarcoma" were the most commonly reported histologies (49% and 34% LN+ vs 73% and 12% LN-, p=NS). Neither age, sex, race nor year of diagnosis (2004-2009 vs 2010-2015) were associated with LN involvement. LN+ patients had inferior DSS (p<0.001), with 1- and 5-year DSS of 69% and 49% respectively, vs 94% and 82% for LN- **[Figure 1]**. Among those LN+, 47% (16/34) underwent LN excision surgery; 31% (11/35) received radiotherapy (RT) vs 13% LN- (p<0.005; NS due to multiple comparisons); and 29% (10/35) received chemotherapy (CT) vs 8.7% LN- (p<0.001). For those LN+ patients, excision of at least one LN was associated with improved DSS (HR=0.22 95%CI 0.07-0.76, p=0.016) **[Table 2]**. Neither RT nor CT were associated with improved DSS (RT: HR=1.16 95%CI 0.40-3.40 p=0.783; CT: HR=0.71 95%ci 0.22-2.26 p=0.560). Due to issues with misclassification of RT and CT in the SEER database, these data cannot exclude a benefit of RT or CT.

Conclusion: LN disease is uncommonly identified at presentation in chondrosarcoma patients. This limits our analysis. However, these data suggest that greater clinical vigilance for regional nodal metastases may be warranted for those that present with specific subtypes, such as extraskeletal or pelvic primary sites, and large/poorly differentiated tumors. Surgical excision of regional nodes is associated with improved DSS, although our analyses do not allow attribution of causation. We find no evidence to support the use of radiotherapy or chemotherapy in initial management, although SEER database limitations do not allow us to exclude benefit definitively. In addition, our analysis focused on types of chondrosarcoma typically managed in an orthopaedic oncology clinic. Thus, the relevance of our conclusions to other types of chondrosarcomas, such as those involving the head and neck, is unclear.

Table 1, Part A. Comparisons of Demographic, Clinic and Pathologic Characteristics of Chondrosarcoma Patients with or without Regional Nodal Involvement at Diagnosis. Bonferroni correction for multiple comparisons: p

Table 1. Comparison of demographic clinical and pathologic characteristic in patients with or without nodal involvement

Characteristic	No regional node involvement (N=2412)	Regional node involvement (N=35)	P-value*
Mean age (range)	53.5 years (4-98 years)	58.3 years (28-85 years)	.2802
Gender			0.306
Male	1363 (56.5%)	23 (65.7%)	
Female	1049 (43.5%)	12 (34.3%)	
Race			0.758
Black	186 (7.7%)	3 (8.6%)	
White	2066 (85.7%)	31 (88.6%)	
Other/ Unknown	160 (6.6%)	1 (2.9%)	
Year of diagnosis			0.866
2004-2009	1145 (47.5%)	16 (45.7%)	
2010 -2015	1267 (52.5%)	19 (54.3%)	
Primary tumor Location			0.001*
Axial	951 (39.4%)	14 (40.0%)	
Appendicular	1438 (59.6%)	17 (48.6%)	
Other/ Unknown	23 (0.95%)	4 (11.4%)	
Primary tissue origin			0.003*
Skeletal	2162 (89.6%)	25 (71.4%)	
Extraskeletal	250 (10.4%)	10 (28.6%)	
Primary bone site			0.000*
Upper extremity	442 (18.3%)	3 (8.6%)	
Lower extremity	741 (30.7%)	4 (11.4%)	
Ribs/sternum	425 (17.6%)	1 (2.9%)	
Spine	105 (4.4%)	0	
Pelvis	409 (17.0%)	13 (37.1%)	
Bone, NOS	23 (1.0%)	4 (11.4%)	
Other/ Unknown	267 (11.1%)	10 (28.6%)	
Histologic type			.009
Chondrosarcoma	1765 (73.2%)	17 (48.6%)	
Juxtacortical chondrocaroma	30 (1.2%)	0	
Chondroblastoma, malignant	26 (1.1%)	0	
Myxoid chondrosarcoma	299 (12.4%)	12 (34.3%)	
Mesenchymal Chondrosarcoma	51 (2.1%)	2 (5.7%)	

Table 1, Part B. Comparisons of Demographic, Clinic and Pathologic Characteristics of Chondrosarcoma Patients with or without Regional Nodal Involvement at Diagnosis. Bonferroni correction for multiple comparisons: p

Clear cell chondrosarcoma	39 (1.6%)	0	
Dedifferentiated chondrosarcoma	202 (8.4%)	4 (11.4%)	
Distant metastasis			0.000*
Yes	110 (4.5%)	12 (34.3%)	
No	2226 (92.3%)	20 (57.1%)	
Unknown	76 (3.2%)	3 (8.6%)	
Grade			0.000*
Well differentiated; Grade I	746 (30.9%)	1 (2.9%)	
Moderately differentiated; Grade II	828 (34.3%)	8 (22.9%)	
Poorly differentiated; Grade III	267 (11.1%)	8 (22.9%)	
Undifferentiated; anaplastic; Grade IV	194 (8.0%)	5 (14.3%)	
Unknown	377 (15.6%)	13 (37.1%)	
Size			0.000*
0.0-8.0 CM	1151 (47.7%)	5 (14.3%)	
>8.0 CM	891 (37.0%)	27 (77.1%)	
No mass/ tumor found/ Unknown	370 (15.3%)	3 (8.8%)	

*Bonferroni correction used due to the multiple comparisons, p<0.005 defined statistical significance

Table 2. Hazard Ratio Derived from Cox Proportional Hazards Analysis for Disease-Specific Survival among Chondrosarcoma Patients with or without Regional Nodal Involvement at Diagnosis.

Table 2. Hazard Ratio for disease specific survival by treatment modality in chondrosarcoma patients with nodal involvement at diagnosis

Characteristic	p	Cox proportional hazard ratio (nodal involvement)	95% confidence interval
Lymph node surgery Yes = 1 No = 0	0.02	0.22	0.07, 0.76
Radiation Yes = 1 No = 0	0.78	1.16	0.40, 3.40
Chemotherapy Yes No	0.56	0.71	0.22, 2.26

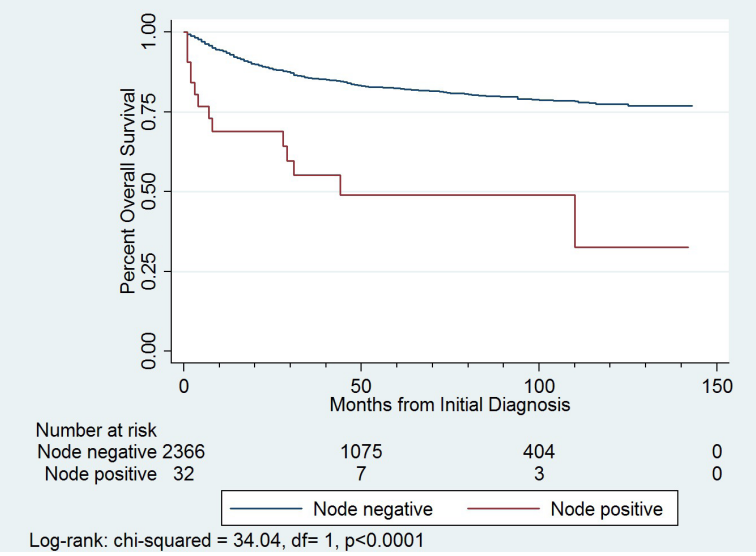

Figure 1. Kaplan-Meier Curve comparing Disease-Specific Survival among chondrosarcoma patients with or without regional nodal involvement at diagnosis.

Poster 117 3025747

CLEAR CELL CHONDROSARCOMA: REPORT OF 7 CASES AND METAANALYSIS OF LITERATURE

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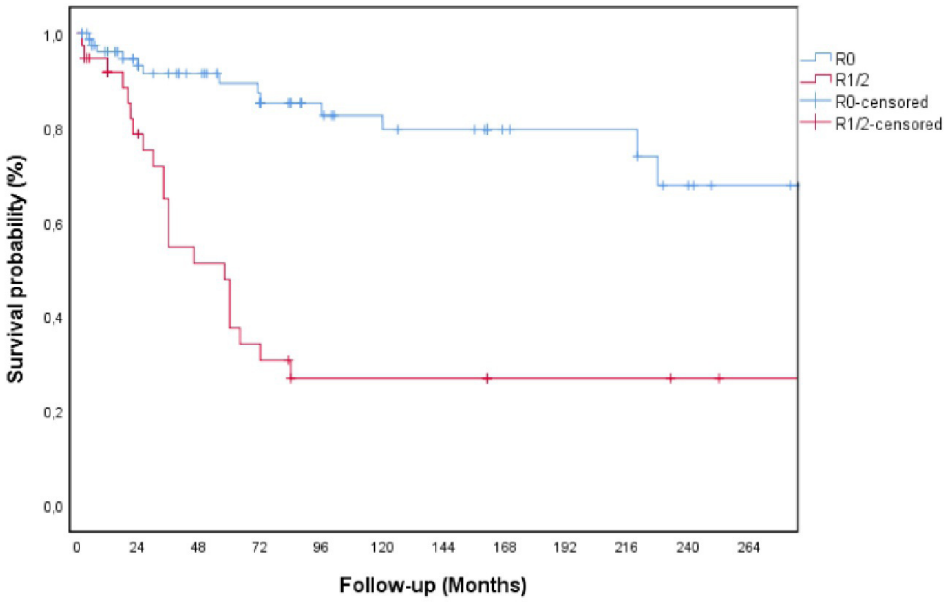
Objective: Clear cell chondrosarcoma is a rare subtype of chondrosarcomas; usually it means a passive, low-grade tumour. The experience of even specialized musculoskeletal centres is limited. The aim of this work is to analyse our own treatment results and those of the published studies regarding the behaviour and outcome of the treatment of clear cell chondrosarcomas.

Methods: We could find 7 cases in the data base of our hospital. 187 cases could be evaluated by the literature research (head as location has been excluded). The mean age at the time of diagnosis was 40 years. Two third of patients were male. The mean follow-up time was 109 months.

Results: Surprising was a high rate of local relapse (32 %) and metastases (24%) compared to low-grade conventional chondrosarcomas. A lot of the recurrences were observed later than 10 years. The uncommon spreading of the metastases with infestation of spine is an additional fact of the special behaviour and higher aggressiveness of clear cell chondrosarcomas. 10-year overall survival was almost 80 %, 10-years disease free survival 60 %. The rate of local relapse was clearly depending on the resection margin; however there was no correlation with grade of differentiation of the tumour. The development of metastases was affected by the factor local relapse; we could not observe a significant association with R1 resection.

Conclusion: With regard of this data the wide resection is surely a single valid treatment option. Clear cell chondrosarcomas seems to be more agressiv tumor compared to low grade chondrosarcomas. Long term follow-up longer 10 years seems to be necessary in the aftercare of clear cells chondrosarcomas.



Poster 118 3042869

PROGNOSTIC FACTORS FOR SURVIVAL IN DEDIFFERENTIATED CHONDROSARCOMA

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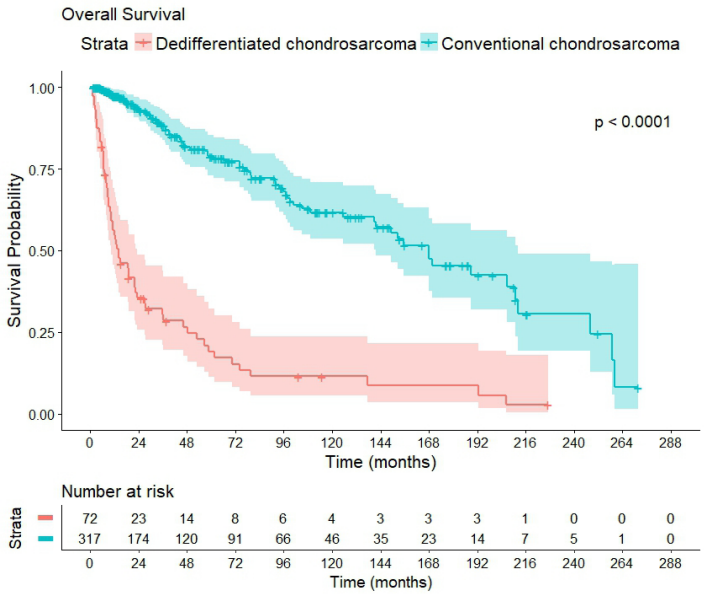
Objective: Dedifferentiated chondrosarcomas (DDCSs) are uncommon cartilaginous tumors that are comprised of both lower-grade conventional chondrosarcoma and high-grade non-cartilaginous sarcoma components. They are highly malignant tumors with a dismal prognosis and present a significant challenge in clinical management. In this study, we aim

to characterize the impact of clinicopathological features and treatment modalities on the clinical outcomes of patients with DDCS treated at our institution.

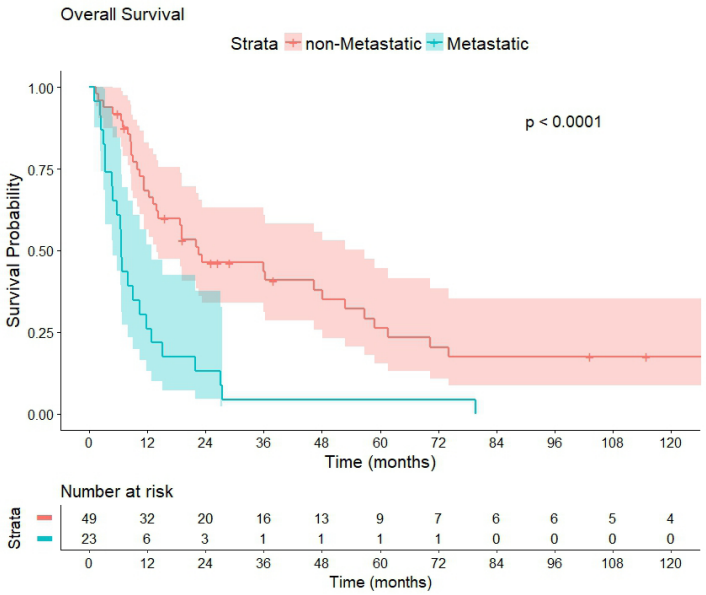
Methods: In an IRB approved retrospective protocol, we identified 72 patients with DDCS treated at our institution between 1993 and 2017 and collected the clinical information. Overall survival (OS), local relapse-free survival, metastasis-free survival, and progression-free survival (PFS) were estimated using the Kaplan-Meier method. The multivariate Cox proportional hazards regression was used to analyze survival outcomes and risk variables.

Results: There were 45 men and 27 women with a median age of 60.5 years (range: 29-92 years). Femur (44.4%), pelvis (22.2%), and humerus (12.5%) were most commonly involved sites. Twenty-three patients (31.9%) presented with distant metastasis at diagnosis, including lungs, bones, soft tissue, liver, and heart, and 3 (4.2%) of them also had regional lymph node involvement. With a median follow-up of 13 months (range: 1-227 months), the median OS was 13.9 months. The 2-year OS and PFS rates were 35.6% and 27.7%, respectively. On multivariate analysis, pathological fracture, larger tumor size, lymph node involvement, metastasis at diagnosis, extra-osseous extension, undifferentiated pleomorphic sarcoma component correlated with worse OS, whereas surgical resection and chemotherapy were associated with improved OS. Among the 49 patients without metastasis at diagnosis, 17 (34.7%) developed a local recurrence. Thirty-one patients (63.3%) developed distant metastases at a median interval of 18.1 months (range: 6.2-30.0 months). On multivariate analysis, R1/R2 resection was related with local recurrence, while macroscopic dedifferentiated component was associated with distant metastasis.

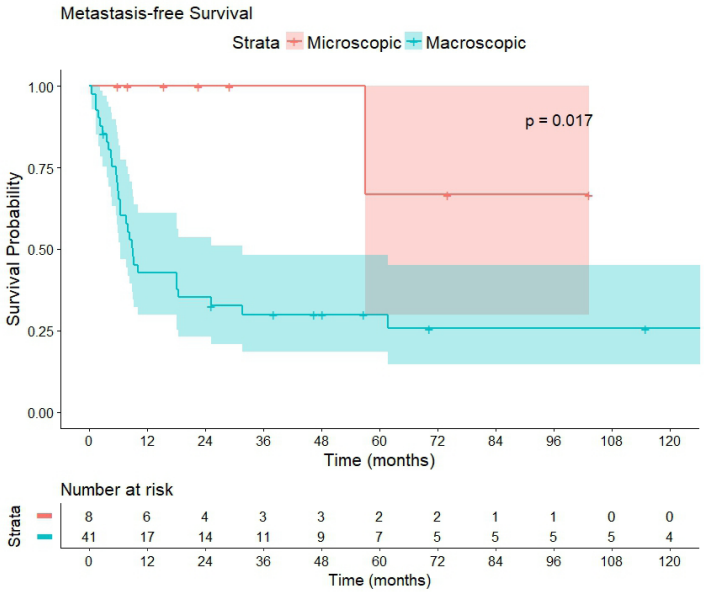
Conclusion: The prognosis of DDCS is worse than conventional chondrosarcoma. Complete surgical resection of the tumor remains a significant prognostic factor for local control. More trials are warranted to further explore the effectiveness of chemotherapy in selected DDCS patients.



Kaplan-Meier curves of overall survival in patients with dedifferentiated chondrosarcoma and intermediate-to-high grade conventional hyaline/myxoid chondrosarcoma.



Kaplan-Meier curves of overall survival in patients with dedifferentiated chondrosarcoma with and without metastasis at diagnosis.



Kaplan-Meier curves of metastasis-free survival in patients with non-metastatic dedifferentiated chondrosarcoma according to the size of dedifferentiation.

Poster 119 3042731

DRUG REPURPOSING AS A SOURCE OF INNOVATIVE THERAPIES IN CHONDROSARCOMA

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Objective: Chondrosarcoma, a rare bone sarcoma arising from transformed chondrocytes, is treated primarily with surgical resection. For non-resectable chondrosarcomas chemo- and radiotherapy are largely ineffective for the most common subtypes of the disease, therefore new treatment options are urgently needed.
Clinical research in OS is hampered by a limited pipeline of new agents. Drug repurposing, an alternative development pathway that seeks to reuse existing drugs as the source of new treatment options, represents an interesting opportunity to solve this issue. The drug repurposing strategy utilises existing data on safety, dosing and clinical experience. Our goal was to list existing drugs, including non-cancer drugs, active against chondrosarcoma to prioritize future research and trials.

Methods: We used the Repurposing Drugs in Oncology (ReDO) list of 255 approved non-cancer drugs. We queried PubMed for each drug and screened all abstracts to assess relevance, type of evidence (in vitro, in vivo, human data). A similar process was used to generate a database of PubMed abstracts for licensed cancer medications with any type of data in chondrosarcoma.

Results: From the 255 ReDO non-cancer drugs, 20 (8%) have evidence of activity against chondrosarcoma. Of these, 4 (2%) are supported by human data (marked with *).

Acetylsalicylic acid	Chloroquine *	Melatonin	Plerixafor
Alendronic Acid	Ciprofloxacin	Metformin	Simvastatin
Amiloride	Disulfiram	Midazolam	Sirolimus *
Caffeine *	Doxycycline	Omeprazole	Valproic Acid
Celecoxib	Esomeprazole	Pioglitazone	Zoledronic Acid *

Few of these repurposed agents show direct cytotoxic effects – mechanisms of action include potentiating the effects of chemotherapy agents and effects on the tumour microenvironment. Additionally, a similar number of licensed cancer medications have some data (case reports, retrospective or clinical trial) of activity in chondrosarcoma, including: cyclophosphamide, imatinib, nivolumab, pazopanib, sunitinib and others.

Conclusion: A range of evidentiary sources indicate that a number of licensed non-cancer and cancer drugs have anti-chondrosarcoma activity. The level of evidence includes human data, including data from case reports, retrospective analyses and small clinical trials. Given that chondrosarcoma is generally accepted to be relatively resistant to standard cytotoxics investigation, pre-clinical and clinical, into the combination of non-cancer and cancer drugs is warranted.

Poster 120 3042764

CISPLATIN IN ADVANCED CHORDOMA: A RETROSPECTIVE CASE-SERIES ANALYSIS

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Objective: There is no standard systemic treatment for patients with advanced chordoma. Few tumor responses to cytotoxic chemotherapy have been reported and mainly refer to high-grade/dedifferentiated chordoma. We report herein on the activity of cisplatin (CDDP) in a retrospective series of advanced adult chordoma patients.

Methods: We retrospectively reviewed a series of adult patients with advanced chordoma treated with weekly cisplatin (CDDP) (20-30 mg/sqm) from Jan 2008 to Jan 2018 in 6 centers of the Italian Rare Cancer Network. Pathological diagnosis was confirmed in all cases by the nuclear expression of brachyury (immunohistochemistry). Treatment was continued according to patient tolerability, until progression or 600 mg/m^2 cumulative dose of CDDP. Tumor response was evaluated according to RECIST 1.1. Survival functions were estimated by Kaplan-Meier method.

Results: Fourteen patients (M/F = 9/5, mean age = 59 yrs - range = 38-83 yrs, locally advanced/metastatic = 11/3, naïve/pretreated = 2/12, conventional/dedifferentiated/chondroid/not specified = 9/2/1/2) were identified. All cases were evaluable for response and were progressing before treatment start. At last follow-up, one patient is still on treatment, 13 pts stopped their treatment (6 due to disease progression; 7 with stable disease, after reaching the limit cumulative dose). Median time on treatment was 7 months (CI 95% 2.7 – 11.7). No serious adverse events related to CDDP were observed, even in patients who received the highest cumulative doses. Best responses by RECIST were: 1 partial response (PR; 7%), 9 stable disease (SD; 64%) and 4 progressive diseases (PD; 28%). The only PR was observed in a dedifferentiated chordoma, while SD was achieved in chondroid and conventional subtypes. At a median FU of 17 months (CI 95% 8.2 – 45.1), the median progression-free survival was 7 months (CI 95% 2.7 – 16.1, range = 1–27). Progression-free survival rate at 6 months was 55% and overall survival was 27 months (CI 95% 21 – nr).

Conclusion: This retrospective series suggests that CDDP has some activity in advanced chordoma. Although the only dimensional response was seen in a dedifferentiated chordoma, more than 50% of patients were progression-free at 6 months, while being all progressing at treatment start. Weekly CDDP was well tolerated and it can be considered a palliative option in selected patients with advanced chordoma, even in the elderly.

Poster 121 3007279

WHAT IS THE RISK OF MORTALITY FOLLOWING LOCAL RECURRENCE OF A SURGICALLY TREATED CHORDOMA OF THE SACRUM?

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Objective: Sacrococcygeal chordomas have historically been treated surgically, with or without additional radiotherapy. However, even with negative margins and adjunctive therapies, there remains a high risk of local recurrence. Although essential for counseling, decision-making, and prognostication, the mortality risk of patients experiencing recurrence remains poorly described. The purpose of this study was to evalate 1) What is the expected mortality of patients undergoing resection of a primary sacrococcygeal chordoma following local recurrence? 2) How does the life expectancy of patients experiencing a local recurrence compare to patients without recurrence? and 3) What is the relationship between patient age, local recurrence, and mortality?

Methods: 193 patients from four tertiary sarcoma centers undergoing resection of primary sacrococcygeal chordomas from 1990 to 2015 were reviewed. Mean patient age was 59 (range 13-88), with 124 males and 69 females and 89 patients received adjunctive pre- or postoperative radiotherapy. Patients were followed for a mean of 7 years (range 1 to 25).

Cumulative incidence functions and competing risks regression for death due to disease and non-disease mortality were employed to analyze mortality trends following local disease recurrence.

Results: *What is the expected mortality of patients undergoing resection of a primary sacrococcygeal chordoma following local recurrence?*
Overall 2-, 5- and 10-Year survival for all 193 patients was 91%, 76%, and 59%, respectively (Figure 1A). During the course of follow-up, 36 patients (19%) experienced a local recurrence. Patients with local recurrence demonstrated 92% 2-Year survival, 72% 5-Year survival and 39% 10-Year survival (Figure 1B).

How does the life expectancy of patients experiencing a local recurrence compare to patients without recurrence?
Patients with local recurrence demonstrated statistically comparable (p = 0.10) survival to those who did not experience local recurrence. However, a trend towards lower survival was noted over time for patients experiencing local recurrence, with 5% lower 5-Year survival and 38% lower 10-Year survival in the local recurrence free group (Figure 1B).

What is the relationship between patient age, local recurrence, and mortality?
All patients experiencing local recurrence and subsequent mortality experienced morality due to disease. For patients with local recurrence, age less than 55 years conferred similar mortality rates (2 Years: 0%, 5 Years: 25%, 10 Years: 75%) compared to patients ≥ 55 years (2 Years: 13%, 5 Years: 30%, 10 Years: 54%) (p = 0.82, Figure 2A). Amongst patients without local recurrence, patients under 55 years of age had similar risk of death due to disease compared to patients ≥ 55 years (8% at 10 years, p = 0.24). In contrast, patients ≥55 were 2.1-fold more likely to experience death due to other causes (30% at 10 years) than patients under 55 (14% at 10 years, p = 0.01, Figure 2B).

Conclusion: Patients with local recurrence following resection of a primary sacrococcygeal chordoma trended towards 38% higher 10 year mortality than those without recurrence. Mortality risk over time is similar in the setting of local recurrence, whether patients are young (< 55 years) or older (≥ 55 years). For older patients without recurrence, death due to non-disease causes occurs over 2-fold more commonly than death due to disease, and should be taken into account during patient counselling and decision making.

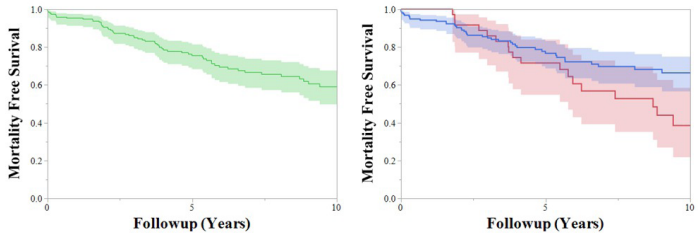

Figure 1A-B: A) Overall mortality free survival for all patients undergoing resection of primary sacrococcygeal chordoma (Green). B) Mortality free survival for patients experiencing local recurrence (Red) and those without local recurrence (Blue).

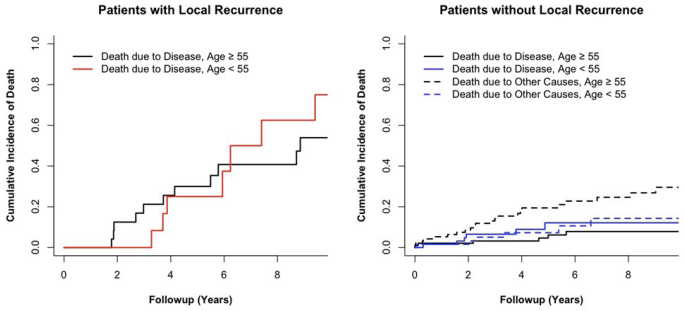

Figure 2: Cumulative incidence of death due to disease and death due to other causes by patient age for A) Patients with local recurrence, and B) Patients without local recurrence.

Poster 122 WITHDRAWN

Poster 123 3019538

FACTORS ASSOCIATED WITH 5-YEAR SURVIVAL IN CHORDOMAS: A NATIONAL CANCER DATABASE STUDY

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Objective: We investigated the largest registry of primary bone tumors, the national cancer database (NCDB), to investigate current treatment trends for chordomas and determine prognostic factors for survival. Our hypothesis was that surgical resection in addition to radiotherapy would be associated with improved survival.

Methods: We retrospectively reviewed 1456 patients in the NCDB from 2004-2015 with a histologic diagnosis of chordoma. Multivariate analysis was performed to determine survival determinants. The study variables included age, gender, race, insurance status, annual income, comorbidity index, high versus low volume surgical center, location of tumor, tumor grade,

tumor size, surgical margin, radiation therapy. The Kaplan-Meier (KM) method with statistical comparisons based on the log-rank test was used to assess survival rates between individual variables.

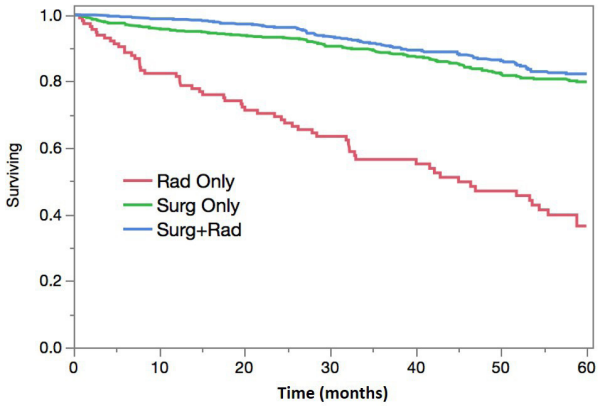
Results: The cohort included 1456 patients; including chordomas of the sacrum (n=563), the mobile spine (n=362), and the skull base (n=531). The overall 5-year survival rate was 75.7%. Skull base chordomas had a 5-year survival of 83.9%, which was significantly improved over chordomas of the sacrum (71.7%, p<0.001) and mobile spine (69.8%, p<0.001). Multivariate analysis demonstrated significantly improved 5-year survival with age <65 years, income above national average, private health insurance, comorbidity index <2, histologic low-grade tumor, tumor size <5cm, location of tumor, surgical resection, and negative surgical margins. Radiotherapy was not associated with improved 5-year survival in the multivariable analysis. Treatment of the chordomas included surgery alone (n=616), surgery and radiotherapy (n=526), and radiotherapy alone (n=115). The 5-year survival rates of surgery alone (79.9%) and surgery and radiotherapy (82.3%) were significantly improved over radiotherapy alone (36.5%, p<0.001). However, the difference between surgery alone and surgery plus radiotherapy did not reach statistical significance. Following surgical resection, achieving a negative margin was associated with improved 5-year survival compared to having a positive margin (84.8% v. 76.4%, p=0.005). Adjunct radiotherapy did not statistically improve survival in patients with a positive surgical margin, compared to no radiation (77.9% v. 73%, p=0.198).

Conclusion: This study is the largest powered study investigating survival determinants in patients with axial chordomas. Surgical resection with a negative surgical margin provides the greatest 5-year survival rate in chordomas. Radiotherapy was not associated with improved survival in the multivariable analysis. Younger age, private health insurance, increased income, fewer medical co-morbidities, low grade tumors, tumor size < 5cm, skull base chordomas, and achieving negative surgical margins were significant factors for improved 5-year survival.

Table 1. Independent predictors of mortality in multivariate proportional hazards analysis

Variable	HR	Lower 95%	Upper 95%	P value
Patient variables				
Age (years) (Ref=0-45)	Ref			
45-65	1.37	0.97	1.94	0.07
>65	3.17	2.08	4.86	**<0.001***
Female sex (Ref=Male)	0.93	0.75	1.15	0.50
Hispanic (Ref=Non-Hispanic)	1.27	0.80	2.00	0.306
Race (Ref=Caucasian)				
African-American	0.83	0.49	1.41	0.50
Asian	0.81	0.48	1.39	0.45
Comorbidity Score >1 (Ref=0-1)	1.79	1.12	2.85	**<0.013***
Insurance (Ref=Private Insurance)				
Medicare	1.29	0.92	1.82	0.13
Medicaid	2.28	1.45	3.59	**<0.001***
No insurance	1.94	1.03	3.68	**<0.04***
Income below median ($48,000)	1.34	1.05	1.70	**0.01***
Tumor and treatment variables				
Grade (Ref=Low grade)				
Intermediate grade	0.75	0.37	1.54	0.44
High grade	2.29	1.26	4.17	**0.007***
Size of tumor (Ref <5cm)	1.78	1.33	2.39	**<0.001***
Surgery (Ref=No surgery)				
All types	0.45	0.32	0.60	**<0.001***
Local resection	0.48	0.34	0.67	**<0.001***
Radical resection	0.42	0.30	0.60	**<0.001***
Surgical margins positive	1.51	1.09	2.10	**0.014***
Radiation use	1.00	0.64	1.56	0.98
Location spine (Ref sacrum)	1.38	1.05	1.82	**0.019***

Figure 1: Kaplan Meier Curve of Survival Based on Treatment Type



Poster 124 WITHDRAWN

Poster 125 3038724

CIRCULATING TUMOR DNA IS DETECTABLE IN TRANSLOCATION POSITIVE RHABDOMYOSARCOMA: A REPORT FROM THE CHILDREN'S ONCOLOGY GROUP (COG)

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Objective: Circulating tumor DNA (ctDNA) and its prognostic value has been studied in a wide range of cancer types. To determine the prevalence of detectable ctDNA in alveolar rhabdomyosarcoma (aRMS), we utilized two next-generation sequencing (NGS) assays. TranSS-Seq is a NGS hybrid capture assay developed to detect oncogenic translocations common in pediatric sarcomas, including the *PAX3-FOXO1* and *PAX7-FOXO1* translocation. Tumor copy-number alterations (CNA) can also be detected in cell-free DNA by ultra-low passage whole genome sequencing (ULP-WGS). In a recent pilot study, we demonstrated that both assays can identify ctDNA in a cohort of 7 patients with aRMS. The objective of this study is to determine the prevalence of detectable ctDNA in an expansion cohort of patients with newly diagnosed non-metastatic aRMS using NGS assays designed to detect *PAX*-translocations or copy-number changes.

Methods: Cell-free DNA was extracted from serum samples obtained from patients with newly diagnosed non-metastatic aRMS who enrolled on a single COG trial, ARST0531. Samples were sequenced with a validated custom hybrid capture assay designed to detect oncogenic translocations (TranSS-Seq) and ULP-WGS. BreaKmer and PSTquant algorithms were applied to TranSS-Seq data to detect and quantify a translocation. The IchorCNA algorithm was used to analyze ULP-WGS data to detect and quantify ctDNA by copy-number alterations. We previously demonstrated a limit of detection for the TranSS-Seq assay of approximately 1% ctDNA and 3% for ULP-WGS. Translocations detected at very low allelic fractions

by TranSS-Seq were also confirmed by digital PCR. Clinical data were correlated with ctDNA results.

Results: Serum samples were analyzed from 49 patients, 7 (14.3%) with stage 1, 10 (20.4%) stage 2, and 32 (65.3%) stage 3. Median age at enrollment was 11.53 years (range 0.2-25.02). There were 36 patients with known *PAX3-FOXO1*, 8 with *PAX7-FOXO1* and 5 known to be *FOXO1*-rearranged but the partner was not determined. Two-year event free survival (EFS) and overall survival (OS) were 51% (95%CI, 36.4%-63.9%) and 79.6% (95%CI, 65.4%-88.5%) respectively. ctDNA was detected in 35 (71%) patients overall with 31 (63%) positive by ULP-WGS and 18 (37%) by TranSS-Seq. TranSS-Seq identified *PAX3* as the fusion partner for one patient for which the *FOXO1* partner was previously unknown. The 4 samples that were detected by TranSS-Seq and negative by ULP-WGS had a ctDNA fraction below 3%, consistent with the limit of detection. Stage did not have an impact on detection of ctDNA. There was no difference in ability to detect ctDNA based on fusion type. Interestingly, in some cases for which both methods detected ctDNA, we found that the allelic fraction of the translocation itself was affected by copy-number changes, making it impossible to estimate the allelic fraction of ctDNA by translocation detection alone. We did not observe an association between ctDNA detection and event-free survival. (HR = 1.47 (95% CI = 0.69, 4.94), log-rank p-value = 0.22).

Conclusion: Patients with non-metastatic aRMS have detectable levels of ctDNA that can be measured by NGS assays designed to detect somatic structural events in cell-free DNA. We were able to detect ctDNA in a larger proportion of patients by ULP-WGS despite the previous finding that TranSS-Seq has a lower limit of detection. Sequencing of matched tumor samples are planned to determine the mechanisms of differential sensitivity of each assay. Importantly, the frequency of copy-number alterations seen in this disease make quantification of ctDNA by translocation detection very challenging. Conversely, higher numbers of copy-number changes per sample can be expected to improve the sensitivity of ULP-WGS. Ongoing efforts to analyze a larger cohort of prospectively collected samples will continue to utilize both assays in an effort to confirm which assay will have the most clinical utility.

Poster 126 3042621

RELATIVE FUSION GENE LEVEL IN CIRCULATING CELL-FREE DNA SERVES AS A PROGNOSTIC BIOMARKER IN EWING SARCOMA

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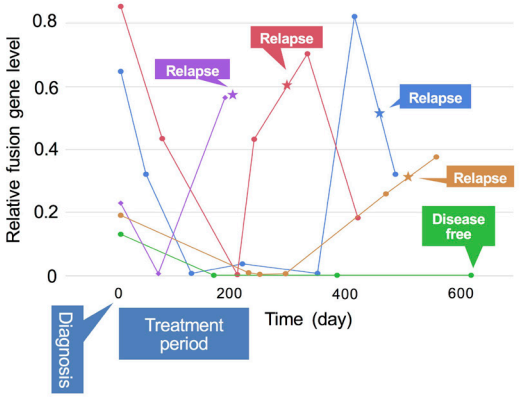
Objective: Circulating cell-free DNA (cfDNA) is fragmented DNA derived from tumors that circulates in the blood of patients. Recent studies demonstrated that the tumor-specific fusion gene could be detected in cfDNA of Ewing sarcoma (ES) patients; however, the potential to be used to monitor tumor burden during the treatment or to predict tumor relapse during the follow-up has been as yet elusive. The objective of this study was to identify whether tumor-specific fusion gene level in cfDNA serve as a prognostic or predictive biomarker in patients with ES.

Methods: Eight patients with ES were treated at Chiba Cancer Center by induction chemotherapy, local treatment, and consolidation chemotherapy from 2008 to 2016. cfDNA was extracted from the serum of each patient, which was drawn at multiple time-points (pre-treatment, completion of the treatment, and follow-up). Multiplex long-range genomic PCR was performed to detect patient-specific genomic breakpoints in each patient using 11 nested primer pairs covering both of the EWS gene and FLI1/ERG genes (Berger M et al, 2013). Real-time PCR probes for digital PCR (ddPCR) were designed based on the genomic breakpoint of each patient. cfDNA quantification was performed by ddPCR (BioRad Qx-200). Relative fusion gene level (RFL; fusion gene copy number / wild KRAS copy number) were calculated in each sample.

Results: Tumor-specific fusion gene in the cfDNA were detected in six (75%) of eight patients with high specificity. In the prognostic and predictive analysis, RFL at pre-treatment status significantly correlated with disease relapse and showed trend toward the bone metastases, although did not associated with tumor necrosis rate after induction chemotherapy. Five patients could be traced the change of RFL during and after the treatment, and those RFLs were highest in the pre-treatment samples and decreased as the treatment progressed. Four patients with relapse displayed an elevation of RFL in advance of clinical manifestation or elevation of lactase dehydrogenase. By contrast, one patient who had never relapsed kept the RFL level under the detection level.



Conclusion: Tumor-specific fusion gene level in cfDNA would be useful as prognostic biomarker in patients with ES.Tumor-specific fusion gene level in cfDNA would be useful as prognostic biomarker in patients with ES.

Poster 127 3042631

PILOT STUDY EVALUATING THE CONCORDANCE OF CIRCULATING TUMOR DNA ALTERATIONS WITH TUMOR-BASED SEQUENCING IN SOFT TISSUE SARCOMA

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Objective: Soft tissue sarcomas (STS) represent a diverse population of tumors with mutations that are often diagnostic and/or actionable. Platforms to detect circulating tumor DNA (ctDNA) have rapidly increased in popularity as they may avoid the morbidity associated with standard invasive biopsy techniques. However, the optimal STS subtype for ctDNA profiling and its concordance with comprehensive genomic profiling (CGP) from the solid tumor are poorly characterized. To this end, we report the preliminary outcomes of a single institution experience comparing mutational results from ctDNA and solid tumor CGP in advanced STS patients.

Methods: We performed a single-institution biomarker trial (IRB: OSU-17159) and identified STS patients who had undergone FoundationOne Heme/Sarcoma (F1H/S) CGP in four distinct cohorts: dedifferentiated liposarcoma (DDLPS), leiomyosarcoma (LMS), malignant fibrous histiocytoma/undifferentiated pleomophic sarcoma (MFH/UPS), and gastrointestinal stromal tumor (GIST). STS patients within these cohorts who had radiographically measurable tumors were then approached for additional profiling using the FoundationAct ctDNA panel (FACT). Genes and specific exons overlapping on both CGP panels were reviewed for concordance using descriptive statistics. We defined complete concordance describes all possible matching genes on both panels. Partial concordance was defined as at least one gene matching but not all possible genes.

Results: As of this writing, 20 of a planned 24 sarcoma patients have successfully completed FACT profiling. Complete concordance rates by subgroups are as follows: LMS, 4 of 5; DDLPS, 1 of 6; GIST 0 of 6; MFH/UPS, 1 of 3. Mutations in NF1 and TP53 were the most concordant genes: NF1 = 3 of 3, TP53 = 6 of 8. Contrarily, alterations in CDKN2A and gene amplifications were poorly recognized in FACT profiling: CDKN2A = 0 of 2, CDK4/MDM2 amplification=2 of 12. Of note, 1 out of 5 GIST patients were partially concordant. FACT profiling identified additional mutations in 3 of 6 DDLPS patients and zero additional mutations in all other cohorts.

Conclusion: Sarcoma subtype heterogeneity likely drive the concordance of ctDNA profiling with solid tumor CGP. The noise inherent in untargeted ctDNA sequencing approaches where mutational statuses are unknown may be a limiting factor when compared to the detection of previously established alterations. Nevertheless, the high concordance in LMS may justify the usage of the FACT panel in this subtype but further confirmatory studies and mining of existing additional data sources will need to be performed.

Poster 128 3042674

CIRCSARC; NON-INVASIVE MONITORING OF SARCOMAS PATIENTS BY CIRCULATING TUMOUR DNA IN PLASMA

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[1]Department of Tumor Biology, Oslo University Hospital, Oslo, Norway; [2]Department of Pathology, Oslo University Hospital, Oslo, Norway; [3]Department of Surgery, Oslo University Hospital, Oslo, Norway; [4]Department of Core Facilities, Oslo University Hospital, Oslo, Norway; [5]Department of Oncology, Haukeland University Hospital, Bergen, Norway; [6]Department of Clinical Science, University of Bergen, Bergen, Norway; [7]Department of Oncology, Oslo University Hospital, Oslo, Norway

Objective: Advances in technology allows today to use blood plasma as a “liquid biopsy”, examining circulating tumour DNA (ctDNA) shed by the tumour cells into peripheral blood. ctDNA in plasma carries tumour-specific alterations that can be used to monitor minimal residual disease, tumour burden and evolution throughout the course of the disease. The CircSarc study aims to provide new insights into the clinical utility of liquid biopsies in soft tissue sarcomas.

Methods: In the CircSarc Soft Tissue Sarcoma study, we have enrolled 35 high-grade STS patients with localised disease that have received surgery with a curative intent. Patient’s tumour and germline DNA have been exome sequenced to identify tumour-specific mutations. Plasma from each patient have been collected before and after surgery, and longitudinally throughout the course of their disease, with a follow-up up to 54 months. Circulating tumour DNA has been isolated and sequenced using a comprehensive 900 cancer gene panel to identify and quantify the levels of somatic mutations in plasma throughout the course of the disease.

Results: We have successfully detected somatic mutations in plasma, at time of surgery, in 44% of the samples. Mutations

present at an allele frequency > 20% in tumour can be robustly identified in plasma. In a proof-of-concept study, we have shown that that levels of tumour-specific mutations in liquid biopsies correlated to clinical manifestation of metastatic disease in aggressive sarcoma. Currently we are analysing longitudinal samples to reveal the presence and levels of ctDNA in plasma throughout the course of the disease.

Conclusion: Our study has successfully detected the presence of ctDNA in sarcoma patients and will provides new insights into the clinical significance of ctDNA in sarcomas. By repeated sampling of liquid biopsies, somatic mutations identified in ctDNA can be used as a unique non-invasive tumour-specific biomarkers for monitoring tumour burden throughout the disease course.

Poster 129 3042933

ULTRA-SENSITIVE DETECTION OF TRANSLOCATIONS IN THE CELL-FREE DNA OF PEDIATRIC SARCOMA PATIENTS

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Objective: A major challenge in the care of pediatric sarcoma patients is to develop highly sensitive, non-invasive methods to accurately diagnose and monitor disease. Currently, biopsy serves as the gold standard for diagnosis, but the risks of anesthesia and surgical complications, along with a failure to characterize the true heterogeneity of disease make this method less than ideal. Disease progression and response to therapy are monitored by radiologic exams, however these studies are expensive, difficult to interpret, lack the sensitivity to detect early relapse, and may actually increase the risk of future malignancies due to ionizing radiation. One approach to address this challenge is the analysis of circulating tumor DNA (ctDNA). Cell free DNA (cfDNA) is released into the plasma of individuals from healthy, inflamed, or tumor cells as they undergo apoptosis and necrosis. ctDNA represents a small fraction of cfDNA in cancer patients and contains tumor-specific alterations. It holds promise as a highly sensitive and specific biomarker. A limitation in applying liquid biopsy in clinical practice is the need to develop PCR or other DNA analysis methods to detect alterations specific to a single patient. We have developed a more widely-applicable “off-the-shelf” test that does not involve a patient-specific design.

Methods: Our CAPP-Seq (CAncer Personalized Profiling by deep Sequencing) technique involves designing a “selector” comprised of custom-designed oligonucleotide probes that tile across genomic regions of interest. These oligonucleotide probes are used to enrich for the relevant ctDNA via hybrid capture, followed by ultra-deep sequencing to analyze alterations in the selected regions. Our selector was applied to pre-treatment plasma samples from newly diagnosed or newly relapsed pediatric sarcoma patients. Additionally, plasma samples were analyzed at key timepoints over the course of treatment.

Results: Pediatric sarcoma patients had higher levels of cfDNA, when compared to published levels in adult cancer patients. Canonical translocations were detected in the plasma of 13/14 (93%) pediatric sarcoma patients. This was confirmed by analysis of matched tumor samples, when available. Patients with metastatic disease had higher ctDNA levels, compared to non-metastatic patients. ctDNA levels correlated with clinical course and, in some cases, rising ctDNA levels predicted relapse, earlier than was clincally apparent by imaging studies.

Conclusion: ctDNA analysis holds promise as an ultra-sensitive and specific tool for monitoring tumor burden. Our assay was able to detect ctDNA in the plasma of metastatic and non-metastatic pediatric sarcoma patients at diagnosis. Furthermore, we demonstrated that ctDNA levels correlated with clinical response to therapy. In some cases, ctDNA levels proved more sensitive than imaging, detecting minimal residual disease and predicting relapse.

Poster 130 3043078

NONINVASIVE MOLECULAR PROFILING AND RESPONSE MONITORING BY CELL-FREE DNA ANALYSIS IN OSTEOSARCOMA

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Objective: Innovative approaches to monitoring and management of patients with osteosarcoma (OS) are urgently required. Noninvasive molecular profiling using plasma cell-free DNA (cfDNA) has shown great promise in the management of adult cancers, but little is known in the pediatric setting. The challenge of applying cell-free DNA based profiling in OS is the lack

of recurrent genetic markers to track tumor-derived information in plasma. We have adopted a tiered approach utilizing multiple methodologies to non-invasively monitor disease burden and screen for clinically relevant mutation signatures via molecular profiling of cell-free DNA in osteosarcoma.

Methods: Plasma cfDNA samples were serially obtained from osteosarcoma patients for whom targeted exome sequencing and matched normal were available. Whole genome sequencing (WGS) was performed at a shallow depth (~0.1x) and genome-wide Z-scores, a metric to determine tumor-derived median mutant allele fractions (MAFs), were compared with clinical disease burden. For those patients with high tumor fractions (z-score of 2.5 or above corresponding to ~10% mutant allele fraction in cfDNA) whole exome sequencing was then performed. These exomic analyses were used to investigate (i) signature analyses (ii) other somatic mutations or copy number alterations that are enriched at the time of disease progression.

Results: Shallow whole-genome sequencing was found to accurately identify copy number changes when compared with tumor profiling data, and genome-wide Z-scores were found to correlate with clinical disease burden. In patients for whom genome-wide Z-scores were 2.5 or greater, whole exome sequencing and mutational signature analysis was feasible via cfDNA samples.

Conclusion: A tiered approach using multiple methodologies allows for serial and non-invasive molecular profiling and response monitoring in patients with osteosarcoma. Testing of additional approaches, including both patient specific and disease specific targeted exome panels for monitoring of minimal residual disease in the post-treatment setting are underway, and will complement the approaches described here.

Poster 131 3016587

RNA-SEQUENCING OF TUMOR-EDUCATED PLATELETS, A NOVEL BIOMARKER FOR BLOOD BASED SARCOMA DIAGNOSTICS

Kimberley M. Heinhuis[1]*; Sjors In 't Veld*[2]*; Govert Dwarshuis*[2]*; Daan van den Broek*[3]*; Nik Sol*[4]*; Myron Best*[2]*; Anne Miek Koenen*[6]*; Winan J. van Houdt*[6]*; Frits van Coevorden*[6]*; Rick Haas*[5]*; Tom Wurdinger*[2]*; Neeltje Steeghs*[1]
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Objective: *Introduction:* Sarcoma is a rare and heterogeneous group of malignancies arising from soft tissues. The potential of development of metastases is high and methods for early diagnostics are poor. Blood-based liquid biopsies may overcome this clinical problem. Recently, it has been shown that platelets play a major role in tumor microenvironment. Tumor-educated platelets (TEP) can ingest circulating mRNA and they show specific splice events in response to external stimuli. This leads to a highly dynamic mRNA repertoire with potential applicability for cancer diagnostics.

Aim: To evaluate the potential of TEPs for blood-based diagnostics and monitoring of patients with sarcoma.

Methods: Sarcoma patients with current disease and former sarcoma patients (cancer free for at least 3 years) were included from the NKI. RNA-sequencing data was mapped to the human genome, and quantified read counts were subjected to ANOVA statistics and a support vector machine (SVM) classification algorithm. Highly correlating mRNAs of a sarcoma subtype tumor (liposarcoma, leiomyosarcoma, gastrointestinal stroma or 'miscellaneous') were compared to all other tumor subtypes and to healthy donors (HD) from the VUmc to find a sarcoma specific signature.

Results: We successfully sequenced the spliced platelet RNA collected from 25 sarcoma patients, 15 former sarcoma patients, and 61 age- and gender-matched HD. Differential splicing ANOVA analysis indicated a distinctive platelet RNA expression pattern of 189 genes (FDR<0.05) in sarcoma (n=15) compared to non-sarcoma; [HD (n=6) and former sarcoma patients (n=9)]. Development of a machine learning classification algorithm for the blood-based diagnosis of sarcoma reached an accuracy of 85% in the 20-samples sized validation cohort (AUC: 0.84, p<0.001). Analysis of a combined HD plus former sarcoma patients cohort versus sarcoma patients indicated that the platelet RNA of cancer-free patients regresses towards those of HD. The high number of genes found with low FDR thresholds between healthy and sarcoma signaled that institutional bias may be present.

Conclusion: Our data indicates that TEP RNA-based liquid biopsies might enable for blood-based sarcoma diagnostics. This technique could potentially be used for the monitoring of tumor recurrence in post-operative sarcoma patients. Thus far,

the number of samples analyzed remains small, and potential bias introduced by the two institutes of sample origin needs to be taken into account.

Poster 132 3042854

TREATMENT MONITORING IN PATIENTS WITH PEDIATRIC SARCOMAS USING CIRCULATING TUMOR DNA ANALYSIS: A FEASIBILITY STUDY

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Objective: Accurate treatment monitoring can help optimize management of pediatric cancer patients. Currently, there are no effective circulating biomarkers for monitoring response to treatment or detecting minimal residual disease in pediatric sarcoma. Using a novel sequencing approach that we developed called TARgeted DIgital Sequencing (TARDIS), we evaluated feasibility of circulating tumor-derived DNA (ctDNA) analysis for monitoring treatment response.

Methods: Pediatric patients with malignant solid cancers were enrolled in a prospective observational study. Tumor and germline DNA from 4 sarcoma patients was extracted and analyzed using whole exome sequencing. Primers targeting patient-specific founder somatic mutations and rearrangements were designed. Cell-free DNA from plasma was extracted using MagMAX Cell-Free DNA isolation kit and an in-house droplet digital PCR assay was used to assess cfDNA yield and fragmentation. Feasibility of ctDNA detection in plasma samples was evaluated using TARgeted DIgital Sequencing (TARDIS), a multiplexed approach that combines linear pre-amplification, adapter ligation, molecular tagging and informatics to achieve high sensitivity and precision for ctDNA detection and quantification.

Results: In 4 sarcoma patients (3 Ewing sarcomas, 1 rhabdomyosarcoma), exome sequencing yielded 20-148 founder somatic mutations per tumor. We designed target-specific multiplexed primer panels for 4-14 mutations per patient. In preliminary results, we analyzed equivalent of 900 µL or less plasma volume using TARDIS from 4 time points each in the first two patients. In patient 1, all 5 targeted mutations including an EWSR1-FLI1 fusion were detectable at diagnosis at an average allele fraction (AF) of 8.2%. ctDNA became undetectable after the first cycle of chemotherapy, but 1/5 mutations (mutation AF: 0.05%) were detectable prior to local control with an average AF of 0.012%. ctDNA became undetectable 6 weeks after local control, consistent with no viable tumor detected on resection or imaging. In patient 2, 1/4 targeted mutations was detected at diagnosis at 0.034% AF, became undetectable after first cycle of chemotherapy. Prior to local control, ctDNA became detectable again at 0.008% AF and continued to rise after local control to 0.033% AF.

Conclusion: Preliminary results show that TARDIS enables disease monitoring in pediatric solid tumor patients using circulating tumor DNA analysis, using multiplexed analysis of patient specific somatic mutations and genomic re-arrangements. On-going work involves analysis of additional plasma volume and ctDNA analysis in additional pediatric sarcoma patients.

Poster 133 3042867

DESMOID TUMORS: A SINGLE INSTITUTION EXPERIENCE

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Objective: Desmoid Tumors (DT) are rare, locally invasive, non-metastasizing mesenchymal proliferations. The most common primary sites are abdominal wall (ABW), extremities (EXT), trunk (TRU) and mesenteric areas (INT). Most DT occur sporadically, but they can be associated with familial adenomatous polyposis syndrome (FAP). Management of DT requires a multidisciplinary approach because of the unpredictable disease course given that spontaneous regression, long-lasting stable disease and disease progression could occur without reliable and validated predictive factors. In last years, the mainstay of treatment switched from the surgery-first approach to more conservative approaches, ranging from wait and see policy to multimodal therapies including hormonal therapy, nonsteroidal antiinflammatory drugs (NSAIDs), chemotherapy and radiation.

Methods: We conducted a retrospective study of 122 confirmed cases of sporadic DT observed at our Institution. Medical

records, operative reports, radiological charts and pathology were reviewed. Demographics, clinical, pathological and treatment variables were analyzed. We calculated event free survival (EFS) based on the occurrence of relapse or residual disease after surgery or change in treatment strategy during non-surgical approach.

Results: A total of 122 patients, 82 (67.2%) females and 40 (32.8%) males, were observed with median age of 38 years (IQR 32-47). Mean dimension of the primary tumor was 45 mm (IQR 31-70); tumor locations were the following: ABW 58 (47.5%), TRU 28 (23.0%), EXT 24 (19.7%), INT 12 (9.8%). As first approach, upfront surgery was performed in 92 patients (75.4%), wait and see strategy in 26 patients (21.3%), systemic therapy in 4 patients (3.3%). However the approach has significantly changed over the years, being the wait and see approach the most frequent treatment in the last five years. Relapse or residual disease after surgery was observed in 42 pts (45.6%), change in first treatment strategy during non-surgical approach in 13 patients (44.8%). In our study spontaneous regression occurred in 2 (8%) patients who were firstly managed with a wait and see approach. Median survival was 17.2 months for DT of the trunk, 26.4 months for DT of the extremities, not reached for ABW and INT group. Median survival was 36 months for the surgical group and 17.9 month for non-surgical group (*p=ns*).

Conclusion: The choice of first treatment of DT (surgery vs wait and see approach) did not influence the EFS. Therefore, wait and see policy has to be take into account, considering the less invasive nature of this approach. Factors influencing the outcome of DT remain unclear. A multidisciplinary management of DT is mandatory to evaluate benefits and risks associated with the proposed treatment.

Poster 134 3042336

YOUNG PATIENTS WITH DESMOID FIBROMATOSIS HAVE HIGH RATES OF LOCAL RECURRENCE: IS IT TIME TO RETHINK TREATMENT STRATEGIES IN THIS SUBSET?

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Objective: To evaluate long-term outcomes in patients with desmoid fibromatosis treated with radiation therapy (RT), with or without surgery, to characterize factors associated with increased risk of local recurrence.

Methods: We reviewed the records of 209 consecutive patients with desmoid fibromatosis treated with RT, either alone or as combined modality therapy (CMT) with surgery, at our institution from 1965 to 2015. Local control was defined as stable disease or regression of gross tumor on serial imaging in cases where there was tumor present at the time of RT or no disease recurrence in patients receiving CMT.

Results: Median follow-up time was 98 months (range, 1-509). The 5-year and 10-year OS was 99% and 93%, respectively. The patients were more commonly female (n=130, 62%) with a median age of 34 yrs (range, 8-85) and median tumor size of 7cm (range, 1-24). Patients receiving RT alone had larger tumors (>10cm, 31% vs. 15% with CMT, *P*=0.001), and patients receiving CMT were more commonly ≤30 yrs (55% vs. 34% RT alone, *P*=0.003). The median RT dose was 56 Gy among all patients (range, 44-75) with a median of 56 Gy receiving RT alone and 50.4 Gy for those receiving CMT.

The 5-year and 10-year LC was 71% and 69%, respectively. 59 patients (28%) experienced a local recurrence at a median time of 23 months (interquartile range, 15-38 months) with the majority occurring in-field (n=41, 70%; marginal n=12, 20%; out-of-field n=6, 10%). Among all patients, on univariate analysis there were several patient- or treatment-related factors significantly associated with an inferior 5-year LC including: younger age (≤30 yrs 57% vs. >30 yrs 82%, *P*<0.001), tumor site in the lower extremity (LE) (61% vs 73%. non-LE, *P*=0.047), tumor size (>10cm 58% vs. 5-10cm 71% vs. ≤5cm 84%, *P*=0.009), and treatment approach (RT alone 64% vs. CMT 80%, *P*=0.01). However, on multivariate analysis, adjusting for anatomic site, size, age, treatment era (>2005 vs. ≤ 2005), treatment approach (RT alone vs. CMT), and an interaction between age and treatment, we found only age ≤30 yrs (HR 2.94, *P*=0.005, 95% CI 1.38-6.27) and large tumor size >10cm (HR 2.51, *P*=0.03, 95% CI 1.09-5.78) to be correlated with poorer LC.

The RT alone and the CMT cohorts were analyzed separately. Notably, for patients receiving RT alone the 5-year LC was 43% for patients ≤30 yrs vs 75% for >30 yrs (*P*<0.001) compared to 68% for patients ≤30 yrs vs 95% for >30 yrs (*P*<0.001) when CMT was used. Separate multivariate analyses were performed for patients receiving RT alone and CMT, and adjusted for anatomic site, size, age, and treatment era. For patients receiving RT alone, the only factor

associated with inferior LC was age ≤30 yrs (HR 2.87, *P*=0.001, 95% CI 1.51-5.47). The same was true for patients treated with CMT; age ≤30 yrs was the only factor associated with inferior LC (HR 5.36, *P*=0.01, 95% CI 1.40-20.58). There were 32 patients (15%) that had a RT-related complication at a median time of 43 months (range, 2-476) resulting in a 10-year complication-free survival of 87%. Several factors were associated with a poorer 5-year complication-free survival including: patient age ≤30 yrs (83% vs. 93%, *P*=0.002), use of RT alone (85% vs. 94%, *P*=0.03), and RT dose >56 Gy (77% vs. 92% ≤ 56 Gy, *P*<0.001).

Conclusion: Among all patients with desmoid fibromatosis, RT provides adequate tumor control rates at doses ≤56 Gy with low risk of toxicity. However, young patients ≤ 30 yrs have notably high rates of local recurrence regardless of treatment strategy. Perhaps given the high risk of relapse in young patients, stronger consideration should be given to strategies that do not include radiotherapy. These complex patients benefit from referral to large centers where a multidisciplinary approach is prioritized, especially for young patients for whom local control is more challenging.

Poster 135 3042570

FAP-RELATED DESMOID TUMORS TREATED WITH LOW-DOSE CHEMOTHERAPY: RESULTS FROM A MULTICENTRE RETROSPECTIVE ANALYSIS

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Objective: Desmoid tumours (DTs) are monoclonal neoplasms with fibroblastic-myofibroblastic differentiation and they represent the most common extra-intestinal manifestation of familial adenomatosis polyposis (FAP). DTs are often multifocal and, even in the absence of a metastatic potential, they represent the first cause of death in FAP patients after colectomy. Data on the activity of chemotherapy in FAP-associated DTs are limited. We specifically examined the activity of chemotherapy with low-dose methotrexate (MTX) + vinca alkaloids.

Methods: We retrospectively reviewed data from all patients treated with MTX + vinca alkaloids for FAP-associated DTs in 5 reference centres and cases included into the National rare cancer network were also reviewed and included if sufficiently informative for the study purposes. Radiological responses were assessed using both RECIST and CHOI criteria.

Results: We identified 28 patients treated with MTX + vinca alkaloids. All patients had progressive disease before chemotherapy; 17 patients and 9 patients had previously received respectively surgery and/or systemic treatments (i.e. hormone therapy, NSAIDs). Chemotherapy was administered for a median duration of 11 months. According to RECIST criteria (CHOI evaluation is ongoing) complete response, partial response, stable disease, and progressive disease were observed in 1, 17, 10, and 0 patients, respectively. The median progression-free survival (PFS) was 78 months; it was 124 months in responding patients. After chemotherapy withdrawal, MTX + vinca alkaloids rechallenge was offered to 11 patients with progressive disease. In these patients, we obtained a control rate of 100%, resulting in a median second PFS of 64 months.

Conclusion: To the best of our knowledge, this is the largest series on the activity of low dose chemotherapy in FAP-related DTs. Our data suggest a tremendous activity of low dose chemotherapy in this very rare subset of patients.

Poster 136 3042280

SIGNIFICANT RISK FACTORS OF LOCAL RECURRENCE AFTER SURGERY IN EXTRA-PERITONEAL DESMOID-TYPE FIBROMATOSIS: A MULTICENTER STUDY IN JAPAN

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Objective: Surgical treatment with wide operative margin had been the mainstay of the treatment modality for patients with desmoid-type fibromatosis (DF). However, many physicians alter the first choice of treatment from surgery to conservative treatment including watchful waiting due to the remarkable high recurrence rate. On the other hand, not a few patients necessitate surgical treatment because of the severe pain and/or exacerbation of involved joints. The purpose of this study is to clarify the risk factors for local recurrence after surgery including the mutation status of CTNNB1, and determine the patients with DF who could be suitable for the surgical treatment.

Methods: The present study was supported partly by the grant from the Ministry of Health, Labor and Welfare of Japan. Co-authors are the members of a research team which conducted “A research for establishment of clinical care guideline for patients with extra-peritoneal DF”. Anonymized medical records were collected from multicenter participating in this study. Frozen or formalin-fixed, paraffin-embedded specimens obtained during biopsy or surgery were also collected, and subjected to DNA isolation and CTNNB1 mutation analyses by direct sequencing. Various factors correlating to the local recurrence were statistically analyzed. Categorical variables correlating with local recurrence were analyzed chi-square test or Fisher’s exact test. Recurrence-free survival (RFS) rate from surgical treatment was calculated using Kaplan-Meier (KM) product limit methods. Log-rank test was used to determine whether the differences in survival between groups. The Cox proportional hazards method was used for multivariate analysis to explore the effect of variables on RFS. P-values of <0.05 were considered to indicate significance.

Results: One hundred ninety-six cases of medical records and tumor specimens were collected from 7 institutions, which are specialized soft tissue tumor center in Japan. Among them, excluding cases with specimens of poor quality for DNA extraction, lack of clinical data, without surgery, total 88 cases composed this study. Local recurrence occurred in 35 cases. Demographic data of cases with or without recurrence is shown in Table 1. KM survivorship analysis showed that 5-year LRF rate was 51.1% (Fig. 1). Univariate analysis revealed that extremity location (P=0.033) and R2 margin (P<0.001) were significant risk factor for local recurrence. Excluding the cases with R2 margin, which may have residual tumors, multivariate analysis demonstrated that extremity location (P<0.001), S45F of CTNNB1 mutation status (P=0.028), recurrent tumor (P=0.041), and R1 margin (P=0.039) were significant risk factors for local recurrence.

Conclusion: Results of this multicenter study suggest that several factors including extremity location, S45F mutation status, and recurrent tumor, would be useful criteria for determination of indication for surgical treatment in patients with extra-peritoneal DF. Validation study will be required for these criteria to be widely used.

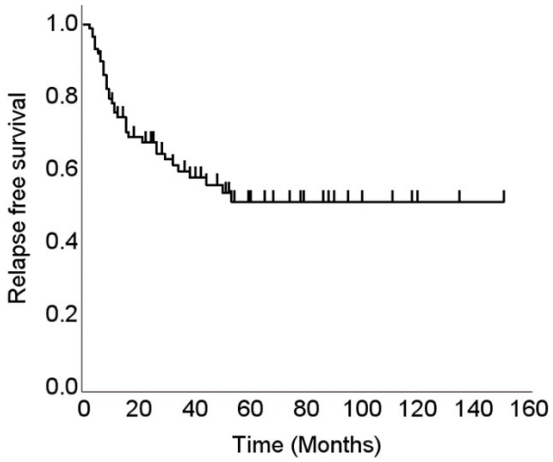

Figure 1. Local recurrence free survival was analyzed with Kaplan-Meier method in patients with surgically treated DF.

Table 1. Factors correlating with local recurrence after surgical treatment.

Factors		Total number	Recur.+	Recur.-	p value
gender	male	31	12	19	
	female	57	23	34	0.88
age	≥36	42	16	26	
	36>	46	19	27	0.76
location	neck	10	2	8	
	trunk	35	12	23	
	abd. wall	13	1	12	
	extremity	28	19	9	
	retroperit.	2	1	1	0.008
primary	primary	76	29	47	
	recurrence	12	6	6	0.64
CTNNB1	41A	38	14	24	
	45F	15	7	8	
	WT	34	14	20	
	45P	1	0	1	0.97
size	≥8cm	42	21	21	
	8cm>	46	14	32	0.061
margin	R0	41	12	29	
	R1	44	20	24	
	R2	3	3	0	0.12

Poster 137 3029766

EFFECTS OF MATRIX STIFFNESS ON CULTURED CELLS OF DESMOID-TYPE FIBROMATOSIS

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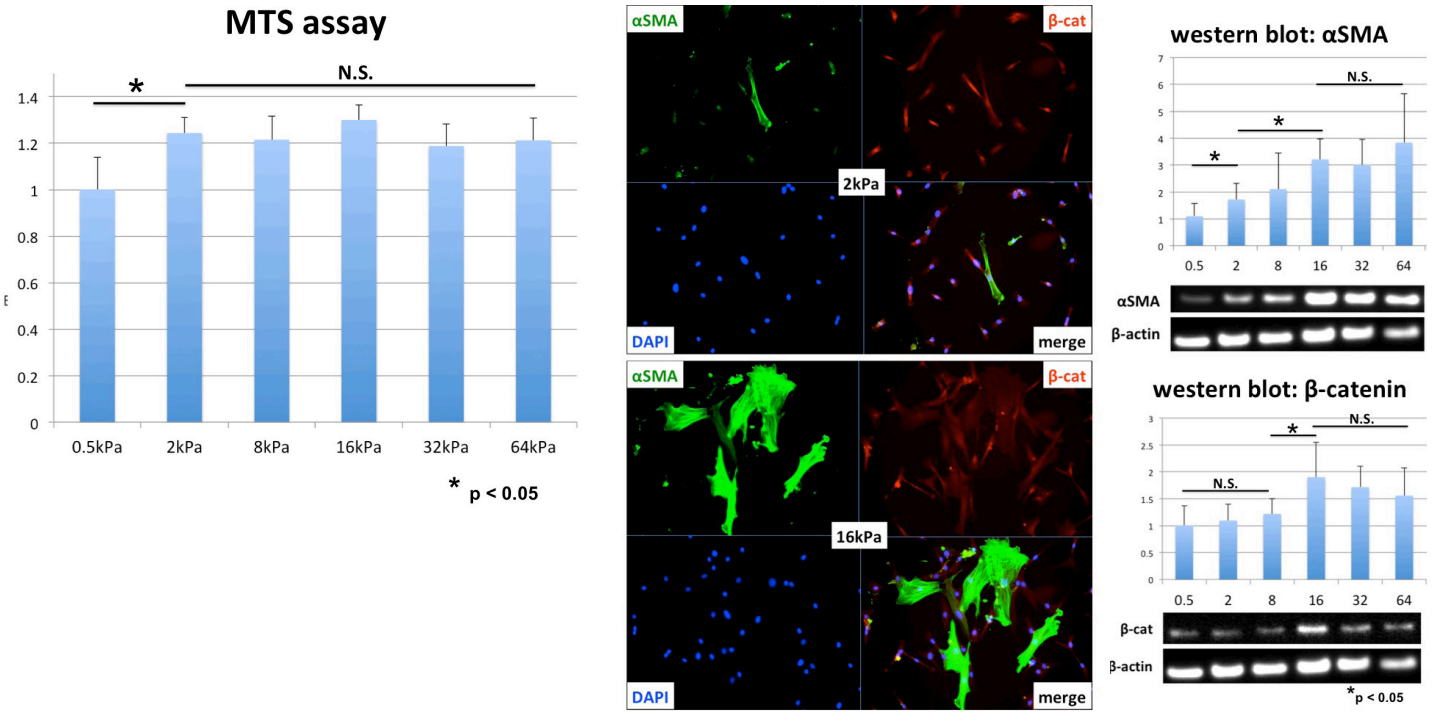
Objective: Desmoid-type fibromatosis (DF) is rare fibroblastic / myofibroblastic tumor with locally aggressive nature. Treatment algorithms for patients with DF are challenging for its high local recurrence rate after surgery and limited available data about the use of systemic therapy. The tumor location is associated with increased propensity for local recurrence, and DF often arise from post-traumatic lesion or surgical scar, these suggest that mechanical stress might affect the behavior of DF. In past studies, it has been reported that matrix stiffness induced myofibroblastic differentiation of fibroblasts, and played important roles in pathogenesis of fibrosis. To investigate the effects of matrix stiffness on DF behavior, we isolated and cultured DF cells on silicon gel substrates of varying stiffness.

Methods: DF cells were isolated from a patient with trunk DF during surgery, the mutational status of the *CTNNB1* exon3 (*T41A*) was determined for both parental tumor tissues and isolated cultured cells. The cells were cultured on silicon gels with stiffnesses ranging from 0.5 to 64 kPa (Cytosoft® 6-well plate, elastic modulus) for 48 hours. The cell proliferation was evaluated by MTS assay, and morphology and expression of a-smooth muscle actin (α-SMA) and β-catenin was determined by immunofluorescence confocal microscopy. These protein concentrations of cellular lysates were also evaluated by western blotting.

Results: As the stiffness of substrates increased, DF cells became spindle-shaped and spread, and the expression of α-SMA protein in the cytoskeleton of DF cells became more dense. In MTS assay, the cell proliferation was significantly higher in the stiffer substrate ($p < 0.05$ 0.5 kPa vs ≥ 2 kPa) (Fig.1). In western blot, the expression of α-SMA protein and β-catenin protein was also higher in the stiffer substrates ($p < 0.05$ α-SMA: 0.5 kPa vs 2, 8 kPa vs ≥ 16kPa, β-catenin: ≤ 8 kPa vs ≥16 kPa) (Fig.2).

Conclusion: Substrate stiffness affected both cell proliferation and expression of α-SMA protein and β-catenin protein in DF cells. The morphologic change and higher α-SMA expression on stiffer substrate suggested that myofibroblastic differentiation might be occurred in these cells. Previous studies reported that mechanoreceptors and mechanotransduction

signals play important roles in myofibroblast differentiation in fibroblasts. Clarifying and regulating the mechanotransduction signals in DF may lead to the development of a novel therapeutic tool of progressive DF.



Poster 138 3042486

MUTATION STRATIFICATION OF DESMOID-TYPE FIBROMATOSIS USING A RADIOGENOMICS APPROACH – PRELIMINARY RESULTS

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Objective: Desmoid-type fibromatosis (DTF) is a rare, borderline, soft tissue tumor that arises from musculoaponeurotic structures. The vast majority of DTF tumors harbor a specific point mutation at the *CTNNB1* (beta-catenin) gene, affecting two codons in exon 3; substituting threonine at position 41 with alanine (T41A) and replacing serine at position 45 with phenylalanine (S45F). Tumors without any mutation in the *CTNNB1* gene are considered to be wild-types. The *CTNNB1* gene mutations serve as a supportive diagnostic tool for the diagnosis of DTF but may also be used as a prognostic or predictive biomarker. Radiogenomics is a promising technique, correlating quantitative imaging features with molecular characteristics, in order to assess mutation status non-invasively. The aim of this study is to evaluate the use of radiogenomics features extracted from T1 weighted Magnetic Resonance (T1w MR) images to predict *CTNNB*1 mutation status (T41A, S45F and wild-type) of treatment naive desmoid-type fibromatosis (DTF) tumors.

Methods: Approval from the Medical Ethics Committee of Erasmus MC, Rotterdam, the Netherlands, was obtained for this study (MEC-2016-339). Cases of treatment naive extra-abdominal and abdominal wall DTF, with available digital T1w MR images, between 1990 and end of 2017, were selected from the pathology database of the Erasmus MC, Rotterdam, the Netherlands. Sanger sequencing on formalin fixed paraffin embedded material was performed to obtain *CTNNB1* mutation status in case of undetermined mutation status. Tumors were semi-automatically annotated on the anonymized, pre-treatment T1w MR images by two persons using custom-made software. A total of 424 image features, quantifying shape, intensity and texture were extracted for each patient, using the segmentations as region of interest. A Support Vector Machine (SVM) was trained and evaluated using these features in a 100x random split cross validation, with the training set consisting of 80% of the patients. For each mutation, an SVM was constructed using a one-vs.-all approach. Classification performance was assessed by the area under the receiver-operating-characteristic curve (AUC).

Results: A total of 49 patients; 14 males and 35 females, with DTF located extra-abdominal (n=37) or in the abdominal wall (n=12) were included. Tumors harbored a T41A mutation in 21 cases, a S45F mutation in 11 cases and 17 tumors were considered to be wild-type tumors. The radiogenomics approach resulted in AUC 95% confidence intervals of [0.28, 0.61], [0.43, 0.73] and [0.61, 0.88] for classification of the T41A, S45F and wildtype mutations, respectively.

Conclusion: The preliminary results of this radiogenomics model showed a promising predictive value for classification of wild-type mutations, but could not differentiate between the various genetic mutations in DTF. The use of a larger, multi-center dataset with the use of additional MRI sequences and more advanced multi-class machine learning approaches could improve the radiogenomics model to develop a prediction model for DTF that can be used both in research and in clinical practice.

Poster 139 3007734

ACTIVITY OF SORAFENIB IN A DIVERSE POPULATION OF PATIENTS WITH DESMOID TUMORS INCLUDING POOR PERFORMANCE STATUS.

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Objective: Desmoid tumors (DT), also known as aggressive fibromatoses, can be classified into three types– those associated with pregnancy, those associated with Gardner's Syndrome and sporadic DT. There is no standard of care in terms of systemic therapy. Previous studies have reported activity for tyrosine kinase inhibitors (TKIs) including imatinib and sorafenib. We report in this abstract the results of patients treated with sorafenib at Smilow Cancer Hospital, Yale Cancer Center.<!--![endif]---->
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Methods: A retrospective chart review from 2015-2017 of all patients treated with sorafenib for un-resectable or recurrent DT was undertaken. Patients enrolled in the randomized phase III Alliance trial were not included. in this analysis. IRB approval was requested from the Yale Human Investigations Committee.

Results: 5 patients were identified with DT who were treated with sorafenib. (Table 1.) The duration of response was the time from the best response until completion of treatment. A wide age group was represented (ages 32-75 years of age). Patient 1 has had a total duration of treatment of 605 days, and patient 4 had stable disease while on treatment but later had a partial response after having stopped sorafenib 11 months earlier. Sorafenib demonstrated response even at a dose of 200 mg qday in some patients.

Conclusion: In our cohort, sorafenib showed activity in all types of DT, across both sexes, regardless of age or location of primary tumor. Our results compare well with those reported previously. Of note is its activity in a patient with a PS of 3, which has not previously been reported to our knowledge. This resulted in an improvement in quality of life and avoidance of a potentially disfiguring surgery. The delayed activity of sorafenib seen in patient 4 is not well understood but may be related to its anti-angiogenic effects. A randomized clinical trial of other TKIs is warranted.

Patient Results

	1	2	3	4	5
Associated condition	Sporadic	Pregnancy	Sporadic	Sporadic	Gardner's
Best Response	PR	SD	SD	SD	SD
Duration of Response (days)	324	605	150	135	266
ECOG performance status (PS)	3	1	1	2	1
Age	32	40	67	75	61
Line of Treatment	1	1	3	1	1
Sex	M	F	F	M	F
Primary Site	Neck	Upper Extremity	Upper Extremity	Abdomen	Abdomen

Poster 140 3036230

A CLINICAL COMPARISON OF FAMILIAL (APC MUTATED) VS SPORADIC (CTNNB1 MUTATED) DESMOID TUMORS

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Objective: Desmoid tumor (aggressive fibromatosis) is a locally aggressive neoplastic proliferation of fibroblasts without the ability to metastasize. Unlike sporadic desmoids that usually contain CTNNB1 mutations, APC associated desmoids are due to germline mutations and occur with increased frequency in patients with Familial Adenomatous Polyposis (FAP). There has long been a hypothesis that APC-mutated desmoids are associated with a higher incidence of local recurrence and second primary desmoid tumors then CTNNB1-mutated desmoids. We sought to obtain scientific data to support this hypothesis.

Methods: Following IRB approval, a search of medical records for patients with desmoid tumors was performed at the M D Anderson Cancer Center (MDACC) from 1954 to 2018. Those who did not have complete electronic records and who had not actually received treatment for their desmoid tumor at MDACC were excluded; 138 patients were identified comprising 48 patients with FAP (APC group) matched with 90 patients without FAP (non APC group); an approximate 1:2 ratio. Variables collected included age, sex, clinical or genetic evidence of APC mutation, date of diagnosis, treatments, dates of local recurrence and/or occurrence of second desmoid, treatments of recurrences and/or second desmoids, vital status and date of last follow-up or death. Patients were categorized according whether they did or did not have genetically confirmed and/or clinically suspected APC mutations and the groups were compared. The recurrence free survival (RFS) was calculated by the Kaplan-Meier method and Log-rank test was applied for testing the stratification of RFS for patients with and without APC mutations.

	APC Mutated Group (FAP)		Non-APC Mutated Group (Non-FAP)		Total		
	N	%	N	%	N	%	p value
Age (Mean, StD)	**30.7 (10.9)**		**42.1 (14.7)**		**38.2 (14.5)**		**<0.001**
SEX							0.268
Male	25	52.08%	38	42.22%	63	45.65%	
Female	23	47.91%	52	57.77%	75	54.34%	
Primary Desmoid Site							0.079
intra-abdominal	35	72.91%	52	57.77%	87	63.04%	
extra-abdominal	13	27.08%	38	42.22%	51	36.95%	
Number of treatments required for primary desmoid							0.555
1	96	69.56%	61	67.77%	35	72.91%	
2	28	20.28%	20	22.22%	8	16.66%	
3	9	6.52%	6	6.66%	3	6.25%	
4	3	2.17%	1	1.11%	2	4.16%	
5	2	1.44%	2	2.22%	.	.	
5-year recurrence free survival (%) (n=87)	**65.28**		**74.43**		**71.35**		**0.339**
Intra-abdominal (n=87)							
Incidence of multiple primary desmoids	3	8.57%	0	0.00%	3	3.45%	0.062
Number of treatments required for primary desmoid							0.428
1	23	65.71%	37	71.15%	60	68.97%	
2	7	20.00%	9	17.31%	16	18.39%	
3	3	8.57%	5	9.62%	8	9.20%	
4	2	5.71%	0	0.00%	2	2.30%	
5	0	0.00%	1	1.92%	1	1.15%	
Incidence of Recurrence (n=59)	6	27.27%	10	27.03%	16	27.12%	0.984
Incidence of Second Primary	13	37.14%	0	0.00%	13	14.94%	<0.001
5-year recurrence free survival (%) (n=58)	**73.92**		**73.89**		**73.87**		**0.791**
Extra-abdominal (n=51)							
Incidence of multiple primary desmoids	0	0.00%	0	0.00%	0	0.00%	X
Number of treatments required for primary desmoid							
1	12	92.31%	24	63.16%	36	70.59%	
2	1	7.69%	11	28.95%	12	23.53%	
3	0	0.00%	1	2.63%	1	1.96%	
4	0	0.00%	1	2.63%	1	1.96%	
5	0	0.00%	1	2.63%	1	1.96%	
Incidence of Recurrence (n=29)	5	38.46%	3	18.75%	8	27.59%	0.238
Incidence of Second Primary	7	53.85%	0	0.00%	7	13.73%	<0.001
5-year recurrence free survival (%, year, n=29)	**48.48**		**61.11**		**61.22**		**0.335**

Table 1 – Summary of findings

FAP – Familial adenomatous polyposis

StD – Standard Deviation

Results: In the APC group there were 25 (52.1%) males and 23 (47.9%) females (total 48) and in the non-APC group there were 38 (42.2%) males and 52 (57.7%) females (total 90). The mean age of the patients in the APC group was significantly less than that of the non-APC group (30.7 (SD 10.9) years vs 42.1 (SD 14.5) years, p<0.001). In the APC group, 35 (72.9%) patients had intra- and 13 (27.1%) had extra-abdominal tumors. This was not significantly different from the non-APC group of whom 52 (57.8%) had intra- and 38 (42.2%) had extra-abdominal tumors (p=0.079). Three patients in the APC group but none in the non-APC group had synchronous multiple primaries (p=0.062). There was no significant differences in the number of treatments required, incidence of recurrence, or 5-year RFS between the APC and non-APC groups regardless of whether the tumor was intra- or extra-abdominal. However the chances of a metachronous primary desmoid tumor was significantly higher in the APC group then in the non-APC group for those with both intra-abdominal (13 (37.1%) vs 0 (0.0%), p<0.001) and extra-abdominal (7 (53.9%) vs 0 (0.0%), p<0.001) tumors. Only one patient in the study died as a direct result of their desmoid tumor. Eleven died of other causes. There was a significant difference in the proportion of patients 'alive without disease' (35.5% vs 41.1%) and 'alive with disease' (55.8% vs 54.4%) between the APC and non-APC groups (p=0.021). Overall, more than half of the patients were 'alive with disease' at the end of the study period.

Conclusion: APC mutated desmoid tumors occur in younger patients then non-APC mutated desmoid tumors. In addition, APC mutated desmoid tumors are more likely to be associated with both synchronous and metachronous second primary desmoid tumors. These findings suggest that initial evaluation, as well as follow up and surveillance should be tailored differently for these two groups of patients.

Poster 141 3042762

WNT TARGET GENES ARE NOT DIFFERENTIALLY EXPRESSED IN DESMOID TUMORS BEARING DIFFERENT ACTIVATING BETA-CATENIN MUTATIONS

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Objective: Sporadic desmoid-type fibromatosis (DTF) is a rare soft tissue tumor characterized by local invasive growth and unpredictable growth behavior. Three distinct mutations involving the *CTNNB1* (beta-catenin) gene can be identified in the vast majority of DTF tumors. These mutations affect two codons in exon 3; substituting threonine at position 41 with alanine (T41A) and replacing serine at position 45 with either phenylalanine (S45F) or proline (S45P). The Wingless (Wnt) signaling pathway is critical in the maintenance of beta-catenin levels in the normal cell and is presumed to play a major part in the tumorigenesis of DTF. This study examines whether the different *CTNNB1* mutants (T41A, S45F, S45P and wild-type) occurring in DTF tumors differentially affect Wnt signaling activity, which might explain the different disease course between DTF tumors harboring different *CTNNB1* mutations.

Methods: Real-time polymerase chain reaction (RT-PCR) on 63 formalin fixed paraffin embedded DTF samples with known *CTNNB1* mutation status was used to measure the relative mRNA expression level of Wnt target genes *AXIN2*, *Dickkopf (DKK1)* and *cyclin D1 (CCND1)*. Affymetrix data (Human Genome U133 Plus 2.0 array) of 124 DTF samples with known mutation status were retrieved from the Gene Expression Omnibus. Subsequently, hierarchical cluster analyses were performed based on the expression of a selection of Wnt target genes. Additionally, relevant clinical characteristics like sex, age at the time of diagnosis, tumor size, tumor site and recurrence were added. This study was approved by the Medical Ethics Committee of the Erasmus MC, Rotterdam, the Netherlands (MEC-2016-213).

Results: No statistically significant difference in the relative expression levels of Wnt target genes *AXIN2, DKK1* and *CCND1* was identified between wild-type and *CTNNB1* mutated DTF samples with RT-PCR. Moreover, the clustering analysis for selected Wnt targets did not show any discrimination between the different *CTNNB1* mutants and/ or the wild-type samples. The clustering pattern of DTF samples that was observed did not coincide with clinical characteristics of DTF patients and their tumors.

Conclusion: Based on the results of this study we could not identify differences in the expression levels of Wnt target genes between the different *CTNNB1* mutation types and wild-type DTF tumors.

Poster 142 3042792

DESMOID TUMOURS TREATED WITH ORAL VINORELBINE. A RETROSPECTIVE ANALYSIS OF 14 PATIENTS

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Objective: Desmoid tumours (DT) are rare monoclonal fibroblastic proliferations with a variable clinical course and potential for locally aggressive behaviour. They may be associated with a high symptom burden and functional impairment, which can lead to significant impact on quality of life. The management of DT has evolved over time and surgery at diagnosis in asymptomatic patients has been superseded by an initial approach of active surveillance. Systemic treatment is an option in symptomatic patients with radiological and/or clinical progressive disease. Treatments include anti-hormonal therapy, non-steroidal anti-inflammatory drugs, tyrosine kinase inhibitors, and chemotherapy. The evidence base for many of these treatments is limited, however, at ASCO 2018, 2 randomised trials of systemic therapy in DT were presented (sorafenib versus placebo and pazopanib versus methotrexate plus vinblastine). The side effects of treatment for this chronic condition are of great relevance. Moreover, due to the high cost of tyrosine kinase inhibitors their availability differs world-wide. Therefore, there is a need for effective, well tolerated and affordable systemic therapies for this disease. Oral vinorelbine may be one of these options.

Objective: To evaluate the efficacy, toxicity and radiologic changes of patients with DT treated with oral vinorelbine (VNR).

Methods: A retrospective search of an institutional database was performed to identify DT patients treated with VNR between March 2017 and June 2018. The diagnosis was confirmed in all cases by an experienced soft tissue pathologist. MRI size and signal changes were documented by specialist soft tissue sarcoma radiologist. VRB is given Days 1, 8, 15 every 4 weeks at a dose of 90mg. The cost is €690 per cycle.

Results: Fourteen pts diagnosed with DT and treated with VNR were identified for analysis (8 male [57%], median age 37 years [range: 25-72]). The most frequent anatomical location was upper limb (n=8 [57%]), intra-abdominal location (n=3 [21%]), trunk (n=2 [14%]) and lower limb (n=1 [7%]). The initial management was active surveillance for 7 patients, surgery in 6 and systemic treatment in 1. VNR was the first line of systemic treatment for 4 pts, second for 3 pts, third for 3 pts, fourth for 2 pts and fifth for 2pts. Treatments prior to VNR were surgery for 13pts (second surgery was performed in 3 pts, 2 of them after first recurrence) and another chemotherapy regime for 10pts. One pt received radiotherapy as an adjuvant treatment after a second surgery. Considering systemic treatments only, 10pts received tamoxifen + non-steroidal anti-inflammatory drugs, Caelyx (n=5), pazopanib (n=3), vinblastine + methotrexate (n=3), hydroxyurea (n=1) and vincristine + actinomycin (n=1).

Eleven pts had radiological progressive disease before starting VNR while 3pts had stable disease, but were symptomatic. Overall, 7pts reported symptomatic deterioration before commencing VNR. Results are summarised in Table 1.

VNR was a well-tolerated treatment, with mild toxicities. Only 3 patients [21%] required dose reductions. Frequent toxicities were: anaemia grade 3 (n=1 [7%]); fatigue grade 2 (n=2 [14%]) and grade 1 (n=2[14%]); nausea grade 2 (n=2[14%]) while grade 1 (n=2[14%]); constipation grade 1 (n=3[21%]); diarrhoea grade 1 (n=3[21%]); gastritis grade 1 (n=2[14%]); vomiting grade 1(n=2[14%]).

This regimen was first used in our unit in 2017 and therefore the median duration on treatment was only 5.8 months, with at the time of analysis 12 patients still on VNR.

So far, no patients demonstrated a radiological response by RECIST 1.1 criteria and 4 [29%] demonstrated a decrease in T2 intensity. However, 9 [64%] patients reported an improvement in pain.

Conclusion: Oral vinorelbine is an effective and tolerable systemic treatment for DT, with relatively low cost. Patients can derive symptomatic benefit in the absence of radiological responses and therefore symptom-based endpoints should be used in future prospective studies.

Table 1.

	Best Radiological Response				Change in T2 intensity on MRI following VNR			Change in pain following VNR		
	CR	PR	SD	PD	Decrease	Stable	Increase	Decrease	Stable	Increase
n	0	0	13	1						
					4	10	0			
								9	5	0

CR = complete response, PR =partial response, PD = progressive disease, VNR = oral vinorelbine.

Poster 143 3042308

TEMOZOLOMIDE COMBINED WITH PARP INHIBITOR OLAPARIB SHOWS SYNERGISTIC EFFFECTS IN DESMOPLASTIC SMALL ROUND CELL TUMOR CELLS

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Objective: Desmoplastic small round cell tumors (DSRCTs) are highly malignant soft tissue sarcomas most frequently seen in young males with a characteristic t(11;22)(p13q;q12) translocation resulting in the fusion protein EWS-WT1. Patients are often diagnosed with extensive disseminated disease and the 5-year survival rates remain about 15%. Current treatment consists of chemotherapy, surgery, and radiotherapy which initially often induce responses, at the expense of toxicity, but which are unfortunately often short-lasting. Therefore, more effective and less toxic treatments are necessary. Similar to DSRCT, ES is characterized by a EWS-translocation. PARP1, a DNA damage response enzyme involved in single-stranded DNA break repair, is considered an interesting target for therapy in ES. It is suggested that PARP1 is regulated by the EWS-fusion protein and that PARP1 in return promotes the transcriptional activity of the fusion protein. PARP inhibitors have been shown to be effective in EWS-translocation positive ES cell lines, whereas fusion-negative cell lines were irresponsive to treatment. As such, PARP inhibition might have potential in the EWSR1-translocated DSRCTs. Moreover, PARP inhibitors have been shown to enhance the anti-tumor effects of alkylating agents such as temozolomide (TMZ). Therefore, we aimed to further examine the anti-tumor effects of combined PARP and TMZ treatment in EWSR1-translocation sarcomas, with a focus on DSRCT.

Methods: JN-DSRCT-1 cells were treated with varying concentrations of single-agent olaparib (PARP inhibitor) and TMZ and effects on cell viability were assessed. The effects of single-agent olaparib treatment on cell migration were assessed by scratch assays. Next, DSRCT and ES (ES7 and ES8) cell lines were treated with a combination of olaparib and TMZ. Effects on cell viability, DNA damage and apoptosis were assessed by MTS assay, γH2AX expression and PARP cleavage, respectively. Drug synergy of simultaneously combined olaparib and TMZ treatment was assessed by calculation of the combination index (CI). Synergism, additive effects and antagonism are represented by CI-values <1.0, 1.0 and >1.0, respectively.

Results: As single agents, olaparib and TMZ reduced cell viability in JN-DSRCT-1 cells in a dose-dependent manner with IC50-values of 1.2±0.4μM and 103±35μM, respectively. Olaparib treatment of DSRCT cells equal to the IC25, IC50, IC75 and IC90-values reduced cell migration up to 96h. ES7 and ES8 showed IC50-values of 1.7±0.1 and 1.5±0.3 for olaparib and 143.1±22.1 and 234±49 for TMZ, respectively. Simultaneous combination treatment with increasing concentrations of olaparib (0.625; 1.25; 1.875μM) and TMZ (50; 100; 250μM) showed synergistic effects in DSRCT cells (CI <1.0). Simultaneous combination treatment was superior to sequential treatment in reducing cell viability, inducing apoptosis and increasing DNA damage for all cell lines. With sequential treatments, TMZ prior to olaparib treatment showed higher induction of DNA damage (JN-DSRCT-1, ES7, ES8) and apoptosis (ES7, ES8) compared to olaparib prior to TMZ treatment.

Conclusion: Olaparib combined with TMZ enhances anti-tumor effects compared to single-agent treatment *in vitro*. Simultaneous combination treatment was superior to sequential treatment and synergistic effects were observed when both drugs were combined, already at low-toxic concentrations (from IC25-value). Further research is ongoing, examining the combination in an *in vivo* DSRCT model to further substantiate its value for a clinical study in this rare disease entity.

Poster 144 3042576

PHASE 2 WEEKLY ORAL ONC201 IN DESMOPLASTIC SMALL ROUND CELL TUMOR (DSRCT) AND CLEAR CELL SARCOMA

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Objective: ONC201 is an imipridone that has a unique mechanism of action (DRD2 binding, up regulation of TRAIL) and preclinical activity against the Ewing's family tumor, DSRCT which has the EWS-WT1 translocation (A. Hayes Jordan et al. "Efficacy of ONC201 in Desmoplastic Small Round Cell Tumor", Neoplasia 2018; 20: 524-532). We planned a pilot study to investigate safety and efficacy of this agent in metastatic neuroendocrine cancer including DSRCT and clear cell sarcoma.

Methods: After Case Comprehensive Cancer Center, Cleveland Clinic IRB, and FDA review, an investigator-initiated pilot study with 2 arms (N=12 each) was done (IND 132665, CASE2716; Cleveland Clinic IRB 17-808; Clincaltrials.gov NCT03034200). The pilot study started in August 2017. Patients 14 years and older with no treatment of higher priority and detectable metastases were eligible. The recommended phase 2 dose of ONC201 is 625 mg po weekly. Imaging and labs were done at 1.5, 3, 6, 9, and 12 months after starting ONC201. After 3 months symptomatic lesions could be treated. Indicator lesions on CT scan were measured and analyzed according to RECIST criteria. Adverse events were graded according to CTCAE 4.0. This communication will report results in DSRCT and clear cell sarcoma. DSRCT patients had a median number of 4 prior regimens. Extensive abdominal DSRCT was the presentation in 6/7 and these all DSRCT patients had at least 2 prior surgeries. Abdominal DSRCT patients (6/6) had whole abdominal radiotherapy (WART) and a median of 5 prior regimens. Common prior regimens included VDC/IE (7/7), temozolomide +irinotecan, vinorelbine +oral cyclophosphamide+ temsirolimus, pazopanib, 8H9, doxorubicin +olaratumab, and Doxorubicin liposomes. Primary endpoint of this pilot study was to determine clinical benefit (CD+PR+SD) of at least 25% with maintenance of Karnofsky performance status.

Results: Eight patients with EWS translocation sarcomas were treated (DSRCT N=7 median age 34; clear cell sarcoma N=1). ONC201 at 625 mg po weekly was well tolerated in this cohort. There were no grade 1 drug related AE. No ONC201 related abnormalities in hemoglobin, white blood cell counts, platelet counts, AST, ALT, BUN or creatinine were seen. No nausea, vomiting or alopecia was observed. Performance was maintained while on ONC201 with few side effects. Although the clear cell sarcoma patient (EWS-ATF fusion) had no new lung metastases develop during 3 months of ONC201 therapy, the bilateral lung metastases gradually increased in size between 1.5 months and 3 months and progression by RECIST was seen at 3 months. Best response of DSRCT was stable disease by RECIST; 5/8 patients did not have development of new metastases while on study. Median duration of treatment of DSRCT was 3 months; 2/7 had 6 months of therapy and one DSRCT patient is still on active treatment >9 months without new disease. Reasons for discontinuation of drug was larger DSRCT metastases by RECIST (4/7) and development of new bone metastases (1/7). At time of abstract submission, the clear cell sarcoma patient is on other therapy and remains healthy and 4/7 DSRCT patients were alive and 2/7 on active ONC201 treatment. Best responses against DSRCT were seen with a limited disease burden.

Conclusion: ONC201 was very well tolerated. This study achieved the primary endpoint of clinical benefit; ONC201 may have potential to limit development of new DSRCT metastases. Larger clinical trials of will need to be performed in a selected population (e.g. after initial therapy and/or local control measures) to determine efficacy of ONC201 as an adjuvant therapy.

Poster 145 3042583

IMPROVED 3 AND 5 YEAR SURVIVAL WITH MULTIMODALITY TREATMENT OF DESMOPLASTIC SMALL ROUND CELL TUMOR

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Objective: Desmoplastic small round cell tumor (DSRCT), which harbors EWSR1-WT1 t(11;22)(p13:q12) chromosomal translocation, is an aggressive malignancy that typically presents as intraabdominal sarcomatosis in young males. Given its rarity, optimal treatment has not been defined.

Methods: We conducted a retrospective study of 187 DSRCT patients treated at MD Anderson Cancer Center over two decades. Univariate and multivariate regression analyses were performed. We determined whether chemotherapy, complete

cytoreductive surgery (CCS), hyperthermic intraperitoneal cisplatin (HIPEC), and/or whole abdominal radiation (WART) improve overall survival in DSRCT patients. Critically, since our institutional practice limits HIPEC and WART to patients with less extensive, potentially resectable disease that had benefited from neoadjuvant chemotherapy, a time-variant analysis was performed to evaluate those adjunct treatment modalities.

Results: The pre-2003 5-year overall survival (OS) rate of 5% has substantially improved to 25% with the advent of newer chemotherapies and better surgical and radiotherapy techniques (HR 0.47, 95% CI 0.29-0.75). Chemotherapy response (log rank p=0.004) and CCS (log rank p<0.0001) were associated with improved survival. Though WART and HIPEC lacked statistical significance, our study was not powered to detect their potential impact upon OS

Conclusion: Improved 3- and 5-year overall survival were observed following multidisciplinary treatment that includes ES-based chemotherapy and complete tumor cytoreductive surgery, but few if any patients are cured. Prospective randomized studies will be required to prove whether HIPEC or WART are important. In the meantime, chemotherapy and CCS remain the cornerstone of treatment and provide a solid foundation to evaluate new biologically targeted therapies.

Poster 146 3042655

RECURRENT *FGFR4* AND *ARID1A* SOMATIC ALTERATIONS ARE DETECTED IN DESMOPLASTIC SMALL ROUND CELL TUMORS (DSRCT)

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Objective: DSRCT is a rare, aggressive soft-tissue sarcoma, primarily affecting children and young adults, with a striking male predominance, and characterized by t(11;22) associated pathognomonic, novel EWSR1-WT1 fusion gene. DSRCT frequently presents with widespread abdominopelvic serosal involvement, resulting in ~85% mortality. Secondary somatic alterations in DSRCT are infrequently described. We evaluated whether comprehensive genomic profiling (CGP) might uncover additional genomic alterations (GA) that could open new routes to targeted and immunotherapies for this aggressive form of cancer.

Methods: Tissue from 83 DSRCT patients was assayed by hybrid-capture based comprehensive genomic profiling (CGP), FoundationOne® Heme, next generation sequencing (NGS), analysis which includes both DNA sequencing of 406 genes and RNA sequencing of 265 genes, performed in the course of clinical care to evaluate genomic alterations (Gas), including base substitutions, indels, amplifications, copy number alterations and gene fusions/rearrangements. Tumor mutational burden (TMB) was calculated from a minimum of 1.4 Mb sequenced DNA and reported as mutations/Mb. Microsatellite instability status (MSI) was determined by a novel algorithm analyzing 114 specific loci.

Results: CGP identified several genomically defined DSRCT subgroups. Significant GA included *FGFR4* (n=7; 8%), *ARID1A* (n=9; 11%), *TP53* (n=8; 10%), *MSH3* (n=12; 14%), and *MLL3* (n=13; 16%). Additionally, *ARID1A* alterations and *TP53* alterations were mutually exclusive of *FGFR4* and, with one exception, of each other. While at least 2-3 patients harbored *MLL3* or *MSH3* in addition to either *FGFR4* or *ARID1A*, a majority of those were also mutually exclusive. As expected, male patients comprised 81%, and female 19% of the cohort, with a median age of 25 (range of 6-67). No (0%) DSRCT were TMB High (H, ≥20 mut/Mb) or MSI high.

Conclusion: Secondary somatic alterations in *ARID1A*, *MLL3*, *MSH3*, *TP53*, and *FGFR4* were more commonly detected than previously reported, identified in more than 50% of DSRCT, and were almost always mutually exclusive, suggesting different factors may drive pathogenesis. These alterations may have both prognostic and therapeutic implications. Further studies of CGP in DSCRT to define opportunities for precision therapies for this devastating disease appear warranted.

Poster 147 3042812

PRECLINICAL EFFICACY OF ANDROGEN RECEPTOR-BASED ANTI-SENSE THERAPY FOR THE TREATMENT OF DESMOPLASTIC SMALL ROUND CELL TUMOR

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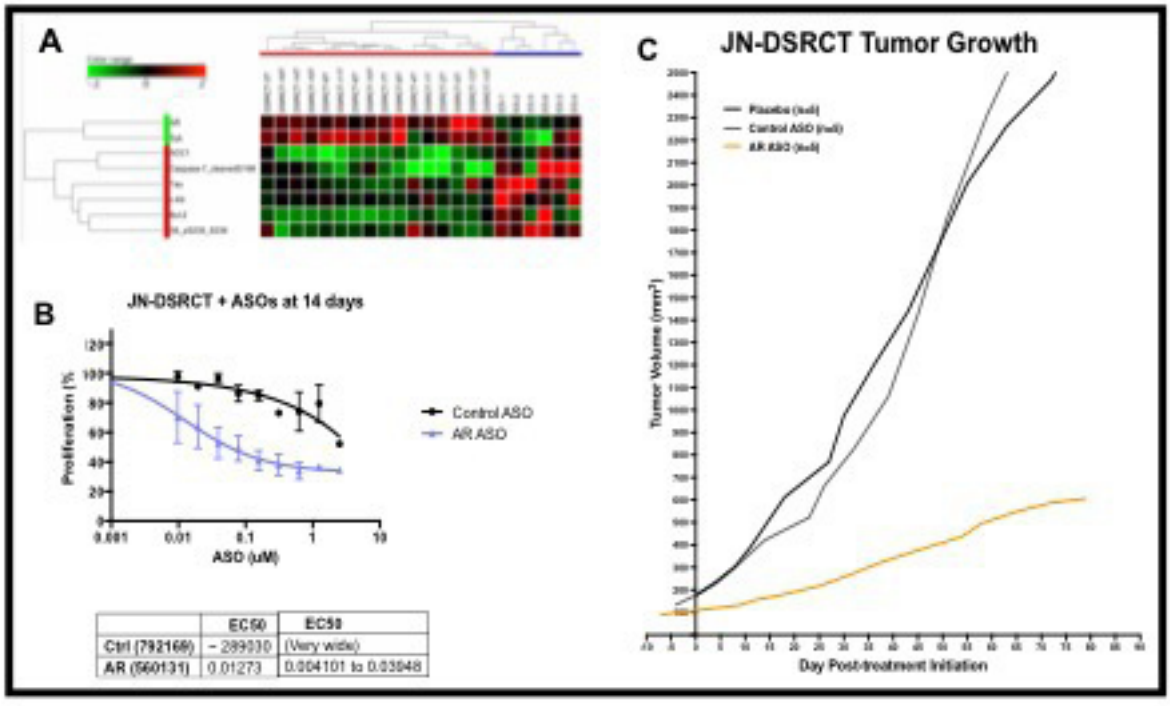
Objective: Desmoplastic small round cell tumor (DSRCT) is a rare, aggressive soft tissue sarcoma in adolescents and young adults characterized by the reciprocal EWSR1-WT1 t(11;22)(p13:q12) chromosomal translocation. Given a lack of prospective clinical trials due to its rarity and the molecular and morphological similarities to Ewing sarcoma (ES), DSRCT is typically treated with ES-based chemotherapies despite differing both in clinical presentation and prognosis. Only recently have molecular characterization efforts and proteomic profiling identified a number of aberrations that distinguish DSRCT from ES. Among these, androgen receptor (AR) is highly expressed in DSRCT patients and may represent a promising therapeutic target.

Methods: To assess expression of AR in DSRCT vs ES patients, protein lysates were created from DSRCT & ES patient tumors, protein concentrations were determined, and individual protein expression was measured using a well-validated reverse-phase protein array (RPPA). Selected proteins that were strongly and consistently upregulated in DSRCT or ES patients were subsequently validated by western blotting. In vitro cell proliferation assays and xenografts drug-testing were performed to evaluate the preclinical efficacy of AR-based anti-sense therapy for DSRCT.

Results: The JN-DSRCT cell line and DSRCT patient samples expressed high levels of AR compared to ES samples (Fig. 1A). Stimulation of DSRCT, ES TC-71 and prostate cancer LNCaP cell lines with exogenous 5a-dihydrotestosterone (DHT, an AR native ligand) showed increased proliferation in the DSRCT & LNCaP cell lines at high levels of DHT, but not in the TC71 ES cell line which lacks AR expression. Additionally, inhibition of AR in the JN-DSRCT cell line by anti-AR anti-sense oligonucleotide (ASO) showed a significant decreased proliferation at both 7 and 14 days (Fig. 1B). Finally, JN-DSRCT tumor-bearing NSG immunocompromised mice treated with anti-AR ASOs showed considerably reduced tumor burden and improved survival compared to mice in the placebo- and control ASO-treated groups (Fig. 1C, p=0.0129).

Conclusion: Proteomic profiling confirms increased expression of AR in both DSRCT patients and cell line samples as part of a molecular characterization to distinguish DSRCT from ES. AR stimulation enhanced in vitro cell proliferation, an effect that was mitigated using anti-AR targeted ASOs. As AR-targeted ASOs have already entered early-phase clinical trials as an experimental therapy for prostate cancer, the addition of a DSRCT cohort would allow rapid clinical validation. Future investigations will determine if AR ASOs can be safely combined with EWSR1-targeted ASOs, which have separately been reported to inhibit DSRCT tumor growth.

Figure 1



Poster 148 3015504

IMPACT OF WHOLE ABDOMINOPELVIC RADIOTHERAPY AND INTRAPERITONEAL RADIOIMMUNOTHERAPY AFTER COMPLETE RESECTION ON SURVIVAL IN PATIENTS WITH DESMOPLASTIC SMALL ROUND CELL TUMOR

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Objective: Desmoplastic small round cell tumor (DSRCT) is a rare sarcoma typically arising from the peritoneum. The prognosis for patients with DSRCT remains dismal despite aggressive multimodal therapy. Tumors are partially chemosensitive and complete resection has been shown to improve outcome. The role of post-resection treatment is unclear. We analyzed the effect of post-resection whole abdominopelvic radiotherapy (WAP-RT), intraperitoneal anti-B7H3 radioimmunotherapy with ^{131}I-omburtamab (IP-RIT) administered on a phase I study (NCT01099644), or both on survival in patients with DSRCT.

Methods: After approval from MSKCC Institutional Review Board we retrospectively analyzed records of patients with DSRCT undergoing surgery. Complete resection (R1-resection) was defined as surgical removal of all radiologically evident disease within and outside the abdominopelvic cavity with ≤1cm^3 residual AND the absence of active liver disease. Progression-free (PFS) and overall survival (OS) from day of surgery were calculated using Kaplan Meier methods.

Results: Of 149 patients treated at MSKCC from 2000-2017, R-1 resection was achieved in 92 patients, 86 undergoing R1-resection without prior progression. Radiation records were available for review in 81/86 patients: these are the subjects of this report. Fifty-one patients received WAP-RT after R1-resection: 42 with IMRT and 5 with conventional radiotherapy. The type of WAP-RT was unknown in the remaining 4. Thirty patients did not receive radiotherapy due to patient/physician choice (n= 29) or very early relapse (n=1). All patients receiving radiotherapy were dosed at 3000cGy to the whole abdominopelvic region. Of the 51 patients receiving WAP-RT, 20 also received IP-RIT before WAP-RT. PFS and OS for patients receiving WAP-RT was significantly better than those not receiving WAP-RT. For the former and latter groups, median PFS was 11.5±0.8 and 22.1±5 months ($p < 0.005$) respectively; median OS was 32.3±7.5 and 74.3±23.6 months respectively ($p=0.001$). Two-year PFS for patients treated with WAP-RT and those not receiving WAP-RT was 18±7% and 47±8% respectively; 5-year OS in the respective groups was 14±7% and 60±8% respectively ($p<0.05$ for both PFS and OS). For patients treated after 2009 (when IP-RIT was first introduced), survival for those receiving IP-RIT+WAP-RT (n=20) was superior to median those receiving WAP-RT alone (n=11) ($p<0.05$ for OS). Both therapies were well tolerated and administered on an outpatient basis.

Conclusion: WAP-RT after R1-resection significantly improved survival in patients with DSRCT and WAP-IMRT due to its improved toxicity profile should be considered standard-of-care in patients with DSRCT who can undergo R1-resection. IP-RIT with ^{131}I-omburtamab in addition to WAP-RIT appears to improve outcome further and deserves further investigation in phase II/III studies.

Poster 149 3042568

ADVANCED EPITHELIOID HAEMANGIOENDOTHELIOMA: FEVER, PAIN AND PLEURAL EFFUSION PREDICT A WORSE OUTCOME

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Objective: Epithelioid hemangioendothelioma (EHE) is an exceedingly rare soft tissue sarcoma subtype. Most patients present at diagnosis with multifocal/multicentric disease. EHE clinical behavior is highly unpredictable, with indolent as well as very aggressive presentations. Though surgical resection is standard treatment for primary localized cases, in advanced patients a close, active surveillance (AS) is often selected, delaying any treatment to evidence of disease progression. We report on a retrospective study aimed at identifying clinical features associated with a more aggressive behavior.

Methods: Patients affected by advanced EHE treated in 6 centers of the Italian Rare Cancer Network were retrospectively reviewed. An expert sarcoma pathologist confirmed the diagnosis and molecular analysis was performed. Baseline clinical features were evaluated, including the presence of systemic symptoms (fever, weight loss, anorexia), tumor related pain and pleural effusion, number of organs involved (1 vs >1 and 1-2 vs >2), mitotic index (<2 vs ≥2 mitosis/10 high power fields - HPF). Response and progression were defined according to RECIST 1.1. Survival functions were estimated by Kaplan-Meier method and prognostic factors were evaluated in a multivariate model.

Results: 52 patients were identified (M:F = 31:21; mean age = 42 yrs - range = 16-78; median number of mitosis/10 HPF = 2 - range 0/8; systemic simptoms Y:N = 17:35; fever Y:N = 14:38; tumor-related pain Y:N = 18:34; pleural effusion Y:N = 6:46). All patients had metastatic disease; 20 had only one organ involved, while 32 had multicentric disease (13 of them with >2 viscera). At the time of initial diagnosis, all patients were naive from any systemic therapy and underwent exclusive AS. With a median FU of 28 months (range: 3-212), 31 (63%) patients progressed, while 22 (37%) remained stable. No spontaneous regressions were observed. Median PFS was 29 months (range 2-115). Median OS was 52 months (range 3-146). Age, gender, mitotic index, number of involved organs, anorexia and weight loss did not correlate with median PFS (m-PFS). Fever correlated with shorter median PFS (8 vs 43 months, *P*=0.007), as well as pain (10 vs 41 months, *P*= 0.03) and the presence of pleural effusion (5 vs 44 months, *P*=0.001). In addition, fever and pleural effusion correlated with a shorter median OS [32 vs 61 months (P=0.02) and 12 vs 73 months (P<0.001), respectively]. Similarly, the presence of pain corresponded to a non significantly worse median OS (42 vs 56 months, *P*=0.12).

Conclusion: Although in a small number of cases, this retrospective study suggests that in advanced EHE patients fever and/or tumor-related pain and/or pleural effusion is associated with a more aggressive clinical behavior, with a median PFS of <1 year. Pleural effusion was associated with the worst outcome, with a median OS of 12 months. These data are worth confirming on a larger patient population to help define prognostic factors in such an ultra-rare condition.

Poster 150 2998833

THE PROGNOSTIC SIGNIFICANCE OF SURGICAL TREATMENT FOR EXCESSIVE ELDERLY PATIENTS WITH SOFT TISSUE SARCOMA

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Objective: Soft tissue sarcoma (STS) mainly occurs in middle-aged and senior citizens. In recent years, the incidence of STS in older patients has been increasing, and an older age has been reported as one of the factors indicating a poor prognosis. Although radical resection is important in the treatment of STS, less aggressive treatment is sometimes selected in elderly patients because of their comorbidities and decreased performance status. It has been reported that surgical treatment for elderly STS patients improves their prognosis. However, few studies have examined advanced elderly patients. We evaluated the clinical features of advanced elderly patients with STS.

Methods: One hundred and forty-four patients were included in this retrospective study, and we divided them into two groups based on a cut-off age of 85 (Older and Younger groups). In these patients, a total of 25 patients (17.3%) were older than 85 years. The histological diagnoses were: undifferentiated pleomorphic sarcoma, myxofibrosarcoma, dedifferentiated liposarcoma, pleomorphic liposarcoma, myxoid liposarcoma, and synovial sarcoma. The patients' informations, including age, sex, tumor type, anatomical location of the tumor, period from onset to consultation, size, past inappropriate excision, metastasis at diagnosis, AJCC stage, FNCLCC classification, treatment-related factors, local and distant relapse, follow-up period, and outcome, were collected. We obtained some information about the type of local therapy and surgical margin (Enneking criteria) in those with surgery as a treatment-related factor. We compared the clinical courses between the 2 groups. In addition, we examined factors affecting the prognosis of older patients.

Results: No patients died of complications during the perioperative period. In all patients, the frequency of chemotherapy in the older group (4.0%) was significantly lower than in the younger group (30.3%) (P<0.01), and the follow-up period in the older group was significantly shorter than in the younger group (P<0.01). Surgical treatment was refused more frequently in the older group (P=0.01). The 3- and 5-year overall survival (OS) rates of the older group were 36.8 and 28.5% and those of the younger group were 58.2 and 54.4% respectively, showing no significant difference between the 2 groups. However, Kaplan-Meier overall survival curves in the older group revealed a significantly poorer prognosis than that of the younger group (P<0.05). In patients with localized disease at presentation treated with surgery, the 3- and 5-year OS rates of the older group were 58.3 and 57.1 % and those of the younger group were 71.8 and 64.7%, respectively, showing no significant difference between the 2 groups. Kaplan-Meier overall survival curves between the 2 groups showed

no significant difference. Both in uni- and multivariate logistic regression analyses, only surgical treatment affected the prognosis of older patients (P<0.01).

Conclusion: Although the prognosis of advanced elderly STS patients is generally poor, that of STS patients with surgical treatment is not poor. Only surgical treatment intervention strongly influences the prognosis, and so the prognosis may be improved with aggressive surgical treatment.

Poster 151 3039056

CLINICAL OUTCOMES AND COSTS FOLLOWING UNPLANNED EXCISIONS OF SOFT TISSUE SARCOMS IN THE ELDERLY: DOES PREOPERATIVE PLANNING CHANGE OUTCOMES?

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[1]*UC Davis Medical Center, Sacramento, CA, USA*

Objective: Surgical guidelines for soft tissue sarcoma (STS) emphasize pretreatment evaluation, and reports of the perils of unplanned excision exist. Given the paucity of population-based data on this topic, our objective was to analyze outcomes of planned versus unplanned STS excisions in the Medicare population.

Methods: We analyzed 3,913 surgical STS patients ≥66 years old from 1992 to 2011 using SEER-Medicare. Planned excisions were classified based on preoperative MRI and/or biopsy, whereas unplanned excisions were classified by excision as the first procedure. Inverse probability of treatment weighting with propensity scores was used to adjust for differences in clinicopathologic characteristics. Re-excisions, complications, and Medicare payments were compared with multivariate regression and generalized linear models. Overall (OS) and disease specific survival (DSS) were analyzed using cox proportional hazards and competing risk models.

Results: Prior to the first excision, 24.3% had a MRI & biopsy, 27.3% had a MRI alone, 11.4% had a biopsy alone, and 36.9% were unplanned. Re-excision rates were highest for unplanned excisions: 47.3% compared to 18.9% for MRI & biopsy, 36.7% for MRI alone, and 30.9% for biopsy alone (p<0.0001). Complication rates for the first excision and for all excisions combined were higher among patients with a MRI & biopsy (24.5% and 27.3%) and MRI alone (17.5% and 23.5%) compared to unplanned excisions (14.1% and 20.1%, p<0.05). There was no difference in DSS or OS between groups (p>0.05, Figure 1). Planned excisions were associated with increased Medicare costs ($23,562 for MRI & biopsy, $22,563 for MRI alone, & $27,413 for biopsy alone vs. $20,059 for unplanned, p<0.05), with the first resection contributing to the majority of costs. Subgroup analyses by histologic grade and tumor size revealed similar results.

Conclusion: Survival was comparable with greater complications and healthcare costs in elderly patients undergoing planned STS excision. Although unplanned excisions remain a quality of care issue with high re-excision rates, these data have important implications for the surgical management of STS in the elderly.

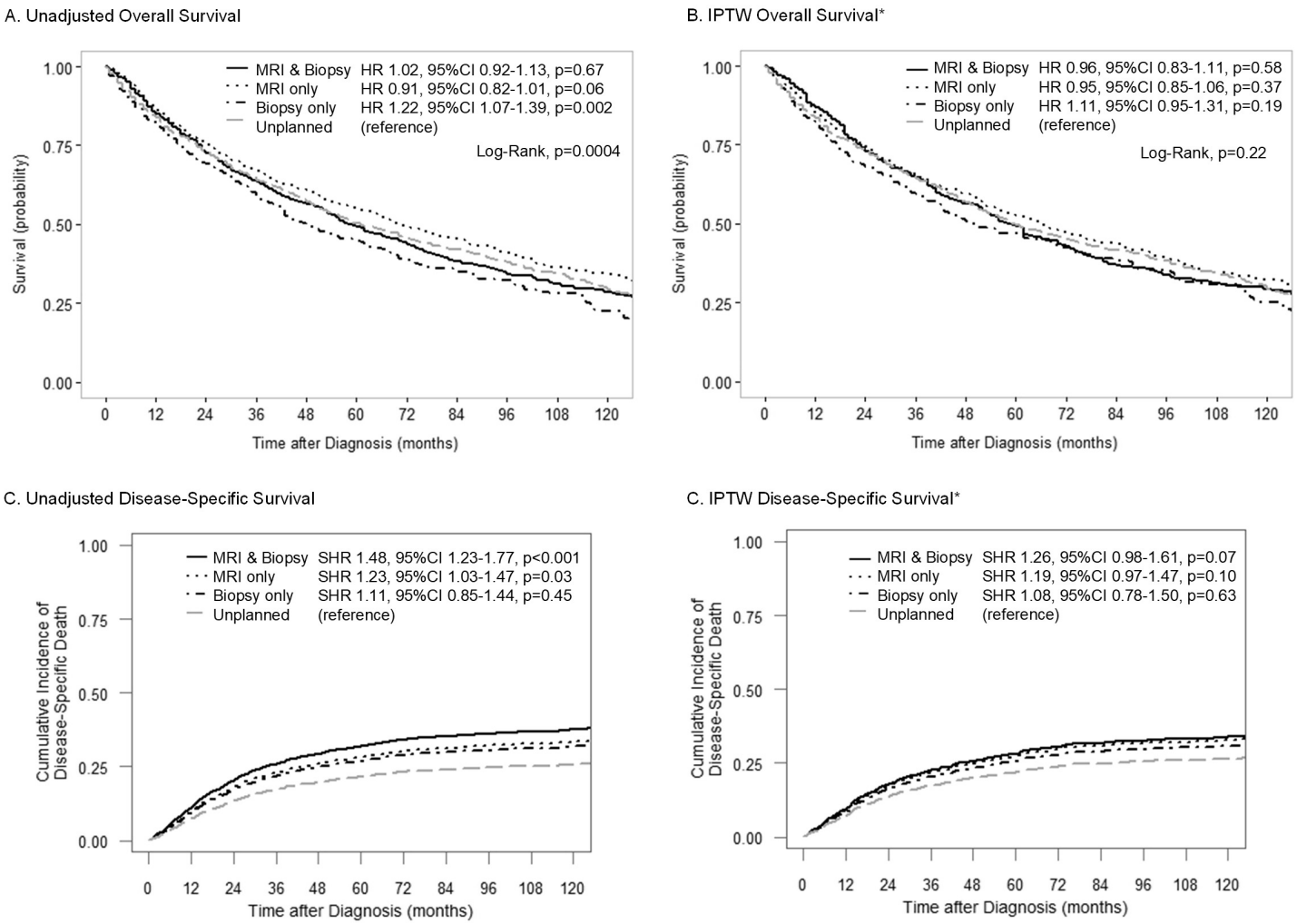

Figure 1. Survival for planned versus unplanned excisions with (A) unweighted and (B) inverse probability of treatment weighted (IPTW) Kaplan Meier curves for overall survival and (C) unweighted and (D) IPTW cumulative incidence curves for disease specific survival. *Model adjusted with IPTW (using propensity scores created from model with covariates: age, gender, race, CCI, tumor histology, size, grade, site, depth, and year of diagnosis) and for chemotherapy and radiotherapy. SHR, subhazard ratio.

Poster 152 3041503

EXTREMITY SOFT TISSUE SARCOMA IN THE ELDERLY: ARE WE OVERTREATING OR UNDERTREATING THIS VULNERABLE PATIENT POPULATION?

Alicia A. Gingrich[1]; Sarah B. Bateni[1]; Steven W. Thorpe[1]; Arta M. Monjazeb[1]; Amanda R. Kirane[1]; Richard J. Bold[1]; ***Robert J. Canter[1]***

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Objective: The surgical management of elderly patients is a topic of increasing attention, especially as the population ages and the incidence of cancer rises. As few studies have examined differences in patterns of care and surgical outcomes among elderly soft tissue sarcoma (STS) patients, our objective was to analyze the clinical, pathologic, and treatment variables for elderly STS patients, hypothesizing greater short-term morbidity and mortality but preserved superior long term oncologic among elderly STS patients having surgery.

Methods: Using the National Cancer Database (2004-2012), we identified 33,859 adult patients (18 - 99 yrs) with nonmetastatic extremity STS. Using the top quartile of age (≥ 74 years), we compared patient demographics, tumor characteristics, types of treatment and outcomes among the “elderly”. Cox proportional hazard analysis was used to determine multivariate predictors of overall survival (OS).

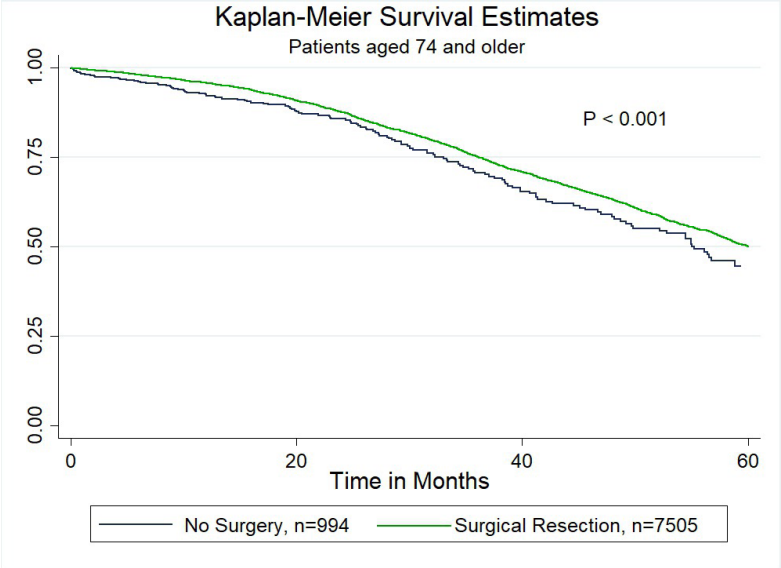
Results: Of the 33,859 patients, 8504 (25.1%) were ≥74. We observed significant differences in histologic grade, histologic

subtype, and facility type (P<0.05) between patients < 74 and ≥ 74, whereas other clinico-pathologic characteristics were similar. Among surgical patients, those ≥ 74 were less likely to undergo R0 resection (59.7 vs. 70% P = 0.001) and more likely to die within 90-days of the operation (4.3% vs. 1.2%, P = 0.001). However, elderly patients undergoing surgery experienced superior OS (median survival 36.8 months with surgery versus 11.4 months without, P=0.001), and multivariate analysis demonstrated surgical resection to be an independent predictor of OS among patients ≥ 74.

Conclusion: Surgical resection remains a key predictor of improved survival among STS patients ≥ 74, but early postoperative mortality is also significantly greater. These data highlight the narrower benefit/risk ratio of surgery among elderly STS patients for whom more age-specific algorithms may be indicated.

Survival by Grade in the Elderly (>74), Extremity STS, Stage I - III

WHO Grade	Median Survival (Months), Surgery	Median Survival (Months), No Surgery	P Value
I	43.9	15.4	<0.001
II	35.5	9.8	<0.001
III	27.8	6.5	<0.001
IV	28.8	6.0	<0.001



Kaplan-Meier Survival Analysis among Elderly Extremity STS Patients (≥ 74 years) Stratified by Receipt of Surgical Resection (excluding patients with metastatic disease or missing data).

Poster 153 WITHDRAWN

Poster 154 3042808

INFLUENCE OF AGE AND SUBTYPE IN OUTCOME OF OPERABLE LIPOSARCOMA

Daniela Greto[1]*; Giulia Stocchi*[1]*; Cristina Muntoni*[1]*; Giorgio Caramia*[1]*; Monica Lo Russo*[1]*; Anna Peruzzi*[1]*; Donato Pezzulla*[1]*; Mauro Loi*[1]*; Isacco Desideri*[1]*; Pierluigi Bonomo*[1]*; Giulio Francolini*[1]*; Domenico Andrea Campanacci*[2]*; Francesco Muratori*[2]*; Filippo Frenos*[2]*; Lorenzo Livi*[1]

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Objective: Liposarcomas (LPS) are rare malignancies that account for less than 20% of all soft tissue sarcomas. LPS derive from adypocytes and they can be classified in well-differentiated (WDLPS), de-differentiated (DDLPS), myxoid (MLPS) and pleomorphic liposarcomas (PLPS).
In this study, we collected and reviewed data from a cohort of patients treated at our institution, in order to evaluate whether clinical outcome in patients with non-metastatic LPS treated with curative intent is affected by clinical characteristics, tumor- and treatment-related features.

Methods: We retrospectively reviewed data of patients with locally advanced, non-metastatic LPS treated between 1990-2015 and with at least 5 years follow up. We identified two subgroups considering patient age, with a cutoff of 65 years. Major endpoints were Local Recurrence Free Survival (DFS-LR), Distant Metastasis Free Survival (DMFS) and Overall Survival (OS).

Results: Data of 186 patients with a diagnosis of LPS were collected. 27.4% of patients were 65 years or older at diagnosis. At a median follow-up of 8.6 years LR, DM and OS were 75.5%, 76.6% and 48.1%, respectively.
KM analysis showed that Age $\geq$ 65, DDLPS and lower limb localization were related to LR (p=0,001, p=0,0001 and p=0,0001,

respectively). Association between LR, Age and DDLPS persisted both at univariate (p=0,003 and p=0,0001, respectively) and multivariate Cox regression (CR) analysis (p=0,024 and p=0,002). Age, tumor depth and grading correlated to distant recurrence, both at KM (p=0,023, p = 0.026 and p = 0.016) and univariate CR (p=0,026, p=0,042 and p=0,012). Age and grading were confirmed at multivariate analysis (p=0,009 and p 0,017). WDLPS and wide excision resulted in a better OS (p=0,001 and p=0,03, respectively), while histologic G3 and age ≥ 65 were related with worse OS (p= 0,008 and p=0,0001, respectively). Age, DDLPS and Grade were related to OS at univariate (p=0,0001, p=0,0001 and p=0,03, respectively) and multivariate CR analysis (p=0,031, p=0,0001 and p=0,001, respectively). Analyzing the specific causes of death, elderly patients died more often due to other causes compared to younger population (p=0.006).

Conclusion: A tailored approach could be helpful in delineating therapeutic management of liposarcomas. Histotype-driven schedules of treatment should be developed to take into account biological heterogeneity of this disease. Further studies are needed to develop tailored treatment strategies in elderly STS, taking into account the frailty and peculiarity of this subgroup.

Poster 155 3042893

WORSE SURVIVAL IN OLDER ADULTS WITH RHABDOMYOSARCOMA: RESULTS OF A LARGE SINGLE INSTITUTIONAL COHORT

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Objective: To review the clinical outcomes of patients 15 years or older with RMS treated between 1969 and 2015 at Massachusetts General Hospital.

Methods: The clinicopathologic features, treatment methods, and disease outcomes were reviewed retrospectively for 138 patients (ages 15 years or older) with RMS who were consecutively treated between 1969 and 2015 at a single institution. Kaplan-Meier curves were used to present the cumulative probability of overall survival (OS) or recurrence free survival (RFS). Log-rank statistics were used to test whether there was a statistically significant difference in the cumulative proportions between groups. We used propensity score methods to minimize bias related to the nonrandom assignment of treatment (by age, site, histology, M-stage) and effect of age (by treatment, site, histology, M-stage). We estimated propensity scores using a logistic regression model that included the covariates. Multivariate Cox model was used to determine the association between various patient, tumor and treatment characteristics and OS. Factors significant on univariate analysis to a level of p<0.10 were entered in a hierarchical fashion using forward selection of the covariates' likelihood ratios.

Results: The mean age was 37 years (range: 15-86 years), the median follow-up time was 20.8 months, (range 0 – 410 months), the median tumor size was 6.15 cm (range: 0.9-26 months) and 69 (50.0%) of patients were female. Patients presented with locoregional (111, 80.4%) and distant (27, 19.6%) extents of disease. Tumor sites included genitourinary/gynecological/pelvic (43, 31.2%), head & neck (28, 20.3%), trunk/extremity (39, 28.3%), and parameningeal (26, 19.8%). RMS histology groups were embryonal (41, 29.7%), alveolar (40, 29.0%), pleomorphic (19, 13.8%), and not otherwise specified (38, 27.5%). Patients were treated according to the following treatment categories: chemotherapy, radiation (RT) and surgery (trimodality therapy; 37, 26.8%), surgery and radiation (10, 7.2%), surgery alone (18, 13.0%), surgery and chemotherapy (14, 10.1%), RT and chemotherapy (40, 29.0%), chemotherapy alone (5, 3.6%), radiation alone (4,2.9%), and no therapy (7, 5.1%). The majority of patients received chemotherapy on presentation (97, 70.3%). Five-year OS and RFS for the entire cohort were 31.8% (95% CI: 20.0-40.5%) and 32.3% (95% CI: 24.1-40.9%), respectively. The median OS was 1.9 years (95% CI: 1.4-3.1 years) and the median RFS was 1.3 years (95% CI: 0.7-1.8 years). When adjusted for age, site, histology, N-stage and M-stage, patients who did not undergo trimodality therapy had significantly higher risk of death than those patients who underwent trimodality treatment (AHR 2.5, 95% CI 1.3-4.5, p= 0.0037). In the Cox model, patients with parameningeal disease (AHR 2.2, 95% CI 1.1-4.6, p= 0.0289) had significantly worse overall survival that patients with malignancies of the trunk and/or extremity. In addition, patients with alveolar histology had a significantly decreased risk of death as compared embryonal histology (AHR 0.5, CI 95% 0.3-1.0, p=0.0379). After matching by propensity score, patients who were age ≥40 years had a significantly lower survival probability as compared to patients age <40 years (logrank p<0.001). Similarly, after matching non-metastatic patients by propensity score, those who received trimodality therapy had a significantly higher survival probability than patients who did not receive trimodality therapy (logrank p<0.0142)

Conclusion: Poor outcomes may, in part, reflect shortcomings in primary treatment; patients who received trimodality therapy had improved overall survival as compared to those who received other treatment. Our study also showed that the survival of patients age ≥40 years was significantly worse than those age <40 years. Further study is needed to elucidate the best way to integrate surgery, radiation, and chemotherapy to improve the outcomes of adult RMS patients.

Poster 156 2998752

PROGNOSIS OF ELDERLY PRIMARY OSTESARCOMA PATIENTS

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Objective: Although osteosarcoma is the most common malignant bone tumor in childhood, this tumor has another peak of incidence in the elderly. Various reports have stated that older patients with osteosarcoma show a poorer prognosis than adolescent patients. However, most of these studies included the sarcomatous transformation of Paget's disease of bone and secondary osteosarcoma after irradiation. Although several reports on only primary osteosarcoma in elderly patients have been published in recent years, few have examined the long-term prognosis. We evaluated the clinical features of elderly patients with osteosarcoma.

Methods: One hundred patients of primary osteosarcoma were included in this retrospective study (53 males and 47 females, with a mean age of 32 years, range: 7-84 years). We divided them into two groups based on a cut-off age of 40 (Older and Younger groups). In these patients, a total of 31 patients (31%) were older than 40 years. The patients' informations, including age, sex, tumor type, anatomical location of the tumor, metastasis at diagnosis, AJCC stage, the stage of the primary tumor, treatment-related factors, local and distant relapse, follow-up period, and outcome were collected. We obtained some information about the type of local therapy, rate of chemotherapy and its histological evaluation (Rosen and Huvos criteria), and the surgical margin (Enneking criteria) in those who had surgery as treatment related factors. We compared the clinical courses between the 2 groups in all and only deceased patients. In addition, we examined factors affecting the prognosis in older patients.

Results: In all patients, enforcement of chemotherapy in the older group (61.3%) was significantly fewer than in the younger group (98.6%) ($P<0.01$), and tumor was significantly often seen in axial bone in the older group ($P<0.05$). The outcome at the final follow-up in the older group revealed a significantly poorer prognosis than that of the younger group ($P<0.05$). The 5- and 10-year overall survival (OS) rates of the older group were 57.1 and 25.0%, and those of the younger group were 61.5 and 52.9%, respectively, showing a significant difference in the 10-year OS between the groups ($p<0.05$) Kaplan-Meier overall survival curves in the older group revealed a significantly poorer prognosis than that of the younger group ($P<0.05$). Only in deceased patients, the rate of chemotherapy in the older group (66.7%) was significantly lower than in the younger group (100%) ($P<0.01$). The 5- and 10-year OS rates of the older group were 42.1 and 0%, and those of the younger group were 13.8 and 4% respectively, showing a significant difference in 5-year OS between the groups ($p<0.05$). Kaplan-Meier overall survival curves between the 2 groups showed no significant difference. Only the existence of metastasis affects the prognosis in older patients ($P<0.01$).

Conclusion: Primary osteosarcoma in elderly patients showed a high incidence of axial bone involvement and low rate of chemotherapy. Although the final life prognosis is poor, the survival may be relatively prolonged. The presence of distant metastases markedly influenced the prognosis.

Poster 157 3031071

POSTOPERATIVE COMPLICATIONS, CLINICAL AND FUNCTIONAL OUTCOME OF ELDERLY PATIENTS WITH PRIMARY HIGH GRADE MALIGNANT BONE AND SOFT TISSUE TUMOR

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Objective: According to the 2017 population statics estimates from Statics Japan (http://www.stat.go.jp/english/index.htm), Japan is considered as a super aging society with 35.15 million people (27.7% of the population) over 65 years old and 17.48 million people (13.8% of the population) over 75 years old. Although the number of elderly patients undergoing surgery for primary high grade malignant bone and soft tissue tumor has also increased in Japan, there have been few previous studies on postoperative complications in these patients. The purpose of the present study was to retrospective analyze the postoperative complications, clinical and functional outcome of elderly patients with primary high grade malignant bone and soft tissue tumors.

Methods: Between April 2013 and December 2017, 764 patients of bone and soft tissue tumor visited to our hospital, 121 of whom were aged over 75 years. Twenty of 121 patients who had underwent surgery for primary high grade malignant bone and soft tissue tumor were included in this analysis. There were seven male and thirteen female patients with a median age of 82.9 years (range, 75-93) at the time of diagnosis. The mean follow-up period was 30.1 months (range, 2-73). A median

operative time was 248 min (range, 83-434). The mean hospital stay was 64.1 days (range, 26-158). Anatomical sites of tumor were 17 in extremity and 3 in non-extremity. The stage (AJCC Cancer Staging Manual, 8th Edition) of tumors was composed of 2 Stage2B and 1 Stage4 in three bone sarcomas, and 2 Stage2, 5 Stage3A and 10 Stage3B in seventeen soft tissue sarcomas (Table 1). The pathological diagnosis of three bone sarcomas were chondrosarcoma 2, fibrosarcoma 1, and of the seventeen soft tissue sarcomas were undifferentiated pleomorphic sarcoma 7, liposarcoma 3 (myxoid 2, dedifferentiated 1), synovial sarcoma 2, myxofibrosarcoma 1, others 4. We retrospectively reviewed American Society of Anesthesiologists-Physical Status (ASA-PS) score, Eastern Cooperative Oncology Group Performance Status (ECOG-PS) score at preoperative and hospital discharge period, postoperative complications, surgical margin, local recurrence, distant metastasis, oncological outcome.

Results: Postoperative complications (Common Terminology Criteria for Adverse Events v4.0, grade ≥3) were as follow: delirium (n=5), radiation dermatitis (n=3), wound infection (n=2), deep vein thrombosis (DVT) (n=1), urinary tract infection (n=1), pneumonia (n=1), gastric ulcer (n=1), delayed wound healing (n=1) and nerve palsy (n=1). There were 7 patients with ASA-PS score of 2, and 13 patients with the score of 3 and 4. The mean ECOG-PS score at preoperative period was 1.3, and that at hospital discharge was 1.75. Surgical margin were R0 in 14, R1 in 2 and R2 in 4. Local recurrences and distant metastases developed each in four patients (20%). Overall survival rate at final follow-up was 60%. The causes of death were 50% (4 patients) for original disease and 50% (4 patients) for other causes (Table 2). No significant differences in survival rate were observed between patients with ASA-PS score of 2 and with the score of more than 3 (p=0.0877, Log-rank test).

Conclusion: Incidence of postoperative delirium in age 70 years and older after orthopaedic surgery was 23% in the previous study. We found a 25% incidence of delirium in elderly patients undergoing musculoskeletal oncological surgery, and 50% of postoperative complications were delirium. It should be concerned about delirium after musculoskeletal oncological surgery of elderly patients. ASA-PS score was reported as a significant factor associated with poor prognosis of elderly patients with bone and soft tissue sarcoma. In this study, no significant differences were observed. It would be probably due to small number of cases and the short follow-up observation, thus, accumulation of further cases is necessary.

Table 1. Clinical informations for the elderly patients

All patients (n=20)	Number
Age (years)	
75-79	6
≧80	14
Gender	
Male	7
Female	13
Anatomical site	
Extremity	17
Non-extremity	3
Tumor size	
0-5 cm	2
5-10 cm	7
10-15 cm	6
>15cm	5
AJCC stage 8th	
Bone tumor	
IIA	0
IIB	2
III	0
IVA	0
IVB	1
Soft tissue tumor	
II	2
IIIA	5
IIIB	10
IV	0

AJCC, American Joint Committee On Cancer

Table 2. Complications, clinical and functional outcome

All patients (n=20)	Number
ASA-PS	
1	0
2	13
3	5
4	2
ECOG-PS	
Preoperative	
0	7
1	5
2	4
3	3
4	1
Discharge	
0	1
1	7
2	8
3	4
4	0
Surgical margin	
R0	14
R1	2
R2	4
Local recurrence	
No	16
Yes	4
Distant metastasis	
No	16
Yes	4
Oncological outcome	
CDF	10
AWD	2
DOD	4
DOC	4

CDF; continuous disease free, AWD; alive with disease, DOD; dead of disease, DOC; dead of other causes

Poster 158 3007555

THE ADDITION OF CYCLES OF IRINOTECAN/TEMOZOLOMIDE TO CYCLES OF VINCRISTINE, DOXORUBICIN, CYCLOPHOSPHAMIDE (VDC) AND CYCLES OF IFOSFAMIDE, ETOPOSIDE (IE) FOR THE TREATMENT OF EWING SARCOMA (ES).

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Objective: Treatment for ES in North America has evolved to include cycles of VDC and IE. A regimen including these 5 agents with interval dose compression has achieved 5 year EFS of 73% for localized ES. At Memorial Sloan Kettering (MSK) we have instead used the strategy of increasing doses of alkylating agents to achieve dose intensification and reported similar results. The combination of irinotecan and temozolomide (i/T) given as irinotecan 20 mg/m2/day for 10 days with temozolomide 100 mg/m2/day for 5 days has achieved objective responses for patients who recur after initial therapy with the 5 drug combination. Our prospective protocol incorporates cycles of i/T with cycles of VDC and IE for the treatment of newly diagnosed patients with ES.

Methods: We designed a prospective trial for the treatment of newly diagnosed patients with Ewing sarcoma. Patients were stratified by the absence (localized) or presence (metastatic) of clinically detectable metastatic disease at initial presentation. For patients with localized ES we administer high dose alkylator therapy with 4 cycles of VDC and 3 cycles of IE, followed by 6 cycles of i/T (Table). For patients who present with metastases we intercalate 10 cycles of i/T with the same 7 cycles of high dose alkylating agent therapy (Table). Local control for the primary tumor is scheduled following cycle 3. Patients with pulmonary metastatic disease receive whole lung radiation following completion of planned systemic therapy. Radiation is administered to all other metastatic sites when possible.

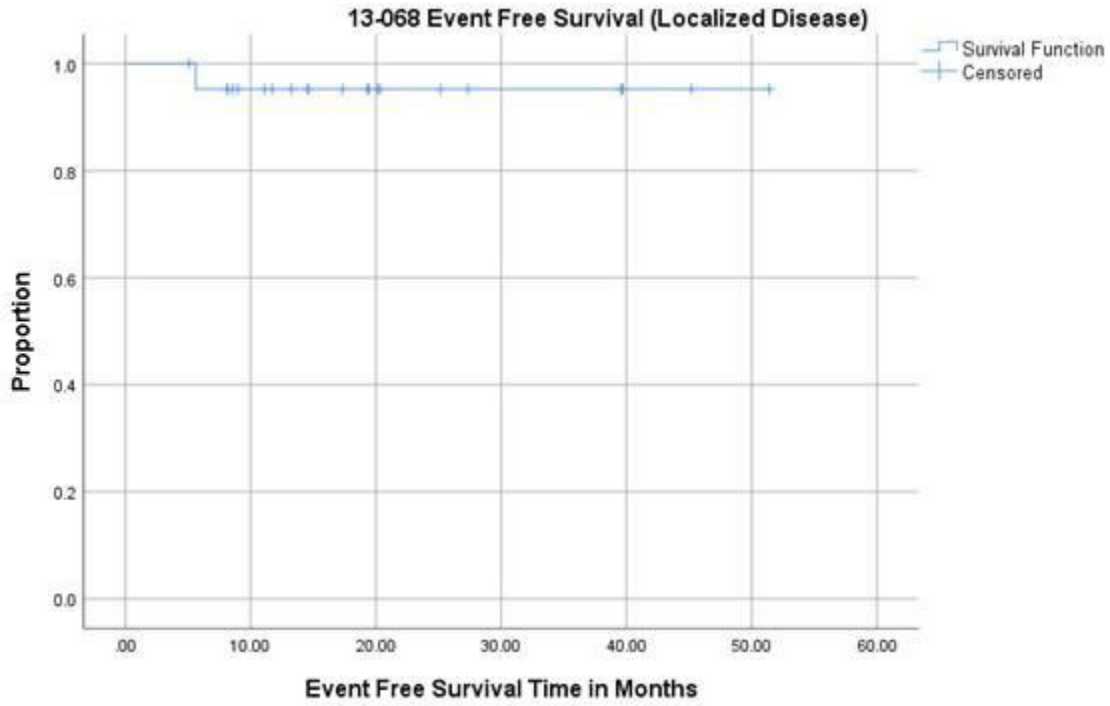
Results: We have enrolled 22 patients with localized and 17 patients with metastatic ES. With a median followup of 16 (5-52) months, patients with localized ES have achieved a 3 year EFS of 95% and overall survival (OS) of 95% (Figure). With a median followup of 21 (2-52) months, patients with metastatic ES have achieved a 3 year EFS of 50% and OS of 70%. Patients with metastatic disease limited to the lungs have a 3 year EFS and OS of 85%.

Conclusion: The addition of multiple cycles of i/T to conventional 5 drug therapy for ES is feasible and may be associated with an improved probability for both EFS and OS.

Ewing Sarcoma Treatment Regimen

Cycle	Localized Stratum	Metastatic Stratum
1	VDC	VDC
2	VDC	VDC
3	VDC	VDC
Local Control	Local Control	Local Control
4	IE	i/T
5	IE	i/T
6	IE	IE
7	VDC	i/T
8	i/T	i/T
9	i/T	IE
10	i/T	i/T
11	i/T	i/T
12	i/T	IE
13	i/T	i/T
14		i/T
15		VDC
16		i/T
17		i/T

VDC: Cyclophosphamide 2.1 g/m2/day x 2 days; Doxorubicin 37.5 mg/m2/day x 2 days; Vincristine 2 mg/m2/day x 1 day; IE: Ifosfamide 2.8 g/m2/day x 5 days; Etoposide 100 mg/m2/day x 5 days; i/T: irinotecan 20 mg/m2/day x 5 days x 2 weeks (10 total doses); Temozolomide 100 mg/m2/day x 5 days;



Poster 159 3027523

INVESTIGATING THE ROLE OF LSD2 IN EWING SARCOMA

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Objective: Ewing Sarcoma (ES) is the second most common solid bone malignancy diagnosed in pediatric and young adolescent populations. Despite decades of research and intensive multi-modal treatment regimes, the 5 year event-free survival rates has remained at 75% for patients with localized disease and 20% for patients with metastatic/relapsed disease, highlighting the need for novel therapeutic approaches. Recent studies have focused on epigenetic misregulation in ES development and potential new targets for treatment. Lysine specific demethylase 1 (LSD1/KDM1A), a flavin-dependent amine oxidase, has been noted to be highly expressed in ES cell lines and tumors. LSD1 plays an important role in epigenetics and serves as a catalyst for oxidative demethylation of mono- and dimethyl-lysine residues. Previous studies from our laboratory with SP-2509, a reversible LSD1 inhibitor have shown that treatment of ES cell lines with SP-2509 reverses the transcriptional signature driven by EWS/FLI accompanied by the induction of apoptosis. In addition, our data suggests that the degree of LSD2 (homolog of LSD1 that shares 31% sequence similarity), mRNA induction following SP-2509 treatment strongly correlates with drug sensitivity. LSD2 is another flavin-dependent histone demethylase which regulates histone lysine methylation, gene expression and chromatin function. Genetic depletion (shRNA) of LSD1 and LSD2 significantly impairs the anchorage independent growth of ES cell lines; however, the role of LSD2 in ES tumorigenesis is not well understood. The purpose of this study is to examine the role of LSD2 in the epigenetic regulation of ES and characterize genes regulated by LSD2 in ES. It is hypothesized that LSD2 is an epigenetic enzyme critical for cell proliferation and oncogenic transformation.

Methods: Endogenous knockdown of LSD2 was achieved through retroviral infection of A673 ES cells with control (iLuc) or two targeted LSD2 shRNAs. Oncogenic and proliferative capacity of A673 cells following LSD2 knockdown was assessed through IncuCyte live cell imaging and soft agar analysis with gene expression changes examined through RNA seq.

Results: Following LSD2 knockdown (maximum 70% protein reduction), the transformation capacity of A673 cells was significantly reduced, with an observed 5.5 fold reduction in colony number compared to iLuc control. Similarly, IncuCyte analysis revealed a significant reduction in proliferative capacity. A673 cells infected with iLuc shRNA control reached 100% confluency at approximately 100 hours post seeding, whereas upon LSD2 knockdown, 100% confluency was reached at approximately 160 hours. Also of note, LSD2 cloning experiments revealed two different isoforms of LSD2 expressed in A673 cells.

Conclusion: Understanding mechanisms of epigenetic misregulation in ES is crucial for our ability to further understand the basic biology of ES. We are the first to show the critical role of LSD2 in ES facilitating both proliferative and transformation capacity. RNA seq analysis is underway and will examine which genes are activated and repressed by the knockdown of LSD2. Furthermore, to confirm that the phenotype seen in cell proliferation and oncogenesis is actually due to loss of LSD2 expression and not an unknown downstream effect, we are currently cloning two overexpression LSD2 constructs, which will be used to rescue endogenous LSD2 expression. Although there are currently no small molecule agents that specifically target LSD2, our results warrant further investigations into agents that can inhibit this histone demethylase as a possible treatment for ES.

Poster 160 3034485

PROGNOSTIC VALUE OF TUMOR VOLUME IN PATIENTS WITH LOCALIZED EWING SARCOMA TREATED WITH INTERVAL-COMPRESSED CHEMOTHERAPY: A REPORT FROM CHILDREN'S ONCOLOGY GROUP STUDY AEWS0031

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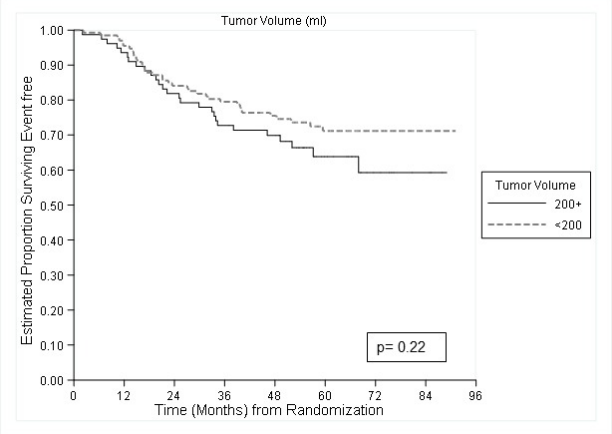
Objective: Data from several large retrospective and prospective studies have demonstrated that initial tumor size or volume is a strong independent prognostic factor in patients with localized Ewing sarcoma (ES). Tumors with either a maximal diameter > 8 cm or an initial tumor volume ≥ 200 mL have been associated with a less favorable outcome. However, none of these studies used interval-compressed (IC) chemotherapy as was given on Children's Oncology Group study AEWS0031, where data point restrictions prevented recording tumor size. Therefore, the prognostic value of tumor size using the North American standard chemotherapy remains unknown. The purpose of our study was to determine the prognostic value of tumor volume and size in patients with localized ES treated on AEWS0031.

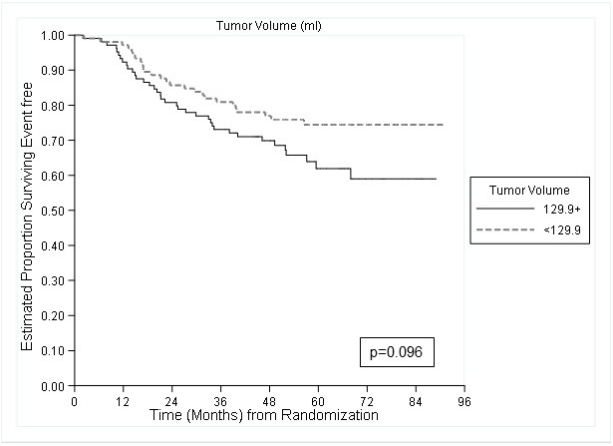
Methods: AEWS0031 (accrual 2001-2005) enrolled patients with localized ES and compared in a randomized fashion giving 5-drug chemotherapy every 3 weeks [standard timing (ST)] versus every 2 weeks (IC). For the purposes of this analysis, tumor measurements from diagnostic imaging studies were retrospectively collected from participating institutions. Patients with measurements obtained only from pathology or ultrasound reports were excluded. All tumors ≥ 20 cm were confirmed with the submitting institution for accuracy. Tumor volume was calculated only for individuals where 3 tumor measurements were provided. Event-free survival (EFS) was estimated using the Kaplan-Meier method, compared using the log-rank test, and modeled using Cox regression models.

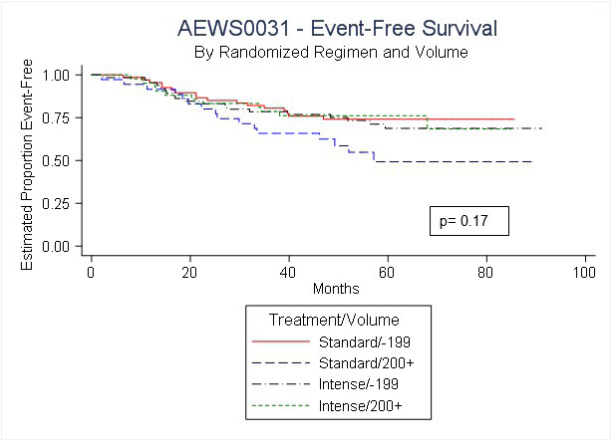
Results: Of the 568 eligible patients, we received at least one tumor measurement on 285 patients (50%). There were 210 patients who had all 3 tumor measurements available for volume calculation. There was no statistical difference in the EFS for patients who had tumor measurements provided compared to patients without tumor measurements. Median tumor volume for the entire cohort was 129.9 mL (range: 0.04 mL – 6696.3 mL). Seventy-eight (37%) of the 210 patients with volume calculations had tumors ≥ 200 mL, and they were equally distributed between treatment groups (p= 0.57). Compared to patients with tumors < 200 mL, those with tumors ≥ 200 mL were more likely to be older (p=0.03) and less likely to have an axial primary site (p=0.02). Patients with pelvic tumors had a higher but not significant proportion of patients with tumors ≥ 200 mL compared to patients with non-pelvic tumors (49% vs. 39%; p=0.13). In the overall cohort, having a tumor ≥ 200 mL was not associated



with inferior 5-year EFS (p=0.22; Figure 1). When we compared 5-year EFS using the median tumor volume (≥ 129.9 mL vs. < 129.9 mL), there was a trend towards inferior EFS among patients with larger tumors though this did not reach statistical significance (p=0.096; Figure 2). The potential prognostic value of tumor volume was more noticeable when analyzed as a continuous variable [hazard ratio = 1.0002 (95% confidence interval: 1.00001 – 1.0005); p=0.086]. Combining tumor volume and regimen demonstrates an apparent benefit in 5-year EFS among patients with tumors ≥ 200 mL who received IC chemotherapy though statistical significance was not met (p=0.17; Figure 3).

Conclusion: Having a tumor volume ≥ 200 mL did not show a statistical difference in outcome from patients with smaller tumors in this retrospective subset treated on the AEWS0031 study. Statistical power was limited by having tumor measurements on only half the subjects. Analyzing tumor volume as a continuous variable may be a better predictor of outcome than dichotomizing this factor. For patients with tumors ≥ 200 mL, IC chemotherapy may produce superior outcomes compared to ST; however, further studies with a larger sample size are needed. Analyses excluding patients who underwent a complete surgical resection are ongoing.





Poster 161 3034977

PATTERN OF TRANSLOCATION TESTING IN PATIENTS ENROLLING TO A COOPERATIVE GROUP TRIAL FOR NEWLY DIAGNOSED METASTATIC EWING SARCOMA: A REPORT FROM THE CHILDREN'S ONCOLOGY GROUP (COG)

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Objective: Molecular diagnostics are playing an increasing role in the diagnosis of Ewing sarcoma. This testing may help to distinguish Ewing sarcoma from potential mimics that lack typical *ETS* fusions. The extent and type of molecular testing being performed on these tumors is not well described.

Methods: COG trial AEWS1221 (NCT02306161) is a phase 3 randomized trial for patients with newly diagnosed metastatic Ewing sarcoma. Patients are required to have a histologic diagnosis of Ewing sarcoma or primitive neuroectodermal tumor, but confirmation of a typical *ETS* fusion is not required. Patients with Ewing-like sarcoma are excluded. Eligible patients are randomized to a conventional chemotherapy regimen or to that same regimen plus the IGF-1R monoclonal antibody ganitumab. At time of enrollment, sites complete a case report form detailing the type and results of any molecular diagnostics performed and these data form the basis for this report.

Results: This interim report is based upon data from 202 eligible patients out of a planned total enrollment goal of 300 eligible patients. The most common type of molecular testing was FISH performed on the primary tumor (147/202 patients; 72.7%). In these 147 patients, testing was positive for *EWSR1* translocation in 129 (87.8%) and technical failures reported in 2 patients. RT-PCR on the primary tumor was performed in 41/202 (20.3%). RT-PCR was positive for *EWSR1/FLI1* or *EWSR1/ERG* in 35/41 patients (85.4%). Only 14% of patients had neither FISH nor RT-PCR performed on the primary tumor.

FISH and RT-PCR testing on metastatic sites were performed in a minority of patients (12.4% and 6.4%, respectively). Next generation sequencing was reported in 2 patients on primary tumor and in 2 patients on metastatic sites. Evaluating all types of testing on either primary or metastatic tumor, 13 / 202 (6%) had no reported translocation testing. Evaluating all results from all testing, 33 / 202 (16%) lacked documentation of a typical *ETS* fusion.

Conclusion: COG sites enrolling to a Ewing sarcoma trial have high rates of testing by FISH or RT-PCR. A small proportion of patients have no translocation testing on either primary or metastatic sites. Next generation sequencing techniques are not yet commonly used in this context.

Poster 162 3042747

EXPERIENCE IN DIFFERENTIAL DIAGNOSIS OF EWING SARCOMA AND EWING-LIKE SARCOMA BY TARGETED RNA-SEQ

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Objective: Ewing sarcoma family of tumors (ESFT) are characterized by a canonical fusion involving *EWSR1* gene in most of cases, and *FLI1* as the most common partner. *Ewing-like* tumors (ELT) morphologically *resemble* ESFT but show a different clinical behavior and distinct chromosomal alterations involving *CIC* or *BCOR*. Therefore, differential diagnosis of ESFT and ELT upon histopathology and FISH can be challenging. Here we explored the potential of targeted RNA-seq as an ancillary technique to improve the precision of diagnostic.

Methods: 28 cases with morphology suggestive of ESFT or ELT were FISH-probed to detect *EWSR1* translocations (break apart probe). These 28 cases and 7 additional cases were assessed with Archer™ FusionPlex™ Sarcoma Panel.

Results: FISH *EWSR1* rearrangement was detected in 18 cases. Targeted RNA-seq identified different *EWSR1-FLI1* transcripts in 17 cases, and *EWSR1-NAFTC2* fusion in a single case, thus achieving 100% sensitivity. 10 cases were EWSR1 FISH negative, and targeted RNA-seq identified 3 cases expressing *EWSR1-ERG*, 3 cases with *CIC-DUX4*, 2 cases with *BCOR-CCNB3*, one case with *EWSR1-FLI1*, and one case without any fusion call. All cases without *EWSR1* FISH data showed fusions consistent with a previously rendered morphologic diagnosis (ESFT or ELT).

Conclusion: Targeted RNA-seq outscores *EWSR1* FISH determinations overcoming common pitfalls such us low performance in detecting *EWSR1-ERG*. Moreover, the RNA-seq panel simultaneously detects ELT gene fusions, circumventing singleplex FISH probing. We propose a diagnostic algorithm for differential diagnosis of ESFT and ELT in which negative *EWSR1* FISH determinations are followed by an RNA-seq targeted panel assess.

Poster 163 3042879

ROLE OF P21-ACTIVATED KINASES IN DEVELOPMENT AND PROGRESSION OF EWING SARCOMA

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Objective: p21-activated kinases (PAKs) are a group of intracellular serine/threonine kinases that regulate signaling pathways involved in critical cell functions including proliferation, anchorage-independent growth, therapeutic resistance, and promotion of invasion and metastasis. While PAKs are frequently overexpressed in a variety of non-sarcomatous malignancies such as melanoma, breast, colon, prostate, ovarian and lung cancers, their role in sarcomas has been extremely limited, particularly in Ewing Sarcoma (ES), where clinically effective molecular targeting has been challenging. In this study, we aim to investigate the role of PAKs in ES tumorigenesis, through demonstration of overexpression, over-activity, correlating that with disease aggressiveness and response to small molecule inhibitors with the goal of providing the preclinical data needed to advance these compounds to the clinical field.

Methods: To assess the expression status and protein abundance of PAKs in ES, we performed quantitative polymerase chain reaction (QPCR) and Western Blot (WB) assays on RNA and protein extracts from wild-type (WT) ES cell lines (CHLA-10, CHLA-9, TC71, A673, and TC32). Additionally, we evaluated the phenotypic effects of PAK pharmaceutical inhibition (using FRAX-597, PF-3758309, and KPT-9274) or knockdown (using small inhibitory RNA) on ES cells through colorimetric cell proliferation and invasion/migration assays. Correspondingly, WB assays were performed on protein isolates from ES cells treated with several PAK inhibitors to quantify total and phosphorylated protein levels. In vivo studies were completed using NOD-Prkdc^{scid}Il2rg^{tmiWjl} (NSG) mice injected with WT ES cells or xeno-transplanted with ES patient-derived xenografts (PDX), observed for first palpable growth, then treated with PAK inhibitors versus placebo

and periodically monitored for tumor growth; mice were humanely euthanized at the end of the experiment and their tumors harvested for histopathology, RNA, and protein extraction.

Results: Our data shows that ES tumor cells have high expression of total/activated PAK1 and PAK4, while molecular perturbation and pharmaceutical inhibition of these kinases have significant effects on tumor cell proliferative, migratory and invasive potential in vitro. Comparatively, small molecule inhibition of PAK4 using KPT-9274 has a significant efficacy towards diminishing primary and metastatic disease in vivo with a corresponding significant reduction in PAK protein levels in harvested tumor tissues.

Conclusion: Altogether, our results indicate that PAKs are pathologically overexpressed in ES cells, contributing to several of their phenotypic characteristics, notably proliferation, invasion, and migration. This is demonstrable through the significant attenuation of such attributes achieved via knockdown or pharmaceutical inhibition of PAKs in ES cells. Moreover, using PAK4 inhibitor (KPT-9274) in ES animal models shows a similar reduction in tumor growth, metastatic burden, and tissue protein levels. These findings support a potential role for PAKs in ES oncogenesis and their targeting in ES therapeutics in the near future.

Poster 164 3042853

ACTIVATION OF SPECIFIC KINASE PATHWAYS ARE REQUIRED FOR CD99 INHIBITION MEDIATED EWING SARCOMA CYTOTOXICITY

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Objective: Ewing sarcoma (ES) is a malignant tumor of unknown primary origin that mainly affects children and young adults. ES cells express high levels of the cell surface protein CD99, which is used for diagnosis of ES. More importantly, the inhibition of CD99 activity results in reduced growth of ES cells *in vitro* and *in vivo*. We aimed to discover small molecule inhibitors of CD99 and establish their molecular mechanism of action.

Methods: We performed a surface plasmon resonance screening experiment to discover compounds that can directly bind to extracellular domain of human CD99 protein. Cellular cytotoxicity was monitored by electric impedance and intracellular kinase cascades were evaluated by western blotting. Specificity of kinase pathways was evaluated by using a kinase inhibitor library screen.

Results: We identified clofarabine and cladribine as selective inhibitors of CD99 in ES cells. Clofarabine and cladribine directly bound to CD99, inhibited its molecular interactions, and regulated CD99 specific intracellular signaling pathways. Clofarabine and cladribine are FDA-approved purine analogs that are currently used in treatment of hematological malignancies due to their ability to inhibit DNA synthesis. We discovered a novel mechanism that functions on the plasma membrane and does not require intracellular activation or inhibition of DNA synthesis. In order to gain further insight into how clofarabine may regulate cellular functions through inhibiting CD99, we utilized a phospho-kinase array to identify changes in phosphorylation levels of 43 proteins in response to clofarabine or CD99 antibody treatment. We identified ERK1/2-MSK1/2-CREB signaling axis as the principal signaling pathway downstream of CD99. These findings were validated in four different ES cell lines and in xenograft lysates that were harvested from clofarabine-treated mice compared to control mice. The phosphorylation events induced by clofarabine treatment was significantly diminished when CD99 was knocked down either by siRNA-mediated knockdown or CRISPR/Cas9-mediated genomic disruption. Time-course experiments on ES cells showed that clofarabine triggers a very rapid signaling cascade through CD99. Cytarabine, a structurally similar pyrimidine analog and an inhibitor of the EWS-FLI1 transcriptional activity that has been failed in clinical trials on ES patients, did not activate ERK1/2, MSK1/2 or CREB phosphorylation on ES cells. In order to test whether the observed changes in phosphorylation levels are required for cell death, we screened a kinase inhibitor small molecule library for their ability to rescue clofarabine-induced cell death of ES cells. We identified TG100-115 (PI3K inhibitor) and rebastinib (c-abl inhibitor) as the most potent kinase inhibitors that showed significant reversal of clofarabine-induced ES cell death, suggesting that clofarabine-induced cell death of ES cells requires specific phosphorylation cascades.

Conclusion: We discovered a novel mechanism of action for clofarabine and cladribine in that their selective cytotoxic effect on ES is through inhibiting CD99 on the cell surface and it is not dependent on their ability to inhibit DNA synthesis. However, this cytotoxic effect requires activation of ERK1/2-MSK1/2-CREB pathway. These findings provide additional mechanistic support for repurposing clofarabine and cladribine for ES indication.

Poster 165 3041795

FUNCTIONAL STUDIES REVEAL DYNAMIC ROLE OF FLI IN EWS/FLI-DRIVEN EWING SARCOMA

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Objective: Ewing sarcoma (ES) is an aggressive bone- and soft tissue-associated cancer that affects pediatric and young adult patients. Despite the discovery of EWS/FLI as the sole oncogenic driver for this cancer almost 30 years ago, an extensive understanding of how this protein drives sarcomagenesis has not been established. Published work on other ETS factors implicates that the FLI domain likely acts in various roles in regulating EWS/FLI activity in ES, but surprisingly, very little work investigating these possible functions has been done. Up until this time, FLI's role in disease development has been viewed largely as the DNA-binding element, but this may be far more complicated than previously thought. It is likely that this lack of knowledge of the FLI domains function is a serious rate limiting step in developing new therapeutic approaches for these patients. Through various molecular biology techniques, this study established an understanding of FLI dynamics and the relationship it has in regulating transcriptional activation by EWS/FLI necessary for disease development.

Methods: EWS/FLI cDNA was used to create FLI mutants (n=9) by deleting specific regions of FLI to determine effects on EWS/FLI function. Luciferase assays were used to measure the transcriptional activation potential of each mutant compared to wild-type (WT) EWS/FLI. Additionally, the EWS/FLI mutants were expressed in A673 cells (a ES patient-derived cell line) to measure cell proliferation rates (IncuCyte Zoom), along with the ability to undergo oncogenic transformation in soft agar assays. RNA-sequencing was also performed to determine whether EWS/FLI mutants differentially regulate gene expression compared to WT EWS/FLI.

Results: Luciferase reporter assays revealed that neither the 5'- nor 3'-regions of the ETS DNA-binding domain (DBD) of FLI are required for EWS/FLI transcriptional activity. Additionally, we observed that only the ETS DBD of FLI (EWS/FLI$_{102\ AA\ ETS}$) was necessary for EWS/FLI transcriptional activation to occur. Studies completed in A673 cells revealed that the mutant EWS/FLI$_{102\ AA\ ETS}$ was able to rescue cell proliferation and oncogenic transformation similar to WT EWS/FLI, though only partial gene expression for commonly regulated targets of EWS/FLI was rescued with this mutant. These results indicate that FLI function is more complex than a simple DNA-binding element. RNA-sequencing experiments are in progress to reveal a possible gene signature attributable to specific regions of FLI.

Conclusion: Published work of other ETS factors indicates that there are various properties attributable to the protein domains in addition to DNA-binding. We are the first to investigate how the FLI domain may be acting in EWS/FLI function. Our findings support a dynamic model of FLI contribution to EWS/FLI activity in ES cells. Future studies to further explore FLI's role in ES include ChIP-seq, gel shift, and fluorescence anisotropy. These studies will help us to fully characterize FLI's role in EWS/FLI function and gain a deeper understanding of the basic biology of this disease. Although the development of inhibitors to specifically target this fusion protein have proven to be exceptionally difficult, it is our hope that our findings will help to elucidate new functions or downstream effectors that can one day be targeted.

Poster 166 3042272

INTEGRIN-MEDIATED SIGNALING AS A NOVEL THERAPEUTIC TARGET IN METASTATIC EWING SARCOMA

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Objective: Metastatic Ewing sarcoma (ES) has an extremely poor overall survival, necessitating investigations into the molecular mechanisms of metastasis to identify novel targets and develop new therapies. We previously performed an *in vivo* study, using our mouse model, designed to provide insights into the transcriptomic and proteomic signatures for metastatic ES to identify potential therapeutic targets. Comparing profiles of primary tumors to corresponding metastatic lesions, we identified aberrant expression of integrin ß3 (ITGB3) and activation of downstream integrin-linked kinase (ILK) in metastatic lesions compared to primary tumors, implicating this pathway as a key regulator in ES metastasis. We hypothesize that upregulation of ITGB3 and its downstream signaling events play a key role in ES metastasis and are viable therapeutic targets.

OBJECTIVE: To investigate the role of the ITGB3-ILK pathway and its downstream signaling events in ES metastasis and to investigate this pathway as a potential therapeutic target.

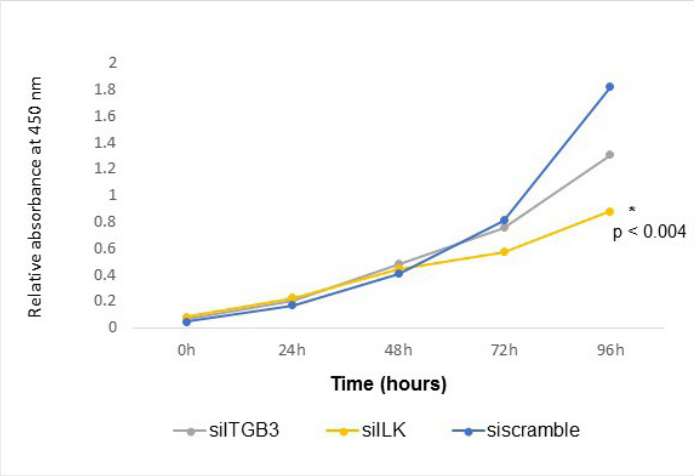
Methods: To begin to investigate the role of the ITGB3-ILK pathway, we used siRNA to knock down ITGB3 and ILK expression in ES cell lines and then performed functional assays *in vitro*, including cell proliferation and invasion/migration

assays. We also tested inhibition of this pathway using small molecule inhibitors targeting ITGB3, ILK and the downstream target activator protein-1 (AP-1), using Cilengitide, Compound 22 and SR11302, respectively. We are currently using these small molecule inhibitors as treatment *in vivo* and assessing rates of metastatic tumor formation in our mouse model compared to controls. We generated stable ITGB3 and ILK overexpression (OE) and knockdown (KD) cell lines, which we are using for similar *in vitro* and *in vivo* investigations.

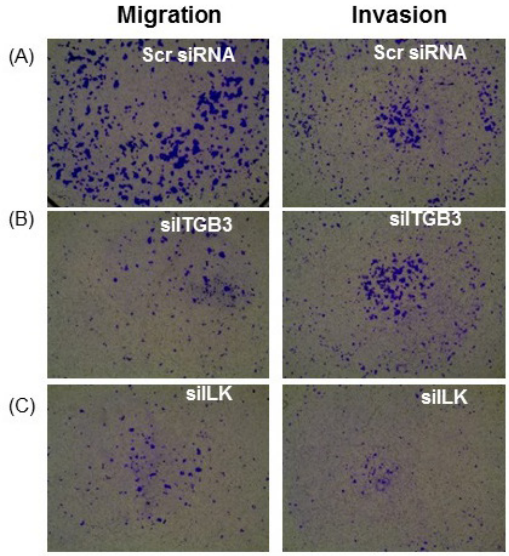
Results: Knockdown of ITGB3 and ILK in our siRNA ES cell lines resulted in decreased tumor cell proliferation and decreased invasion and migration compared to controls (Image 1). We also found significantly decreased ES cell proliferation using each of the small molecule inhibitors *in vitro* (Image 2). Our preliminary studies using Compound 22 *in vivo* established a safety profile and dose escalation is underway to assess the effectiveness of inhibiting ES metastasis in our mouse model, with encouraging initial results.

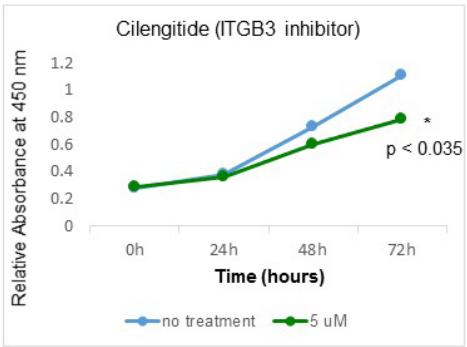
Conclusion: These results support our hypothesis that the ITGB3-ILK pathway and its downstream signaling events play a key role in ES metastasis and may serve as a potential therapeutic target. Therefore, we continue testing the effects of inhibition of this pathway on metastatic tumor development *in vivo* using our mouse model. We are currently investigating our ITGB3 and ILK overexpression and knockdown cell lines *in vivo* as well as several small molecule inhibitors. We are also taking advantage of immuno-precipitation mass spectrometry (IP-MS) to further characterize ILK binding protein complexes and utilizing phosphorylation arrays to analyze the changes in the phosphorylation profile of ILK, both of which will identify additional novel targets for investigation and potential future drug targeting.

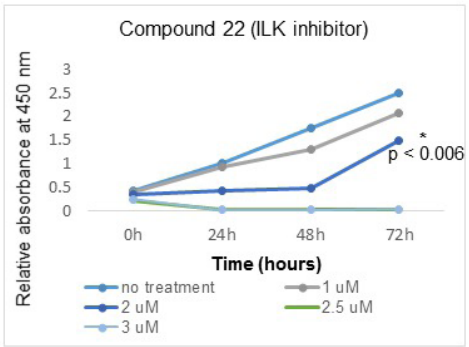
Cell proliferation assay:
Knockdown of ITGB3 or ILK decreases ES cell proliferation

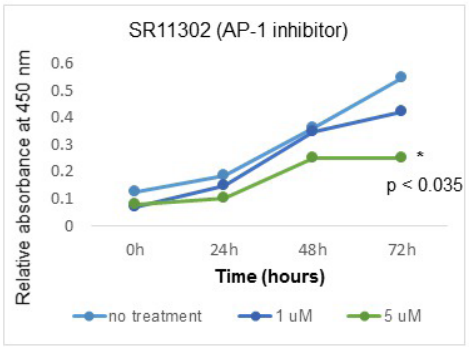


Invasion/migration assay:
Knockdown of ITGB3 or ILK decreases ES invasive and migratory phenotypes









Poster 167 3042275

A RATIONAL COMBINATION THERAPY APPROACH WITH RADIATION THERAPY IN EWING SARCOMA

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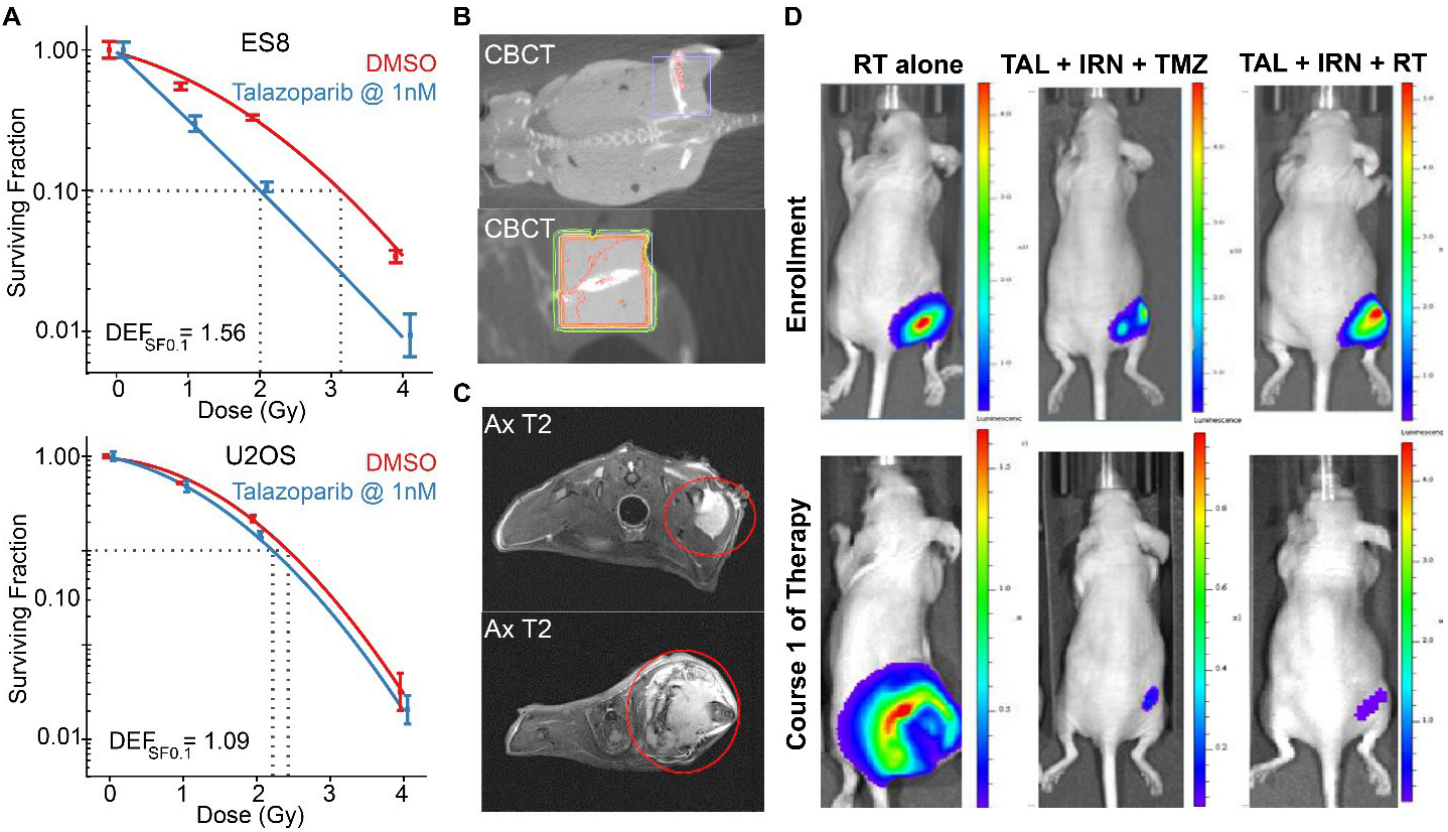
Objective: A central component of treatment for patients with Ewing sarcoma (ES) is radiation therapy (RT). While RT can significantly improve local tumor control, local failure ranges from 7-30% depending on the location of the tumor and other risk factors. RT to sites of metastatic ES has been associated with improved survival outcomes, yet dose and volume effects can influence the probability of long-term RT toxicities. Therefore, it is important to identify novel systemic therapy agents to enhance the therapeutic ratio of RT, as this may improve local tumor control and potentially enable rational RT dose de-escalation to limit toxicities. Given known deficits in DNA damage repair in ES, we hypothesize that compounds selectively targeting the DNA damage response may preferentially increase overall radiation-induced DNA damage in ES tumors relative to other pediatric sarcomas.

Methods: We investigated primary and recurrent standard of care (SOC) chemotherapeutics and late-stage clinical drugs as single agents and in combination with RT in the treatment of human ES cell line, ES8, and the osteosarcoma cell line, U2OS, using colony forming and CellTiter-Glo (CTG) assays. Cell cycle and DNA damage were assessed using immunofluorescence microscopy by quantifying Hoescht intensity and γ-H2AX foci, respectively. The effect of drugs on DNA repair was assessed using a cell-based assay that simultaneously measures the efficiency of homologous recombination (HR) and mutagenic non-homologous end joining (mNHEJ). Drug combinations were tested *in vivo* using orthotopic xenograft models of ES with image-guided fractionated irradiation and tumor burden was monitored via bioluminescence.

Results: At physiologically-relevant concentrations of the PARP inhibitor (PARPi) talazoparib (TAL), the combination RT + TAL potentiated ES cells significantly more than U2OS (at 1nM, Mean inactivation dose (DMSO) / Mean inactivation dose (TAL) = 1.74 vs 1.14, respectively, $p<0.001$, student's t test). The capacity of various clinically-relevant PARPis to potentiate RT-induced cellular lethality and double strand DNA damage in ES cells varied almost 1000-fold and correlated with PARP trapping potential, as assessed by CTG and γ-H2AX staining intensity, respectively. The combination of irinotecan (IRN)-TAL-RT was found to have equivalent tumor growth inhibition to IRN- TAL-temozolomide (TMZ), a combination currently



A). Radiation therapy (RT) and talazoparib (TAL) potentiated ES8 significantly more than U2OS. B). Cone Beam Computed Tomography (CBCT) scan of the tumor. C) MRI images of the tumor. D). The combination of irinotecan (IRN) -TAL-RT was found to have equivalent tumor growth inhibition to IRN- TAL- temozolomide (TMZ) *in vivo*.

under clinical investigation in pediatric patients with recurrent/refractory sarcoma (NCT02392793), both in ES cell lines and in ES mouse xenografts (median survival = 84 days for combination radiotherapy compared to 77 days for chemotherapy alone). Finally, *in vitro* profiling of lead clinical DNA damage repair inhibitors demonstrated that the ATM inhibitor (ATMi) AZD1390 significantly inhibited HR and strongly potentiated RT in ES cells.

Conclusion: The combination of TAL and IRN strongly potentiates the effect of RT in ES and may be a useful combination when RT is used in the progressive disease setting. AZD1390 shows remarkable activity in cell-based assays and warrants further investigation *in vivo*.

Poster 168 WITHDRAWN

Poster 169 3042421

THE ROLE OF HIGH DOSE CHEMOTHERAPY IN REFRACTORY AND RECURRENT EWING SARCOMA: REPORT OF A SINGLE CENTRE EXPERIENCE

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Objective: Five year survival from refractory or recurrent Ewing sarcoma is consistently reported to be less than 20% (1-3). The contribution of high-dose chemotherapy with stem cell transplantation (HDT) to improving survival is debated. As no randomised studies have been undertaken, high quality observational series are essential to inform practice.

Outcomes of all patients with primary refractory or recurrent Ewing sarcoma treated at a single centre over a 22 year period

were examined to identify prognostic factors with a view to developing a treatment algorithm to assist clinical management.

Methods: From 1995-2017, all patients with histologically proven Ewing sarcoma treated for refractory or recurrent disease were reviewed. Of those treated with HDT, 33 have been previously described (4), plus a further 6 patients included from the same period of 1992-94. Case notes were reviewed to identify patient, disease, and treatment factors at the time of primary diagnosis and progression/recurrence.

Results: Two hundred and nine patients were included in the study. Median age at diagnosis was 18 years (range 2-66 yrs). One hundred and fifty- eight patients (75%) relapsed within 24 months of initial diagnosis and 51 after 24 months. Forty-five (22%) patients had primary refractory disease; of these, 15 (33%) had presented with an extremity tumour and 38 (85%) with primary metastatic disease. In patients who developed recurrence, 73 (45%) had an extremity tumour at first presentation and 107 (61%) had localised disease.
At disease progression or recurrence, isolated local or isolated pulmonary recurrence was seen in 35 (17%) and 59 (28%) patients respectively. Sixty-eight (33%) patients were treated with an ifosfamide-containing regimen and 44 (21%) received no chemotherapy. Sixty-two (30%) patients received HDT: of these, 32 (52%) patients had relapsed within 24 months and 7 (11%) had primary refractory disease. Overall median event-free survival (EFS) was 15.2 months (range 2-274, 95% CI 13.5-16.9) but was significantly longer in those treated with HDT (20.1 months, 95% CI 20.8-27.5, p<0.0005). Patients with extra-pulmonary disease at recurrence were significantly less likely to be treated with HDT (chi square p<0.001).
Overall median post-relapse (PRS) and overall survival (OS) were 12.6 months (95% CI 10.1-15.1) and 28.5 months (95% CI 22.3-34.7). HDT patients experienced longer median PRS (84.6 months; 95% CI 9.3-159.9) and OS (115.8 months, 95 % CI 0.0-238.0) compared to 7.7 months (95% CI 5.5-9.9) and 21.1 months (95% CI 17.8-24.4) respectively for non-HDT patients (log rank p<0.0005). Non-HDT combined local and extra-pulmonary relapse showed the poorest outcome with median OS 8 months (95% CI 0-44); there were no long-term survivors in this group. Median OS for HDT patients with isolated local or pulmonary relapse was 205 (95% CI 104-308) and 296 months (95% CI 25-567) respectively. Of the 7 patients with primary refractory disease treated with HDT (2 isolated local and 5 isolated pulmonary progression), 4 are long term survivors (1 local, 3 pulmonary; Mean PRS 188 months, 95% CI 76-300).
Preliminary multivariate analysis showed risk of death was significantly increased by extra-pulmonary disease at relapse (HR 2, 95% CI 1.2-3.4, p<0.009) and significantly reduced by HDT (HR 0.2, 95% CI 0.14-0.4, p<0.0005) and disease recurrence >24 months (HR 0.4, 95% CI 0.24-0.6, p<0.0005).

Conclusion: Prognostic factors have been identified from this large cohort that are predictive of improved outcome from refractory and recurrent Ewing sarcoma. Further, these data support a role for the use of HDT in this setting, particularly for patients with isolated pulmonary or local progression. The data will be used to develop a treatment algorithm to facilitate treatment decisions in this challenging patient group.

Poster 170 3042564

EWINGS SARCOMA IN ADULTS - IS SOFT TISSUE EWINGS DIFFERENT FROM BONY EWINGS?

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Objective: Adult ewings sarcoma is an exceedingly rare and under reported entity. There are few studies addressing the treatment and outcome of these patients .These studies span over decades and patients in these studies were not treated on contemporary protocols.

Methods: It is a multicentric retrospective analysis of adult ewings sarcoma with data collected from April 2016 to May 2018 with 2 centres in New Delhi. Patients were treated uniformly by the standard protocol VAC/IE for nonmetastatic, local treatment included surgery, radiotherapy and VAC for metastatic disease. Survival curves were analysed by Kaplan Meir test, univariate analysis was done by Log Rank test and multivariate analysis was done by Cox regression test. All statistical analysis was done by SPSS version 23. Translocation studies were done whenever required.

Results: There were total of 60 patients with median age 27 years (range 18 to 58) with predominance of males (n=40,67%). Median duration of symptoms to presentation was 6 months, Tumour origin was bony in 31 (51%), soft tissue in 29(49%). Median tumour diameter was 8.7cm (2.5 to 25cm). Disease was localised in 33 (57%) metastatic in 25(43%). Primary sites of disease were appendicular in 30 (50%), head and neck in 4 (6.7%) ,chest in 5 (8.3%),

abd/pelvis in 19 (32%) ,spine in 2 (4%). Metastatic sites were only lung in 10 (16%) , lung & bone in 6 (10%), bone in 4 (6%), bone marrow in 4 (7%) . Univariate analyses was done for nonmetastatic vs metastatic patients, soft tissue vs skeletal involvement and the size of the tumour. On univariate analysis Outcome - median PFS was 16 months, (not reached in localised disease vs 9 months in metastatic group (p value -0.003). Median PFS was not statistically different between the skeletal and soft tissue ewings patients (p value - 0.4). Overall median OS was 18 months, median OS in localised disease was not reached vs 16 months in metastatic group which was not statistically significant (0.07). No difference in OS noted between the soft tissue and bony ewings group. On univariate analysis the size of tumour (<8 vs>=8cm) was statistically significant prognostic factor in terms of PFS (p value -0.041) and OS (p value -0.035). On multivariate analyses nonmetastatic vs metastatic (p value - 0.01) and the tumour size (p value 0.03) were significant prognostic factors.

Conclusion: Adult ewings sarcoma has less of appendicular and arises from soft tissue greater than pediatric patients. Contemporary protocols are well tolerated. Similar to pediatric ewings sarcoma size remains an important prognostic factor. Prognosis of the soft tissue ewings is not different from bony ewings. Longer follow up is required for our study for further data.

Poster 171 3027502

POTENTIAL EWS-FLI1- FOXM1- BUB1B AXIS CONTRIBUTES TO MITOTIC CELL CYCLE CONTROL IN EWING SARCOMA

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Objective: Ewing sarcoma (EwS) is an aggressive high-grade bone tumor in pediatric patients. Currently, high-risk patients are faced with severe treatment-associated toxicities and poor prognosis; therefore, novel treatment strategies are urgently needed. EwS driving mutation most often gives rise to the oncogenic transcription factor EWS-FLI1, which aid in the tumorigenesis and maintenance of EwS. To date pharmacologically inhibition of EWS-FLI1 have failed in clinical approaches. As a result, EWS-FLI1 cooperating pathways have received more scrutiny.
A dysfunctional mitosis spindle checkpoint induces chromosomal instability, aneuploidy and inaccurate distribution of genetic information during cell division. Complete loss of this checkpoint leads to mitotic catastrophe and apoptosis. BUB1B is an essential element of spindle checkpoint assembly (SAC). Dysfunctional mutations and overexpression of BUB1B have already been described in a variety of tumors, including EwS. We observed an association between higher BUB1B expression levels and lower patient survival rates. We hypothesize a potential link between EWS-FLI1 - FOXM1 - BUB1B. A therapeutic interference within this pathway could condition EwS cells to be more sensitive to agents—such as vinca alkaloids—that act at the mitotic and spindle level.

Methods: We targeted 709 human protein kinases with 4.675 distinct shRNAmir constructs (Decode Pooled Lentiviral shRNA Screening Library) and screened in a phenotype related cell model to elucidate candidate genes that are lost and specific to the EwS cell line A673 compared to a control cell line. NGS analysis combined with the application of a novel model-based algorithm, identified EWS-FLI1 dependent target genes that, if lost, are lethal for the oncogene expressing cell line compared to control. Candidate genes those loss leads to phenotype of interest have been validated in single shRNA loss of function approaches with subsequent functional approaches.

Results: Deconvolution of our high-throughput screen using pooled shRNA libraries directed at all human protein kinases, coupled to next generation sequencing lead us to investigate BUB1B. Additionally findings show first evidence that the EWS-FLI1 transcriptional target FOXM1 has a critical role in BUB1B regulation. Initial validation of BUB1B protein expression in distinct tumor cell lines was conducted by western blots. In keeping with our hypothesis, EWS-FLI1 modulation resulted in concomitant BUB1B expression changes. shRNA-mediated loss of BUB1B by means of BUB1B knockdown severely affected colony formation capability and to a lesser extend cell viability, although it was not EWS-FLI1 specific. Flow cytometry analysis of A673 cells treated with Colcemid revealed intact SAC with M-phase arrest, which was lost following BUB1B knockdown, indicating a BUB1B contribution to SAC in ES. We observed a decrease in protein and RNA levels of BUB1B as a result of proteasome inhibition of FOXM1 by Siomycin A in EwS cell lines—indicating a potential interaction between those two proteins.

Conclusion: Our high-throughput target discovery approach together with public data platforms and published literature

lead us to the above hypothesis of BUB1B as an important, EWS-FLI1 modulated element of the mitotic spindle assembly checkpoint in Ewing sarcoma (EwS). We illustrate the first steps towards characterization, functionality and therapeutic options of a potential link between EWS-FLI1- FOXM1- BUB1B in EwS. Our preliminary results support this hypothesis, warranting further investigation. Initial experiments determined protein expression levels, growth inhibition via proteasome inhibitor Siomycin A in distinct Ewing sarcoma cell lines. Further understanding of the EWS-FLI1- FOXM1- BUB1B axis in EwS and the corresponding functions, as well as evaluation of synergistically effects of BUB1B knockdown in combination with vinca-alcaloids, could expand standard therapeutic options.

Poster 172 3028111

CORRELATION BETWEEN PATHOLOGICAL, RADIOLOGICAL AND METABOLIC RESPONSE AFTER NEOADJUVANT CHEMOTHERAPY IN LOCALIZED EWING SARCOMA

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Objective: The pathological response, defined by the tumor necrosis grade after neoadjuvant chemotherapy, is the most important predictive factor in localized Ewing sarcoma. In poor responder patients, intensification of the treatment with high dose chemotherapy is supported by results from prospective studies. When surgery can not be performed, the evaluation of the response is based on imaging, MRI and CT. Previous studies reported that radiological response related with prognosis (Picci P. 1999; Ferrari S. 2011). The aim of this analysis is to evaluate the correlation between radiological, histological and metabolic response after induction chemotherapy in patients with localized Ewing sarcoma treated into the multicentric randomized phase 3 protocol ISG/AIEOP EW-1 (EudraCT no.2008-008361-35).

Methods: Patients enrolled into to the ISG/AIEOP EW-1 protocol from 2009 to 2017 with available pathological response after induction chemotherapy were included. The protocol foreseen randomization into two arms with the same drugs administered with different dose intensities schedules. Poor responders received high-dose chemotherapy followed by autologous stem cell reinfusion in both arms. Pathologic response was graded according to the Picci system: the presence of macroscopic foci of viable tumor (grade I) is defined as poor response, the presence of isolated microscopic nodules (grade II) or complete necrosis (grade III) are defined as good response. Radiological response was defined on the basis of the persistence (poor response) or complete disappearance (good response) of the soft tissue component at MRI. A good metabolic response was defined as SUVmax decreasing of more of 55% from baseline.

Results: 130 patients were identified. The pathologic response was grade I in 46(35%) patients, grade II in 32(25%) patients and grade III in 52(40%). 66(51%) patients had a complete disappearance of the soft tissue component at MRI. In the group of patients with good radiological response, tumor necrosis was grade II-III in 52(79%) cases and grade I in 14(21%) cases ($p<0.01$). In the group of patients with persistence of the soft tissue component at MRI, a grade I necrosis was found in 32(50%) cases, the remaining had a pathological good response: 13(20%) were grade II and 19(30%) grade III. The MRI sensibility and specificity were 70% (95%CI 55-82) and 62% (95%CI 51-72) respectively. The predictive positive value was 50% (95%CI 42-58) and the predictive negative value was 79% (95%CI 70-86). The diagnostic accuracy was 65% (95%CI 56-73). In 26 patients, metabolic response was available. 16(76%) patients with good metabolic response had grade II-III necrosis , 5(24%) patients had grade I. All patients with metabolic poor response had a grade I necrosis. PET sensibility and specificity were 50% (95%CI 19-81) and 100% (95%CI 80-100) respectively. The predictive positive value was 100% and the predictive negative value was 76% (95%CI 63-86). The diagnostic accuracy was 81% (95%CI 61-94).

Conclusion: The persistence of the soft tissue component evaluated by MRI doesn't predict a poor pathological response to neoadjuvant chemotherapy in patients with Ewing sarcoma. When surgery is not feasible, the use of PET seems to offer a better accuracy in order to identify poor responders candidate to intensification of chemotherapy. This evidence needs validation in the prospective forthcoming study.

Poster 173 3040767

INITIAL REPORTS OF LOCAL CONTROL MODALITIES IN EURO EWING 2012: AN INTERNATIONAL RANDOMISED CONTROLLED TRIAL OF CHEMOTHERAPY FOR NEWLY DIAGNOSED EWING SARCOMAS (ES)

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Objective: Euro Ewing 2012 (EE2012) is comparing a vincristine, ifosfamide, doxorubicin and etoposide (VIDE) versus VDC/IE (C=cyclophosphamide) induction chemotherapy strategy in newly diagnosed Ewing sarcoma, and testing the addition of zoledronic acid after induction chemotherapy. Local control of the primary tumour with surgery and/ or radiotherapy follows induction chemotherapy. In EE99 approximately 40 % received local radiotherapy to the primary tumour, and 70 % surgery. Observations from the Euro Ewing 99 study indicated that post-operative radiotherapy (PORT) may improve local control in patients with good risk disease; the radiotherapy guidance in EE2012 extended the indications for PORT especially in those patients with tumour up to resection margins, regardless of the percentage of necrosis. Here we report the initial data of the modalities of local control in EE 2012, just over two thirds through the trial.

Methods: Trial enrolment began in March 2014. Data was analysed only for those patients who had a radiotherapy to the primary tumour case report form (RPTCRF) completed so that the local control details were available, with a cut-off point of 19 February 2018. Data was analysed for radiotherapy received, indications and timing, surgery and reasons for subsequent radiotherapy. We also looked at whether patient age or the country of origin had an impact on local treatment modalities.

Results: At the cut-off date, 433 patients were enrolled in the study, of whom 231 had completed the study with an RPT CRF. Allowing for missing data at this time point, radiotherapy to the primary tumour was given to 64% (148/231), of which 19% (22/117) was pre-operatively. Reasons for pre-operative radiotherapy included risk of marginal resection or inoperable tumour. For the 64% who received radiotherapy, 27% (29/108) was for poor margins, 27% (29/108) for poor tumour necrosis, 27% (29/108) for tumour primary site- pelvis, spine, and the rest was "other" including for tumour fracture. For the UK, 64% (60/94) received radiotherapy, 71% (55/77) in France, 58% (26/45) in Spain, and for the other countries (Czech Republic, Netherlands, Ireland, Hungary and Belgium) 50% (7/14). At age 14 years and over, 67% (89/132) received radiotherapy and 60% (59/98) if less than 14 years old. Of the 77% (181/236) who had surgery to their primary tumour, 56% (102/181) had local radiotherapy as well.

Conclusion: These data appear to indicate that the number of patients receiving radiotherapy to the primary tumour has increased when compared to the previous European study EE 99.The use of radiotherapy shows variability amongst the European groups. The proportion of patients who receive surgery as part of their local control has remained static.

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Poster 174 3042720

EXPRESSION OF SLFN11 AND MGMT IN ARCHIVAL TUMOR TISSUE AS POSSIBLE BIOMARKERS OF RESPONSE TO TEMOZOLOMIDE AND IRINOTECAN IN RELAPSED EWING SARCOMA PATIENTS

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Objective: The combination of temozolomide and irinotecan is commonly used as salvage therapy for recurrent Ewing sarcoma. To date, no biomarkers have reliably correlated with response of sarcoma patients to this therapy. SLFN11 and MGMT are proteins which affect DNA repair, but through different mechanisms. For example, SLFN11 expression inhibits checkpoint maintenance and homologous combination repair, and has been correlated with sensitivity to topoisomerase 1 poisons such as irinotecan. In contrast, MGMT removes adducts placed on DNA by methylating agents like temozolomide, and therefore functions as a mechanism of resistance. We hypothesized that tumors most likely to respond to this combination are those with high SLFN11 and/or low MGMT expression.

Methods: Eligible patients included those with recurrent/refractory Ewing sarcoma who were treated with the combination

of temozolomide and irinotecan. Immunohistochemistry assays were optimized and used to assess SLFN11 and MGMT expression in archival tumors. A histology score (HS) was calculated by multiplying the intensity score (0-3) by the distribution score based on extent of expression (0-3). Expression was characterized as absent (HS =0), low (HS = 1-2), intermediate (HS = 3-4), or high (HS = 6-9). Response was assessed using RECIST (Response Evaluation Criteria in Solid Tumors) version 1.1.

Results: Of 19 consecutive patients identified at two institutions, 14 had tissue for analysis, and 12 were evaluable for imaging response. The median age was 20 years (range 7 to 29), and 8 were female. Patients received a median of 3 cycles of temozolomide + irinotecan (range 1-12), and 2 patients also received other agents with this drug combination (vincristine, olaparib). Seven patients (50%) experienced clinical benefit from this combination, defined as partial/complete response or receipt of 4 or more cycles of treatment. Archival tumors were obtained at diagnosis (n = 6) or at time of relapse/progression prior to temozolomide/irinotecan therapy (n=8). SLFN11 expression by immunohistochemistry was high in all Ewing sarcoma samples, and therefore was not specific enough to be predictive of response. Of note, this appeared to be particular to Ewing sarcoma, as SLFN11 expression was absent in other tumor types such as neuroblastoma and medulloblastoma. On the other hand, MGMT expression in Ewing sarcoma samples was variable, being absent in 6 samples, low in 2, intermediate in 4, and high in 2. In contrast to our hypothesis, low/absent MGMT expression in our immunohistochemical assay did not correlate with benefit from temozolomide and irinotecan. For example, of 7 patients with clinical benefit, 3 had intermediate or high MGMT expression. Similarly, of 7 patients without response, 3 had low MGMT expression.

Conclusion: Although preclinical data suggest that tumors with high SLFN11 and/or low MGMT expression would be responsive to the combination of temozolomide and irinotecan, our immunohistochemical analysis in this initial set of patients was not able to identify patients with expected clinical benefit. Further efforts to develop relevant biomarkers to this combination are underway, including the use of RNA-based techniques.

Poster 175 3042799

IGF-1R/MTOR TARGETED THERAPY FOR EWING SARCOMA: A META-ANALYSIS OF FIVE IGF-1R-RELATED TRIALS MATCHED TO PROTEOMIC AND RADIOLOGIC PREDICTIVE BIOMARKERS.

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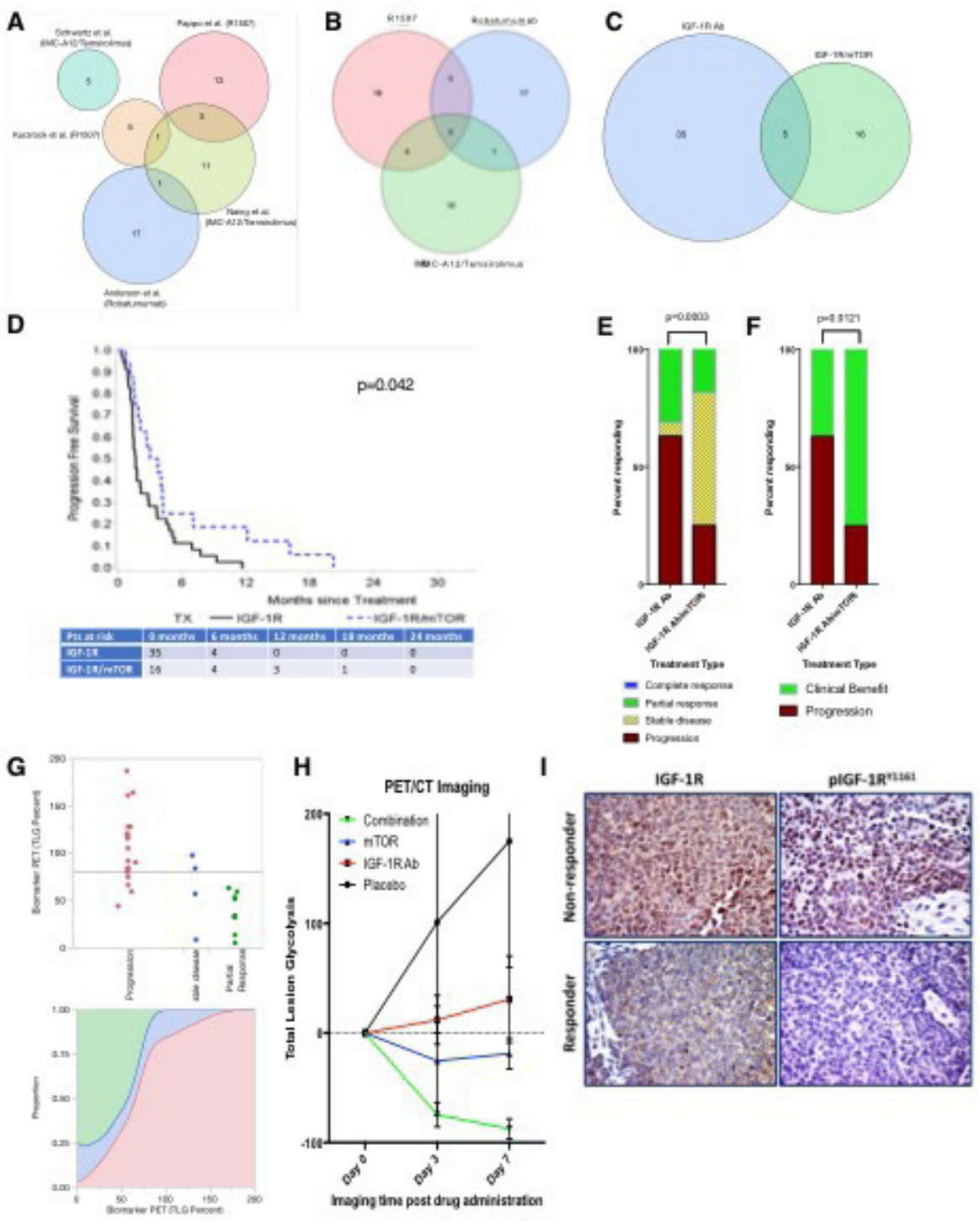
Objective: In the last decade, experimental IGF-1 receptor (IGF-1R)-targeted antibodies (Abs) have been shown to elicit dramatic tumor regression in 10-14% of the ES patients treated. However, the inability to prospectively identify IGF-1R-responders, short-lived 7-week response duration, and paucity of activity outside this orphan tumor type has tempered enthusiasm for additional single-agent IGF-1R-related studies. In addition to performing the first head-to-head comparison of IGF-1R Abs vs. IGF-1R/mTOR inhibitor combination, we sought to identify novel protein and radiologic biomarkers that, if prospectively validated, would improve personalized medicine by predicting which ES patients are most likely to benefit from IGF-1R-targeted therapies.

Methods: Using an IRB-approved clinical protocol, a single-institution meta-analysis was performed to assess the clinical outcome of all ES patients who had received an IGF-1R Ab either alone or in combination with temsirolimus at MDACC (Fig. 1A-C). Clinical and biological data from each of the five ES-focused clinical trials were used to identify proteomic and radiologic biomarkers that predict response to IGF-1R-targeted therapies.

Results: The IGF-1R/mTOR combination led to a superior PFS compared to single-agent IGF-1R Abs (Fig. 1D). Contrary to our expectation, a higher proportion of patients achieved a partial response when treated using single agent IGF-1R Abs (p=0.0003; Fig. 1E). Yet, the clinical benefit ratio (i.e., SD, PR, and CR) strongly favored the combination therapy since far more patients achieved SD in the combination group (p=0.0121; Fig. 1F), an effect attributed to the cytostatic nature of mTOR inhibitors. Clinical responses varied widely, as non-responders almost universally progressed before or during the

first restaging study. Notably, we prospectively validated SARC's data—which demonstrated that early post-treatment (day 9) PET/CTs can predict IGF-1R Ab response—and have identified total lesion glycolysis (TLG) as an even better metabolic biomarker (Fig 1G). Additionally, in vivo ES xenograft modelling suggests PET/CT may be informative as early as day 3 post-treatment (Fig. 1H). For the first time, we show that low pretreatment pIGF-1R expression is associated with improved clinical outcome (Fig. 1I)

Conclusion: The addition of mTORi to IGF-1R Abs led to improved PFS in advanced stage ES patients. Prospective validation of low or absent pIGF-1R as a predictive biomarker of response will require independent confirmation by other laboratories, as our sample set was small and unavailable for every patient. Taken together, protein and radiologic biomarkers of IGF-1R response provide an important first step towards personalized medicine for patients battling advanced stage ES. By identifying those most likely to respond to IGF-1R-directed therapies, the next step will be to identify the best drug(s), mTORi or others, to induce synergistic antineoplastic effects.



Poster 176 3042832

PRECLINICAL EFFICACY OF TARGETING EWSR1 IN EWING SARCOMA AND DESMOPLASTIC SMALL ROUND CELL TUMORS

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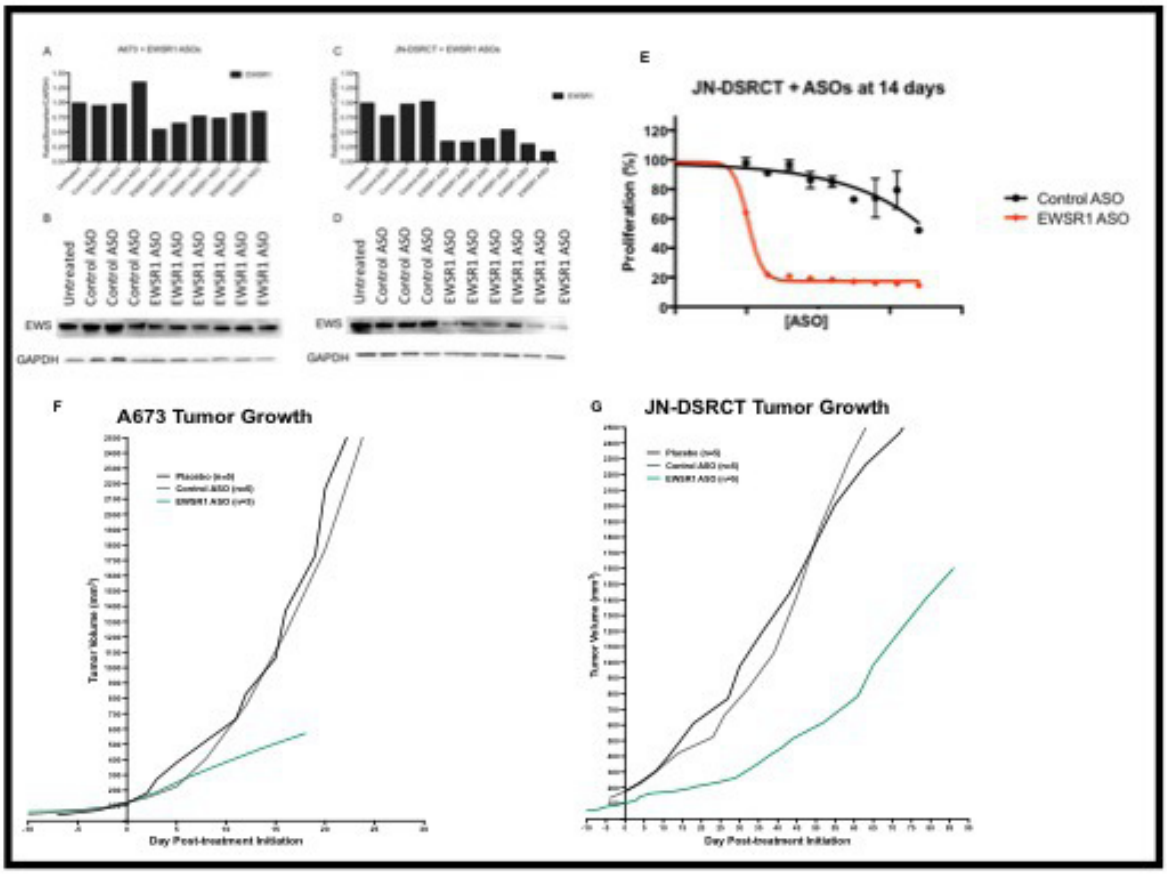
Objective: Ewing Sarcoma (ES) and desmoplastic small round cell tumors (DSRCT) are both aggressive small round blue cell tumors driven by the chimeric fusion between Ewing Sarcoma Breakpoint Region 1 (EWSR1) and various translocation partners. Although molecular profiling of these two sarcoma subtypes has improved our understanding and guided downstream therapies, direct targeting of these pathognomonic fusion proteins (FP) remains difficult. Emerging antisense therapies and other RNA interference options present a promising therapeutic alternative to target these FPs directly.

Methods: Anti-EWSR1 next generation (constrained ethyl, cEt) anti-sense oligonucleotides (ASOs) were screened in ES and DSRCT cell lines and efficiency of EWS protein knockdown was assessed by western blot. Preclinical efficacy was further assessed using WST-1 functional in vitro proliferation cell-based assays and by treating A673 ES and JN-DSRCT mouse xenograft models to evaluate the effect of EWSR1 knockdown on tumor growth in vivo.

Results: Treatment of ES and DSRCT cell lines with tool anti-EWSR1 ASOs led to reduced EWS protein expression compared to controls (Fig. 1A-D). Additionally, inhibition of EWSR1 in the JN-DSRCT cell line decreased cellular proliferation at both 7 and 14 days (Fig. 1E). Finally, mice bearing ES and DSRCT tumors showed reduced tumor burden and significantly improved survival compared to mice in the placebo and control ASO treatment groups. (Fig. 1F-G, p=0.0049 & p= 0.0058, respectively).

Conclusion: Treatment of ES and DSRCT with tool EWSR1-targeted ASOs partially suppressed their respective EWSR1 protein expression in vitro. Subsequent evaluation in xenograft models led to statistically significant delays in tumor growth. Though further investigation is warranted using higher fidelity models such as patient-derived tumor explants, our preclinical results demonstrate the early promise of ASOs in selectively targeting EWSR1 translocation-positive sarcomas. As anti-sense agents can be tailored to bind other gene targets, this technology could be adapted to treat other fusion-positive sarcoma subtypes. Further pharmacodynamics and pharmacokinetic studies paired with additional drug synergy work will help shed more light on these promising anti-sense targeted therapies for ES and DSRCT.

Figure 1



Poster 177 3042870

HOW DO WE ACHIEVE THE GREATER COLLABORATION NEEDED TO IMPROVE OUTCOMES FROM EWING SARCOMA: THE EXPERIENCE OF THE EURO EWING CONSORTIUM

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Objective: Ewing sarcoma, of which about 600 new cases are diagnosed in the European Union each year, is a well-recognised, intensively studied, rare bone cancer from which up to 30-40% of those affected still die despite complex, morbid treatments. Only a small proportion of those diagnosed are offered opportunities to participate in clinical research. Clinical experts in Ewing sarcoma from several European countries therefore joined together to work on improving survival from this disease.

Methods: Investigators responded to a European Commission call to fund “Investigator-driven treatment trials to combat or prevent metastases in patients with solid cancer”. Partners constructed a programme centred on two clinical trials with associated translational studies. The partners agreed approaches to introduce public and patient involvement into the work of the programme.

Results: is a randomised trial using multi-arm, multi-stage methodology to compare 4 chemotherapy regimens in patients with refractory or recurrent Ewing sarcoma. New arms with investigational agents can be added. The study has recruited 241 patients over 41 months from 14 countries.
Funding for biospecimen collection has enabled advances in the understanding of pathways and the identification of potential targets and resulted in 15 publications. Consent for biobanking has been obtained from over 95% patients and collection has been successful with registration of over 100 frozen tumour samples and over 230 FFPE samples. Patient and public involvement has been developed through the EEC project into a group of core patient advocates that give input into the direction of the EEC, grant applications and trial design as well as provide strong links with patient advocacy groups across Europe. Networking has been supported through twice-yearly Consortium meetings and opportunities for new investigators to present their work and to travel to other centres has been made possible through relationships developed through patient advocates.

Conclusion: Strategy-driven programmes of work undertaken through collaboration between investigators may be effective in increasing the rate of knowledge-gain and therefore, therapeutic improvements necessary to improve survival from a rare cancer. Funding support limited to clinical trials programmes is insufficient to maintain productive interaction between all stakeholders including patient advocates and so consortium or networking funding is vital.

Poster 178 3042886

EWS-FLI1 EXPRESSION LEVEL MODULATES T-CELL MEDIATED TUMOR APOPTOSIS IN EWING SARCOMA

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Objective: Metastatic Ewing sarcoma is a deadly bone cancer most commonly diagnosed in children. EWS-FLI1 is the fusion oncoprotein that drives the majority of Ewing tumors, and recent reports have demonstrated that the expression level of EWS-FLI1 in tumor cells dramatically influences the cell metastatic potential. Specifically, lower levels of EWS-FLI1 are associated with cell aggressiveness. Evasion of immune system surveillance is a key mechanism by which tumor cells survive and metastasize. Very little is known about the immune response to Ewing sarcoma tumor cells and whether tumor immune evasion contributes to Ewing sarcoma progression and metastasis. Given the emergence of cancer treatments aimed at enhancing the immune anti-tumor response, elucidating the mechanisms regulating the immune response to Ewing tumor cells may reveal much needed new treatment opportunities for patients with progressive/metastatic disease. In this study, we seek to determine the impact of tumor cell EWS-FLI1 expression level on T-cell mediated Ewing sarcoma tumor cell apoptosis.

Methods: In order to compare the susceptibility of Ewing sarcoma tumor cell EWS-FLI1 ‘high’ or ‘low’ populations to T-cell mediated apoptosis, we performed real-time monitoring of tumor cell caspase 3 activity in tumor/T-cell co-cultures. For this analysis, Ewing sarcoma tumor cell populations with ‘high’ or ‘low’ EWS-FLI1 expression were prepared by either: 1) using flow cytometry to isolate naturally occurring populations or 2) using EWS-FLI1 siRNA to generate EWS-FLI1 ‘low’ cells. Human T-cells were isolated from random donor buffy coat, and T-cells were activated using a CD2/3/28 antibody cocktail for 72 hours. We also directly treated Ewing sarcoma tumor cells with recombinant interferon gamma and the resultant upregulation of immune checkpoint ligands, PD-L1 and PD-L2, in EWS-FLI1 ‘hi’ and ‘low’ cells was compared using RT-PCR and flow cytometry.

Results: We found that Ewing tumor cells readily undergo apoptosis following exposure to activated human T-cells in our co-culture system. Notably, when comparing tumor cells with 'high' versus 'low' expression of EWS-FLI1, we found that EWS-FLI1 'low' cells demonstrate significantly less T-cell mediated apoptosis, suggesting that EWS-FLI1 'low' cells possess an ability to evade T-cell-mediated tumor killing. We next analyzed the influence of EWS-FLI1 level on tumor cell expression of PD-L1 and PD-L2, immune checkpoint ligands known to inhibit T-cell activation. We found that at baseline, EWS-FLI1 'low' cells demonstrate increased expression of both PD-L1 and PD-L2, compared to EWS-FLI1 'high' cells. Further, in comparison to EWS-FLI1 'high' cells, EWS-FLI1 'low' cells respond to interferon-gamma treatment with dramatically greater transcriptional upregulation of PD-L1 and PD-L2. We then assessed the impact of PD-1 blocking antibody on T-cell mediated tumor cell apoptosis and found that treatment of EWS-FLI1 'low' cell/T-cell co-cultures with blocking antibody significantly enhances T-cell-induced tumor cell apoptosis.

Conclusion: We have shown that Ewing cells with lower EWS-FLI1 are more resistant to T-cell mediated apoptosis than cells with higher EWS-FLI1. EWS-FLI1 'low' cells also demonstrate enhanced capacity to upregulate PD-L1 and PD-L2. As such, EWS-FLI1 'low' cells may serve as negative regulators of the immune response in Ewing tumors. These data highlight that Ewing tumor cell heterogeneity can influence the immune response and suggest that immunotherapy agents that block PD-1/ PD-L1 interaction may represent a promising approach to enhancing anti-tumor immune response to EWS-FLI1 'low' tumor cells.

Poster 179 3043033

THE ROLE OF DENOSUMAB IN JOINT PRESERVATION FOR PATIENTS WITH GIANT CELL TUMOUR OF BONE: NOT A MAGIC BULLET?

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Objective: The standard treatment for giant cell tumor of bone (GCTB), a locally aggressive osteolytic condition, remains extended intralesional curettage. Local recurrence continues to be a challenging dilemma for the orthopaedic oncologist treating GCTB, despite the use of surgical adjuvants. We previously reported the local recurrence rate for GCTB following extensive intralesional curettage at our institution to be 12-14%. Denosumab is a monoclonal antibody that competitively inhibits RANK ligand, interrupting the osteoclastic activating pathway responsible for the extensive osteolysis seen in GCTB. Initially Denosumab was suggested for management for unresectable GCTB; however recent interest has led to its increased use as neoadjuvant therapy for operable disease. In this setting, the goal of treatment is to facilitate joint salvage procedures via consolidation of periarticular and subchondral bone in otherwise difficult to resect tumors, as well as to decrease recurrence rates. We previously reported early results in a series of 20 consecutive patients with high risk GCTB treated with neoadjuvant Denosumab, with a local recurrence rate of 15% at a mean of 16 months. The goal of this study was to present updated mid-term follow-up results and to determine if the initial favourable results of Denosumab treatment were sustained.

Methods: Data was collected from our institute's prospectively collected bone tumour registry. All patients with GCTB considered 'high risk' for unsuccessful joint salvage, due to minimal residual periarticular bone, large soft tissue mass or pathologic fracture, were treated with both neoadjuvant Denosumab and extended intralesional curettage were included. Data including anatomical lesion site, surgical reconstruction method, local recurrence and development of metastasis during follow-up were analyzed.

Results: Twenty-five patients with high risk periarticular GCTB were treated with neoadjuvant Denosumab followed by surgical resection with extended curettage between January 2012 and March 2016. The mean average time to follow-up was 42 months. 48% of patients were female and the mean average patient age was 33.8 years. The tumour occurred most commonly around the knee in 17/25 cases (68%). The joint was successfully salvaged in 23/25 patients. Local recurrence developed at a mean average of 23 months in 8/25 patients (32%). One patient developed lung metastases which have been successfully controlled with Denosumab.

Conclusion: Although the early results of a clinical trial of neoadjuvant treatment of GCTB with Denosumab were optimistic, further follow-up demonstrated a higher than expected rate of local recurrence at 32%. While Denosumab leads to an increase in osseous consolidation which facilitates joint preserving surgery, the multi-loculated nature of the new bone matrix may trap stromal tumor cells thereby causing difficulty to determine the true margins of the tumor during intralesional curettage. Although Denosumab continues to have a role in maintenance therapy for patients with unresectable GCTB, its neo-adjuvant usage should be considered with caution in light of these results.

Poster 180 3041709

EPIGENETIC COMPOUND SCREEN REVEALS HISTONE DEACETYLASE INHIBITORS TO EFFECTIVELY TARGET THE NEOPLASTIC CELLS IN GIANT CELL TUMOR OF BONE

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Objective: Giant cell tumor of bone (GCTB) is an intermediate malignant lesion, driven by RANKL secretion of the neoplastic stromal cell leading to accumulation of the characteristic reactive giant cells resulting in osteolysis. Primary treatment is based on surgery and for recurrent or extensive tumor evasion treatment with an anti-RANKL antibody showed to be effective. However, the antibody should be continuously administered and does not target the neoplastic cells. Recently, a heterozygous missense mutation of the histone *H3F3A* gene has been described that result in substitutions at the G34 position, predominantly G34W substitution. The exact mechanism by which this histone mutation leads to neoplastic transformation is yet not understood. We established cell lines from GCTB after denosumab treatment which were confirmed to carry the H3F3A G34W mutation enabling us to perform drug screens to explore therapeutic options targeting the neoplastic cells.

Methods: A compound library containing 67 inhibitors of epigenetic enzymes including histone deacetylase (HDACs), SIRTs, histone demethylases (HDTMs), histone acetyltransferases (HATs), epigenetic reader domain blockers, histone methyltransferases (HMTs) and DNA methyltransferases (DNMTs) were applied on three different GCTB cell lines with verified H3F3A G34W mutation. Reactivity to compounds were measured by metabolic and cell count assays after 72 hours of incubation at two different compound concentrations. Positive hits were selected and dose response curves were established to determine IC50.

Results: A compound library containing 67 inhibitors of epigenetic enzymes including histone deacetylase (HDACs), SIRTs, histone demethylases (HDTMs), histone acetyltransferases (HATs), epigenetic reader domain blockers, histone methyltransferases (HMTs) and DNA methyltransferases (DNMTs) were applied on three different GCTB cell lines with verified H3F3A G34W mutation. Reactivity to compounds were measured by metabolic and cell count assays after 72 hours of incubation at two different compound concentrations. Positive hits were selected and dose response curves were established to determine IC50.

Conclusion: We established unique cell lines derived from GCTB tumor samples carrying the pathognomonic H3F3A G34W substitution. This is the first study in which epigenetic modifier compound screening was done on GCTB cell lines. These samples were sensitive to HDAC inhibitors while no sensitivity was observed using other epigenetic compound inhibitors, such as SIRTs, HDMs, HATs, HMTs, epigenetic reader domain blockers and DNMTs. The treatment with HDAC inhibitors led to direct cell toxicity. In conclusion, our results show that HDAC inhibitors might be used to target the neoplastic cells in GCTB directly. Further validation using xenograft models supporting these finding might serve as the base of a future clinical trial in advanced GCTB.

Poster 181 3041740

GIANT CELL TUMOUR OF DISTAL RADIUS: RESULTS OF WIDE EXCISION AND AUTOGENOUS NONVASCULARIZED FIBULA GRAFT RECONSTRUCTION

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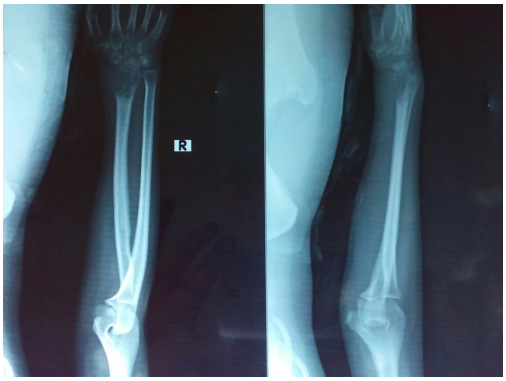
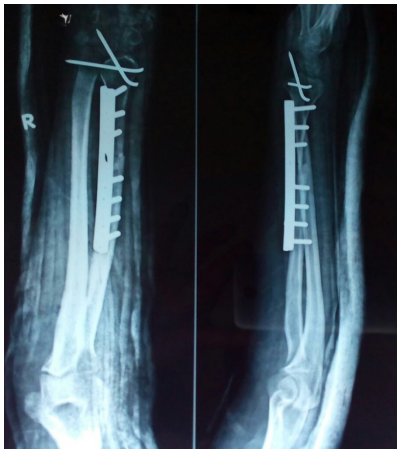
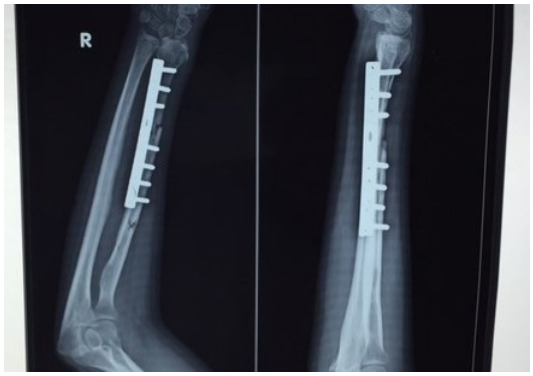
Objective: Treatment options for Giant cell tumour of distal radius include curettage with bone grafting or cementing, enbloc excision and reconstruction with non vascular or vascular fibular autograft, osteoarticular allograft, ulnar translocation, or endoprosthesis. Curettage with bone grafting can be done in Campanacci grade-I tumours but as these tumours are mostly asymptomatic most of our patients present in grade-II and III where enbloc excision and autogenous fibula grafting is the mainstay of treatment. Recurrence rate for primary treatment of GCT is relatively higher for curettage or extended curettage as compared to enbloc excision. Most of the patients of GCT are young adults, in their most productive age. The purpose of treatment includes the full tumor removal and function preservation. In this study we are presenting our results of managing giant cell tumour of distal radius with wide excision and autogenous nonvascularized fibula graft reconstruction.

Methods: We included 21 patients of giant cell tumour of distal radius with a mean age of 33 years(26-48 years).All the patients were evaluated preoperatively by plain X ray and MRI of wrist with forearm and plain x ray chest along with routine haematological investigations.
Wide excision and nonvascularized autogenous fibula grafting secured with plating was done. A k wire was then passed from fibula to ulna to stabilize fibuloulnar articulation . Another k wire was used to stabilize fibulocarpal joint, if thought

necessary but not routinely. Full weight bearing was allowed as tolerated. Above elbow slab was continued for 06 weeks and then K wires were removed and a functional brace was applied thus allowing elbow mobilisation. After 3 months gentle active and assisted wrist exercises were started and gradually increased in intensity depending on tolerance and progress. No heavy activity was allowed for a full one year.
At 06 weeks and then at 03 months, plain radiographs of forearm were repeated to see for union, recurrence of tumour or graft related complications. After first year, follow up was at 3 monthly intervals for one year and 6 monthly in 3rd year. Thereafter patients were evaluated annually till latest follow up. At most recent follow up, functional results were reported using the revised musculoskeletal tumour society score. Results were established as excellent for MSTS score > 90%, good for 80-90%, satisfactory for 60-80% and poor for ≤ 60% score. Results were assessed on the basis of Revised Musculoskeletal Tumour Society Score (MSTS).

Results: Mean follow up period was 3.0 years(1.8 to 3.8 years). Average time for fibuloradial union was 24 weeks (20-42 weeks). Average range of forearm movement was 45° supination to 30° pronation, 45° of palmar flexion at wrist and 30° of dorsi flexion. We reported excellent results in 10 of our patients,08 patients with good results and 03 patients with satisfactory results. We did not encounter any non-union at graft site , 03 of our patients developed stitch line infection and 02 cases developed soft tissue recurrence while 02 cases reported subluxation of wrist joint, another case reported implant loosening.

Conclusion: Wide excision and autogenous nonvascularized fibula grafing is a good option of treatment in giant cell tumour of distal radius despite of fair number of complications. Although it does not provide a wrist as functional to normal wrist but the subjective and cosmetic results are very encouraging. It is a comparatively cheap and easy to perform surgery. It does not require a bone bank or immunosuppressive therapy or a vascular surgeon or any other expensive tool so it can be performed by any orthopaedic surgeon with sound anatomy and basic knowledge of bone tumours management.

Poster 182 3042599

DISCOVERY AND CHARACTERIZATION OF RECURRENT, TARGETABLE ALK FUSIONS IN LEIOMYOSARCOMA

Lara E. Davis[1]*; Kevin Nusser*[1]*; Joanna Przybyl*[2]*; Janet Pittsenbarger*[1]*; Nicolle Hofmann*[1]*; Sushama Varma*[2]*; Sujay Vennam*[2]*; Maria Debiec-Rychter*[3]*; Matt van de Rijn*[2]*; Monika Davare*[1]
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Objective: Leiomyosarcoma (LMS) is the second most common sarcoma and originates from smooth muscle. LMS frequently develops resistance to standard cytotoxic chemotherapy. Here, we report the discovery and functional characterization of recurrent, targetable ALK fusions as potential drivers in a subset of leiomyosarcoma patients. Chromosomal rearrangements of the ALK gene generate chimeric ALK fusion proteins, which are established oncogenic drivers in a subset of non-small cell lung cancer (NSCLC). We highlight that these ALK rearrangements are oncogenic drivers in a lineage specific murine model and are targetable with clinically viable ALK tyrosine kinase inhibitors. Taken together, these data have immediate translational relevance to potentially impact diagnostic approaches, treatment and prognosis in this aggressive cancer subtype.

Methods: We analyzed existing transcriptomic data from LMS clinical samples, including The Cancer Genome Atlas (TCGA) Network's sarcoma genomic dataset. Potentially oncogenic ALK rearrangements were confirmed by application of multiple RNA-sequencing fusion detection algorithms and FISH. We functionally validated the oncogenic potential and targetability

of discovered kinase fusions through biochemical, cell-based (Ba/F3, NIH3T3 and murine smooth muscle cell) and *in vivo* tumor modelling approaches.

Results: We previously discovered ALK rearrangements in clinical NGS data from 5 out of 223 (2.2%) LMS samples. We also examined ALK rearrangements in a LMS tissue microarray: 2 of 97 (2.1%) cases evaluable by FISH exhibited ALK rearrangement. We then interrogated the TCGA sarcoma dataset and identified 3 of 57 (5.3%) LMS samples with markedly imbalanced ALK gene expression. Analysis of controlled access data revealed two ALK fusion transcripts: *ACTG2-ALK* and *KANK2-ALK*. In total, we identified likely ALK rearrangements in 10 of 377 (2.7%) LMS patients.
We show that KANK2-ALK and ACTG2-ALK are transforming oncogenic drivers in that stable expression of both fusions provided sufficient signaling drive for rapid and sustained IL-3-independent Ba/F3 outgrowth. Growth and viability of both Ba/F3 ACTG2-ALK and Ba/F3 KANK2-ALK cell lines were inhibited to varying degrees by multiple ALK inhibitors (Figure 1). We injected a stable lineage-specific murine smooth muscle cell line that expressed a transdominant negative p53 construct (p53DD) and KANK2-ALK into the flanks of Nu/Nu mice. Mice were treated with vehicle, crizotinib or lorlatinib, by oral gavage. Lorlatinib resulted in near immediate tumor regression (Figure 2A). Median survival of tumor-bearing mice improved modestly with crizotinib treatment (36 vs 47 days), but was significantly extended with lorlatinib treatment (median OS not achieved, p<0.001) (Figure 2B).

Conclusion: A clinically-meaningful subset of leiomyosarcomas harbor ALK fusions that retain the targetable ALK kinase domain. Systematic, hypothesis-based interrogation of existing datasets, such as the approach employed here, may identify targetable oncogenes in sarcoma. ALK and potentially other kinase fusions may be present in previously unrecognized subsets of soft-tissue sarcoma patients. Advanced molecular diagnostics should be employed more often in the sarcoma patient population.

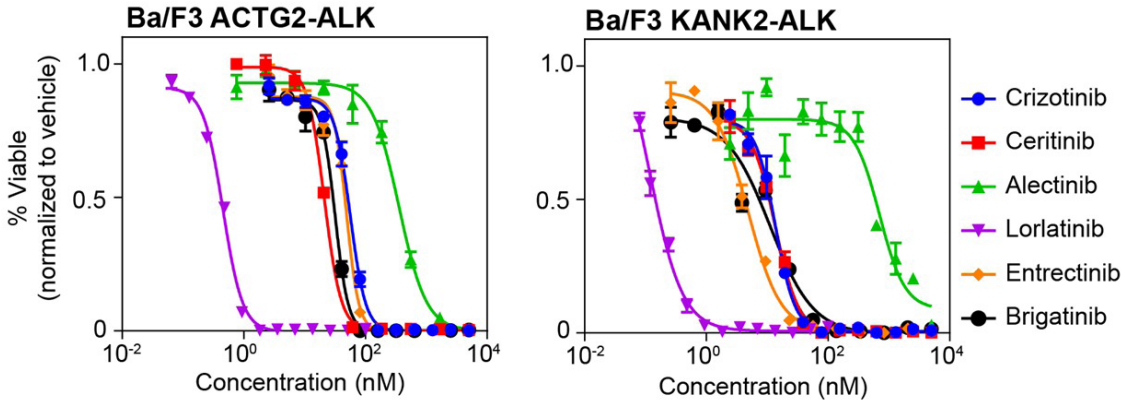

Figure 1. Leiomyosarcoma KANK2-ALK and ACTG2-ALK fusions are sensitive to ALK inhibitors. Onco-addicted Ba/F3 ACTG2-ALK and KANK2-ALK cells were exposed to multiple ALK inhibitors in dose-response cell viability assays.

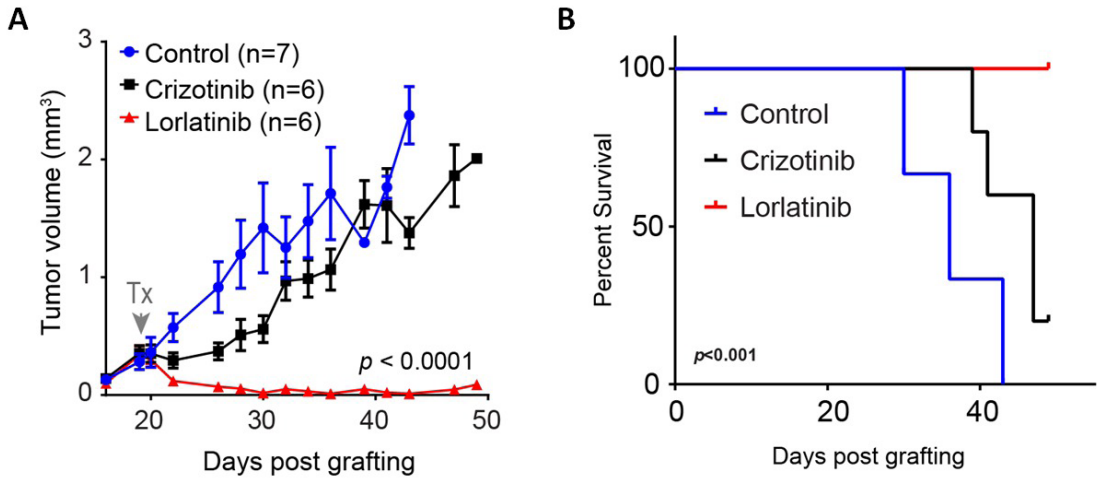

Figure 2. KANK2-ALK driven murine smooth muscle tumors are exquisitely sensitive to lorlatinib *in vivo*.

Poster 183 3014793

GENOME INFORMED THERAPY FOR OSTEOSARCOMA

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Objective: Osteosarcoma (OS) patients who relapse after initial therapy or present with metastatic disease have an extremely poor prognosis. Chemotherapy regimens for these patients have limited efficacy and significant toxicities. Thus, new therapeutic approaches are urgently needed. OS is characterized by numerous copy-number alterations (CNAs) and structural variations (SVs) in cancer-relevant genes.In contrast, recurrent point mutations are not seen. Thus, OS is a “C-class” (copy number driven) rather than an “M-class” (mutation driven) cancer. However, little is known with regards to whether copy-number alterations can be used to select therapies for aggressive cancers such as OS. The genomic heterogeneity of OS suggests that there may be different oncogenic drivers in subsets of patients. Thus, a systematic effort to identify targetable, patient-specific key driver genes (likely CNAs) is required.

Methods: We established a clinically annotated patient derived tumor xenograft (PDTX) bank of 16 OS samples obtained at diagnosis, after surgical resection and from metastasis, thus representing the full spectrum of disease. Comparison between PDTXs with a corresponding matched primary tumor demonstrated high correlation in copy number (by WGS for 12 samples) and gene expression (by RNAseq for 13 samples), suggesting that PDTXs are faithful preclinical models for OS. To identify recurrent CNAs, we analyzed this WGS dataset together with a public dataset of OS WGS samples. With this combined dataset of 69 samples from 52 patients, we searched for recurrent CNAs across an actionable cancer gene list and identified genes amplified at least 4-fold in at least 2 samples. The two most frequently amplified genes in OS are *CCNE1* and *MYC*. Other frequent alterations were those in the PI3K pathway (PTEN loss and/or AKT amplification), AURKB amplification, CDK4 amplification and VEGFA amplification. Importantly, all of these CNAs were reflected in at least one PDTX model. We hypothesized that in OS some of these CNAs are key cancer drivers that can be targeted for cancer treatment. To test this hypothesis, we rank-ordered the CNAs in 10 PDTXs by the amplitude of the copy number gain. We used this simple heuristic to identify candidate drivers for individual samples. We then identified 6 drugs that could be used to target specific amplified genes and tested these drugs in corresponding CNA-matched PDTX.

Results: In all cases, we saw significant growth inhibition in “matched” PDTXs whereas the effect was minimal in PDTXs treated with “unmatched” therapies. This result was statistically significant (p value <.04 by meta-analysis). In parallel to these studies an in order to further define the evolutionary trajectory of OS, we have carried out a comprehensive analysis of both spatial and temporal changes that occur in OS samples from the same patient. This has allowed us to define the role of whole-genome duplication events and chromothripsis as well as loss of heterozygosity in the evolution of OS. We are directing our current efforts towards merging this evolutionary analysis with knowledge of possible targetable events to further identify key vulnerabilities that could be exploited for therapeutic benefit. Further studies to characterize the role of intratumor heterogeientiy using single cell RNAseq are also currently being performed.

Conclusion: Osteosarcoma is a heterogeneous disease characterized by SCNAs. Many of these SCNAs are stable over time when comparing diagnostic and metastatic samples. Many SCNAs also contain key cancer driver genes that have available targeted agents. Using PDX models, we demonstrate that it is possible to subclassify OS tumors by key drivers and that targeted therapy against these drivers leads to significant response in preclinical models. These studies provide a rational basis for the design of genome-informed clinical trials in osteosarcoma.

Poster 184 3042488

DISTINCT EVOLUTIONARY TRAJECTORIES UNDERLIE GENOMIC HETEROGENEITY AND COMPLEXITY IN UNDIFFERENTIATED SARCOMAS

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Objective: Undifferentiated sarcomas (USARC) of adults are diverse, rare and aggressive soft tissue cancers that exhibit one of the highest burdens of structural aberrations across human cancer. The ability to probe the functional nature of genomic complexity is important because genomic instability is a key catalyst in cancer evolution, fuels tumour heterogeneity and is relevant therapeutically. The karyotypic complexity inherent in USARC also suggests that interrogating and distilling structural aberrations in these tumours may yield large returns in our understanding of the disease.

Methods: Whole genome sequencing of 53 histologically well characterised samples of USARC were coupled with methylation profiling and ploidy cytometry analysis. This was supplemented by a new informatic framework to identify regions of chromothripsis, to distil the complex rerrangement landscape and associated copy number patterns. The results were validated in the TCGA sarcoma dataset and extended to a separate cohort profiled by targeted sequencing and SNP arrays.

Results: Whole genome sequencing analysis demonstrated clinically relevant mutational subgroups including a hypermutator phenotype that was present in up to 13% of USARC. We developed a copy number signature informatic framework which revealed four divergent models of USARC development. Using this method, we show similar distinct evolutionary tumourigenic pathways in the cohort of 206 sarcomas from the Cancer Genome Atlas. Diversity estimates of the copy number patterns showed clear mechanistic differences between different sarcoma subtypes and corroborate the genomic similarites between myxofibrosarcoma and USARC. Mutational timing analysis of both cohorts revealed that the period prior to and between genome doubling events may represent clinically relevant interventional points in sarcoma development.

Conclusion: The karyotypic complexity in USARC is unpicked through the development of a copy number signature framework that has proved to be a practical method to infer evolutionary dynamics at a structural level. The evidence from copy number signatures, mutational timing and ploidy analysis suggest four routes to USARC tumourigenesis, all beginning with early driver mutations. Furthermore, patients with hypermutated sarcomas could be eligible for immune checkpoint inhibitor clinical trials.

Poster 185 3042669

COMPREHENSIVE GENOMIC PROFILING OF SYNOVIAL SARCOMAS IDENTIFIES GENOMICALLY DEFINED SUBGROUPS WITH CHARACTERISTIC ALTERATION PATTERNS

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Objective: Synovial sarcoma (SS) are characterized by translocation t((X;18) but demonstrate heterogenous clinical courses. We queried whether different genomic profiles between SSX1 vs. SSX2 fusion tumors might assist in stratification of molecularly guided clinical trial design and inform new treatment opportunities.

Methods: Tissue from 205 synovial sarcoma patients was assayed in the course of clinical care using hybrid-capture based comprehensive genomic profiling (CGP) to evaluate genomic alterations (GAs, including base substitutions, indels, amplifications, copy number alterations, and fusions/rearrangements) for targeted therapy opportunities. Tumor mutational burden (TMB) was calculated from a minimum of 1.4 Mb sequenced DNA and reported as mutations/Mb. Microsatellite instability status (MSI) was determined by a novel algorithm analyzing 114 specific loci. ShareMD, the Synovial Sarcoma Patient Registry sponsored by the Live For Others Foundation (www.L4OF.org; Hummingbird IRB approval #2018-14)

collated patient disease history and treatment outcomes in combination with genomic signatures in selected patients. Descriptive statistics were used to summarize the data.

Results: 205 synovial sarcomas (SS18-SSX1,146 pts and SS18-SSX2, 57 pts) were confirmed with CGP. Nearly one quarter (22%) of SS patients had alterations in genes targeting histone H3, including *MLL3* (8%), *MLL2* (5%), *SETD2* (7%), and *ATRX* (5%). Notably, these genes were mutually exclusive ($p<0.05$), with 3 exceptions. Other common GAs included *FAT3*, *MSH3*, and *RELN* (each at 5%). GA in chromatin remodeling pathways were also identified in SS, and targetable *EGFR*/*ERBB* alterations were found in 7% of SS patients. No SS in this series were either TMB High (≥20 mut/Mb) or MSI high, despite alterations in mismatch repair genes. We also reviewed whether SSX1 versus SSX2 fusion differences altered mutational prevalence. STK11 was altered exclusively in SSX2 (5%, vs. 0%, nominal p=0.02); CTNNB1 and KIT were altered exclusively in SSX1, and MLL3 was altered in 8% of SS overall, but more frequently in SSX1, while MLH3 was altered in 5% of all SS, but almost exclusively in SSX1 tumors (not quite statistically significant). Clinical correlates for a majority of patients are actively being accrued and comparisons to the genomic subgroups is ongoing.

Conclusion: This represents one of the largest efforts to identify GAs in synovial sarcoma. Histone H3 GAs may potentially define a distinct subgroup. Integrated outcomes findings will be required to confirm this finding and to inform future clinical trial development.

Poster 186 3042566

THE FUSION LANDSCAPE AND ACTIONABLE ALTERATIONS OF SARCOMA REVEALED BY "REAL WORLD" GENOMIC SEQUENCING

Jason Roszik[1]*; Anthony P. Conley*[1]*; Roman Groisberg*[1]*; Roberto Carmagnani Pestana*[1]*; Shiraj Sen*[1]*; Vivek Subbiah*[1]
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Objective: Oncogenic fusions occur when two genes are connected by a chromosomal rearrangement or deletion, translocation, inversion, duplication, or when two genes are read in a single transcription event. Fusions are identified in a growing number of hematologic and solid tumor malignancies and may lead to constitutive activation of a driving tyrosine kinase resulting in cell growth. Tyrosine kinase inhibitors are in development to target even rare fusions like NTRK and RET. Our objective was to catalog these alterations among diverse sarcomas.

Methods: We analyzed fusion events in the AACR project Genomics Evidence Neoplasia Information Exchange (GENIE) database. The GENIE registry contains CLIA-/ISO-certified genomic data. We also reviewed sarcoma patient data with fusions that were matched to targeted therapies in a large clinical trials unit.

Results: Among the 253 patients with sarcomas and gene fusions, 148 were categorized as soft tissue sarcomas (58%), 59 were bone sarcomas (11 osteosarcoma, 40 Ewing's sarcoma, and 3 chondrosarcoma). Others characterized included 20 uterine sarcomas (8%), breast sarcomas (2%) and one gliosarcoma. 204 distinct fusions were identified. Most common fusions were EWSR1-FL1 (n=31 pts, 12%), EWSR1-WT1 (n=25, 10%), and STAT6-NAB2 (n=17, 7%). 40 patients had intragenic fusions in 31 distinct genes, most commonly in ATRX (n=4), NF1 (n=4), and TP53 (n=3). Actionable fusions were also identified in the MAPK pathway (n=2, 0.8%), PI3K/AKT/mTOR pathway (n=2, 0.8%), CDK4 (n=2, 0.8%), FGFR (n=5, 2%), PDGFR (n=2, 0.8%), and DDR pathway (the ATM and ATRX pathways, n=4, 1.6%). Clinical responses included one patient each with KIAA1549-BRAF fusion (BRAF + mTOR), EWSR1-CREBL1 fusion (c-MET + VEGF), DCTN-1-ALK fusion (ALK+ VEGF), and EWS-FLI fusion (IGF1R+mTOR).

Conclusion: Genomic profiling identifies unique driver fusions that may be diagnostic or actionable in sarcoma subtypes. Inclusion of genomic profiling may add a potential line of therapy to management of sarcomas that have little or no standard of care. Inclusion of such rare tumors in targeted therapy basket/umbrella trials with a national registry is warranted. Further studies are needed to identify molecular mechanisms of response and resistance to fusion-targeted therapies.

Poster 187 3042919

BRINGING A PERSONALIZED MEDICINE PIPELINE TO THE CLINIC: A CROSS-SPECIES APPROACH REVEALS NEW THERAPIES AND NEW CHALLENGES

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Objective: Sarcoma, a group of neoplasms that originate from mesenchymal tissue, are exemplary of rare, genetically diverse cancers that are still poorly understood with few therapeutic options. Despite abundant preclinical discovery, testing, and validation, more than nine out of ten attempts to bring novel anti-cancer drugs into the clinic fail. To address this gap between preclinical research and clinical success, we developed a mouse-dog-human (MDH) personalized medicine pipeline that provides preclinical validation of therapies for patients at high risk for recurrent or metastatic disease. We hypothesize that high-risk patients could benefit from clinical decisions that incorporate preclinical validation of novel therapeutics.

Methods: We recruited a three-year-old male Golden Retriever who developed seven synchronous leiomyosarcomas (LMS) to test our pipeline. We generated a patient-derived cell line and patient-derived xenograft (PDX) model from one of the seven primary tumors. A pilot drug screen of 119 FDA approved chemotherapeutics was performed *in vitro* followed by an expanded drug screen of 2,100 compounds, which together identified alvespimycin (HSP inhibitor) and bortezomib (proteasome inhibitor) as top candidate drugs that were validated *in vivo*. Eight to 10-week-old SCID/beige mice were injected subcutaneously with 150 ul of homogenized PDX tissue-PBS suspensions at 150 mg/ml concentration in the right flank. When the tumor volumes reached 100-150 mm^3, mice were randomized (n=5 per group) and treated with control 100 ul of 5%DMSO, 1 mg/kg bortezomib (i.p) and 25 mg/kg alvespimycin (i.p) three times a week.

Results: *in vitro* drug screens identified both standard-of-care therapies and novel therapies for LMS, including HSP inhibitors and proteasome inhibitors. *in-vivo* validation of alvespimycin and bortezomib demonstrated the critical importance of *in vivo* validations, as alvespimycin had no effect on tumor growth. Unlike HSP inhibitors, however, bortezomib treatment showed significant tumor growth inhibition compared to control ($p<0.05$). During the course of our *in vivo* preclinical testing for bortezomib, the patient developed lesions in the mediastinal and iliac lymph nodes, nasal mucosa, and local recurrence at the right pelvic limb. The veterinary oncologist utilized preclinical data from this personalized medicine pipeline to treat the metastatic and recurrent lesions with bortezomib. The canine patient was treated with bortezomib infusions at 1.3mg/m^2 twice weekly for one month and also received local palliative radiation therapy (RT) to the right pelvic limb due to pain. While measurements of the right limb lesion during concurrent RT and bortezomib showed an interval decrease in tumor size, at the completion of RT, the tumor size increased despite systemic bortezomib therapy. Metastatic lesions in other locations also increased in size on CT imaging at the conclusion of bortezomib treatment.

Conclusion: This pipeline provides a novel approach to guide clinical decision making for patients with rare cancers. Our work with the canine leiomyosarcoma patient confirms that our pipeline can seamlessly integrate into the clinical setting to provide robust *in vitro* and *in vivo* preclinical data that can alter oncologic decision making for patients who have disease relapse. Though there was initial response to bortezomib in the setting of adjuvant radiation therapy for the local recurrence, the lack of overall treatment response for all sites of disease does not preclude the utility of this platform. Ongoing research will attempt to address how preclinical data can best be used to guide patient decision making.

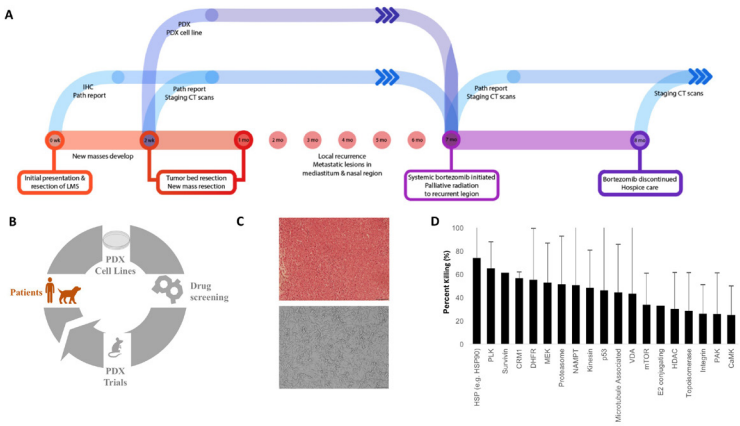

Figure 1. Integration of the MDH personalized pipeline throughout the clinical course of a dog (JSD48) with leiomyosarcoma from diagnosis to metastatic disease. A. Patient clinical history, relevant diagnostic interventions, and integration of preclinical modeling are listed in red, blue, and purple, respectively. B. Workflow of mouse-dog-human personalized medicine pipeline. C. Development of patient derived xenograft (PDX) cell line. H&E stain of PDX mouse tissue and cell culture image of PDX cell line. D. Drug screening of JSD48X cell line using NIH 2,100 bioactive compound assay identified novel drug candidates including HSP inhibitors and proteasome inhibitors.

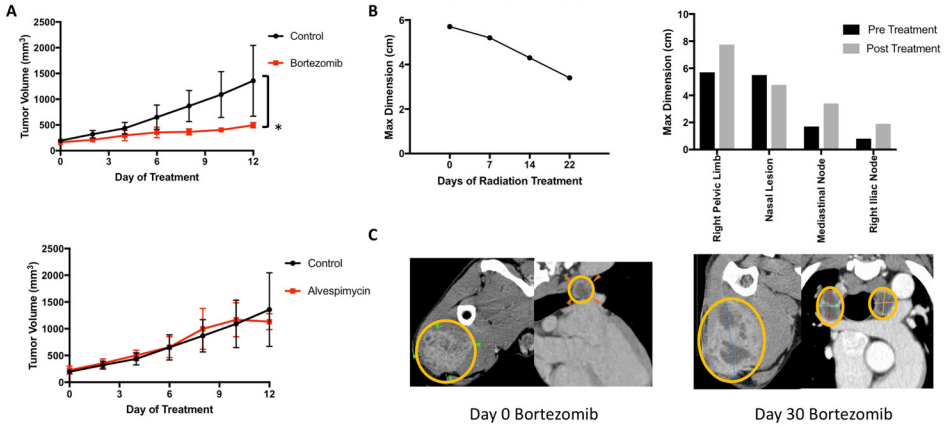

Figure 2: in vivo validation of top drug candidates bortezomib and alvespimycin, showed that only bortezomib has both in vitro and in vivo efficacy. Clinicians utilized information gleaned from the preclinical pipeline to treat the patient's recurrent disease. A. Bortezomib significantly reduced tumor growth (p

Poster 188 3042711

UTILITY OF FOUNDATIONONE HEME PROFILING IN SARCOMA: INSTITUTIONAL EXPERIENCE AND CLINICAL OUTCOMES

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Objective: The primary objective was to explore the utility of extended tumor profiling with next generation sequencing (NGS) in sarcoma. The second objective was to develop a tool to collect profiling information and clinical outcomes.

Methods: The records of all patients seen at the University of Rochester Wilmot Cancer Center Sarcoma Clinic with FoundationOne testing were reviewed. Responses to agents suggested on the report, if known, were analyzed. Reported fusion events were compared with FISH results when available. Gastrointestinal stromal tumor (GIST) and dermatofibrosarcoma protuberans (DFSP) were excluded from matched therapy analysis for known benefit.

Results: 33 patients were identified by screening and 31 were included for benefit analysis. For all 33 sarcomas surveyed, 30 (90.9%) had a therapeutic suggestion in the body of the report; 14 (42.4%) had an available FDA approved targeted therapy in a different tumor type. There were 11 fusions reported, 3 of which had been negative by FISH. Twenty-seven patients with measurable/unresectable disease were reviewed for efficacy; 11 (40.7%) received a therapy mentioned on the profile report. Four had partial responses and 1 patient has achieved disease stabilization after steady progression for a clinical benefit rate of 18% (5/27). A patient with an NTRK fusion went on a clinical trial of larotrectinib with ongoing response for over two years at the time of this publication. A patient with chordoma who had been steadily progressing was found to have a PIK3A amplification and mutation had disease stabilization on first set of scans after starting everolimus. The patient with a PML-JAK1 fusion had a mixed response to ruxolitinib but overall clinical progression.

Conclusion: NGS profiling in sarcoma had a benefit rate in this cohort that was comparable to most FDA approved second line interventions. On reviewing patterns of use and responders, we would suggest that tumor profiling is most valuable when it is sent early in the course of metastatic disease, such as when starting standard first line therapy. Testing may also be beneficial if there is a molecular diagnostic question in the non-metastatic setting. Benefit analysis in patients with an already identified alteration was limited due to small sample size. Multi-institutional collaboration to track outcomes of matched therapy could help further characterize the efficacy of matched therapies in rare cancers. To promote such collaboration, we have developed a REDCap database for this purpose and the data collection template is available for download.

Poster 189 3041968

METASTATIC INITMAL SARCOMA CASE WITH NTRK3 GENE REARRANGEMENT TREATED WITH ENTRECTINIB

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Objective: We describe here the report of patient with metastatic intimal sarcoma with confirmed NTRK3 rearrangement treated effectively with entrectinib in the clinical trial.

Methods: 38-year old male was admitted to the hospital in December 2016 due to hemoptysis, dyspnea, fever and vena cava

symptom. In chest angio-computed tomography (CT) the features of advanced neoplasm in the right lung with pleural fluid and tumor masses in right pulmonary artery were detected. ECOG performance status was 3. The biopsy was performed and pathological diagnosis in reference center confirmed rare type of soft tissue sarcoma with mdm2 overexpression – intimal sarcoma. The patient has been treated since January to March 2017 with 1st line chemotherapy with doxorubicin and ifosfamid (4 cycles). In chest CT (13.04.2017) disease progression was confirmed with new metastatic lesion in segment 3 of right lung and chemotherapy was changed into gemcytabine with docetaxel. Initially good response to the therapy was observed (on CT – July 2017 – PR), but in subsequent imaging (16.10.2017) the increase of lesions in right lung was noticed and new lesions in the middle lobe of right lung.

Results: Thereafter the molecular tests detected fusion in *NTRK3* gene, so the patient was enrolled into the clinical trial STARKTRK-2. Patient is treated with entrectinib 600mg/d from 13.11.2017 with good tolerance. Currently the patient is in good clinical performance status ECOG 0 with stable disease in consecutive imaging.

Conclusion: The molecular screening of rare sarcomas for targetable genetic abnormalities may lead to introduction of patients in clinical trials with new active molecular targeted agents, e.g. entrectinib.

Poster 190 3041764

EXTENDED CONTICAGIST ANALYSIS ADDS TO THE AMENDED PROGNOSTICATION IN GIST BASED ON TUMOR KIT/PDGFRA GENOTYPE STATUS

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Objective: Although the mutational status in gastrointestinal stromal tumors (GIST) can predict the response to treatment with tyrosine kinase inhibitors (TKI), the role of tumor genotype as a prognostic factor remains debatable. Within the ConticaGIST initiative we study the impact of *KIT* and platelet derived growth factor receptor alpha (*PDGFRA*) type of mutations on the time-to-progression (TTP) in primary, TKI-naïve GIST, aiming at including the mutational status in the risk classification, in addition to tumor size, site and mitotic index.

Methods: We assessed the information available from patients diagnosed between October 1998 and June 2016 in 19 reference institutions from six European countries. Only patients >18 years of age, with localized disease at diagnosis, with detailed *KIT/PDGFRA* status, without any pre- or postoperative systemic treatment were included in the study. Risk stratification was defined according to the modified NIH classification. Only the most frequent types of mutations were taken under statistical evaluation, i.e. *KIT* exon 11 deletions that include codons 557 and/or 558 (*KIT*del_inc557/8), other *KIT* exon 11 alterations (*KIT11*_oth), *KIT* exon 9 p.Ala502_Tyr503dup and mutations affecting *PDGFRA* exon 18 (*PDGFRA18).* Univariable and multivariable Cox proportional hazard models were used to determine associations between variables of interest and TTP. The strengths of associations were reflected by hazard ratio (HR) and corresponding 95% confidence interval (CI). Multivariable models were compared using test for difference in C-indexes (C) and integrated discrimination improvement (IDI). The value of $p < 0.05$ was interpreted as statistically significant.

Results: A total of 1844 patients were included in the study. The mean age was 61.1±13.7 years (range 18.6 – 98.0) and 50.1% of patients were male. Majority of tumors were of gastric origin (56%), the overall median tumor size was 6.0 cm (0.2 – 45.0 cm), median mitotic index 4.0 per 50 high power field (HPF) (0 – 325 per 50 HPF). In 5.37% of patients the tumor rupture during the surgery was recorded. *KIT or PDGFRA* mutations were found in 70% and 13% of tumors, respectively. In the studied cohort tumor site (gastric *vs*. non-gastric), size, mitotic index and tumor rupture had a prognostic significance in the univariable analysis, but the later lost its significance in the multivariable evaluation. Based on the univariable model,

mutations were classified as “unfavorable” (*KIT*del_inc557/8 and p.Ala502_Tyr503dup) and “favorable” (*KIT11*_oth and *PDGFRA18*) with HR 2.240 and 95% CI 1.895-2.649 (p<0.0001). There was a significant correlation between tumor site and mutational status (p<0.0001), which was taken into the account in the multivariable model, showing adverse effect of tumor size >10cm (HR: 3.632, 95% CI: 1.586-8.314; p=0.002), mitotic index 6-10 per 50 HPF (HR: 2.464, 95% CI: 1.853-3.278; p<0.0001) and >10/50 HPF (HR:4.668, 95% CI:3.677-5.926; p<0.0001); however, “unfavorable” mutations presented a worse prognosis only in gastric tumors (HR: 2.582, 95% CI: 1.866-3.572; p<0.0001) in contrast to GIST from non-gastric location (HR: 1.115, 95% CI: 0.880-1.414; p=0.367). Multivariable model including mutational status showed a better discriminative value than the one without this molecular variable (C-index 0.800 *vs*. 0.792; p=0.019; IDI: 0.023, 95% CI 0.009-0.041; p<0.0001).

Conclusion: Specific tumor genotype is an independent molecular prognostic variable associated with gastric GIST and should be included in prognostic classification, to optimize adjuvant imatinib treatment of primary GIST patients.

Poster 191 3031895

ONCOLOGICAL OUTCOME AFTER DIAGNOSTIC BIOPSIES IN GASTROINTESTINAL STROMAL TUMOURS

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Objective: Preoperative transluminal or transcutaneous biopsies have been widely used for diagnosing gastrointestinal stromal tumours (GIST). The aim of this study is to analyze whether a pre-operative biopsy influences oncological outcome in GIST patients.

Methods: Patients who underwent resection of a primary GIST between 1996 and 2014 were identified from a prospectively maintained database from two tertiary referral centres. Clinical data were either obtained from the database or from the clinical patient files retrospectively. Survival data were obtained using the Kaplan-Meier method. Possible confounders were identified by using univariate analysis. Only confounders with a p-value below 0.1 were subsequently included in a multivariate Cox regression. The primary endpoint was local recurrence free survival, where local recurrences were defined as intraperitoneal recurrences. Secondary endpoints were all (local and distant) recurrence free survival and disease specific survival.

Results: A total of 232 patients were included, with a median age of 62 (17-86) years and a median follow-up of 53 (0-204) months. Patients were subdivided into 3 groups; no biopsy (n=43), transcutaneous biopsy (n=70) and transluminal biopsy (n=117). Out of the 187 biopsies, only 20 were performed with fine needle aspiration (FNA). From all 70 patients with a transcutaneous biopsy, only 1 patient (1.4%) developed a needle tract recurrence. When compared to the other groups, the transcutaneous biopsy group had larger tumours, were more often located in non gastric locations and were more often treated with imatinib (all p<0.001). Local recurrence free survival, all recurrence free survival, and disease specific survival were all significantly higher in the transcutaneous biopsy group (all p<0.001). However, in a multivariate Cox regression analysis the route of biopsy did not significantly influence local recurrence free survival, all recurrence free survival or disease specific survival. For local recurrence free survival and for all recurrence free survival, larger size (p=0.024, p<0.001 respectively), high mitotic rate (p=0.004, p<0.001 resp.) and positive resection margin (p=0.001, p=0.019 resp.) were independently associated with a higher local recurrence rate and a higher all recurrence rate. For disease specific survival, larger size (p=0.012) and positive resection margin (p=0.001) were significantly correlated with worse disease specific survival.

Conclusion: Transluminal or transcutaneous biopsies for diagnosing GIST do not significantly alter the risk of recurrent disease or disease specific survival. Furthermore, the risk of needle tract seeding in this study was very low.

Poster 192 3042644

PAEDIATRIC, ADOLESCENT, WILD TYPE, SYNDROMIC GASTROINTESTINAL STROMAL TUMOURS (PAWS-GIST) UNITED KINGDOM (UK) NATIONAL CLINIC: A JOINT PATIENTS/CARERS/SPECIALISTS INITIATIVE

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Objective: Paediatric, adolescent, wild type and syndromic Gastro Intestinal Stromal Tumours (PAWS-GIST) consortium was formed in UK as a joint effort between GIST specialists, patients and carers. The aim was to raise awareness, centralise expertise, understand the biology, undertake research and develop new treatments.

Methods: The national clinic was established in Cambridge, UK in 2014 and is held 3 times a year. Patients with wild type GISTS were invited to register for the clinic on website (www.pawsgistclinic.org.uk). Patients were reviewed by a panel of experts- oncologists, surgeon, pathologist, endocrinologist, specialist nurses and cancer geneticist. 6-8 patients were seen in each clinic. Molecular testing including KIT, PDGRA, BRAF mutational testing, succinate dehydrogenase (SDH) B immunohistochemistry, sequencing of SDH genes, SDHC promoter hypermethylation were performed. Patients and families were offered germline testing of the SDH genes after counseling. All patients and carers were actively encouraged to provide feedback on their experience.

Results: 70 patients were seen in the UK PAWS GIST Clinic as of April 2018. Male:female 23:47. Median age 38 years (range 14-76 years). Primary tumour location-67% were gastric and 33% small bowel. SDHB deficient GISTs (n-27) were gastric, with male:female ratio of 9:18. SDH germline testing results so far showed SDHA subunit mutations being the most common followed by mutations in SDHC, B and D subunits and 4 patients had epimutations in SDHC.14 patients. had Neurofibromatosis (NF-1). NF1 GISTs were mostly located in small bowel and often multifocal. 24 patients have been treated with tyrosine kinase inhibitors. No objective responses were seen with imatinib in SDH deficient GISTs. Stabilization/ slowing down of disease progression was seen with both sunitinib and regorafenib in SDH deficient GIST patients. 1 NF-1 patient had transient partial response to imatinib followed by rapid progression.No objectivre responses to sunitinib or regorafenib were seen in NF-1 GIST patients.

Conclusion: The United Kingdome PAWS-GIST clinic is the second clinic of its kind in the world after the National Institute of Health USA clinic in Bethesda. The emphasis during first three years was raising the awareness, data collection, gaining experience and developing a research platform. UK national GIST tumour bank has been established. The clinic has helped us to focus on the needs of the patients and carers and to collaborate with other national and international teams for developing new therapies for this rare subgroup of GIST patients.

Poster 193 3026367

THE RELATIONSHIP BETWEEN POSITIVE RESECTION MARGINS, TUMOUR RUPTURE AND PROGNOSIS IN GASTROINTESTINAL STROMAL TUMOUR. A POPULATION-BASED ANALYSIS

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Objective: According to guidelines, adjuvant treatment or re-excision should be considered after R1 resection of gastrointestinal stromal tumours (GISTs). However, the prognostic significance of R1 resection is uncertain and tumour rupture confounds its assessment. Here, the impact of positive margins is examined and related to rupture in a population-based cohort.

Methods: Patients undergoing surgery for non-metastatic GIST since 2000 were identified in the sarcoma database of Oslo University Hospital. Margins were coded according to the residual tumour (R) classification and tumour rupture defined according to the Oslo criteria.

Results: Among 410 patients, there were 47 with R1 resection and 52 with tumour rupture. The relative risk of R1 resection with rupture was 3.55 (95 per cent confidence interval [CI] 2.09-6.03; P<0.001). In patients without rupture, there was no

difference in estimated 5-year recurrence-free survival after R0 *versus* R1 resection (88 *versus* 93 per cent; hazard ratio [HR] 0.71, 95 per cent CI 0.17-2.98; *P*=0.638); nor was there any difference in patients with rupture (37 *versus* 31 per cent; HR 1.31, 95 per cent CI 0.68-2.54; *P*=0.420). In multivariable analysis, tumour rupture but not R1 resection was independently associated with recurrence. Twenty-four patients at very low, low or intermediate risk did not receive adjuvant imatinib after R1 resection and remained recurrence-free.

Conclusion: Positive resection margins are strongly associated with tumour rupture. R1 resection does not independently influence prognosis. In patients without rupture or other high risk features, adjuvant imatinib is not justified after R1 resection.

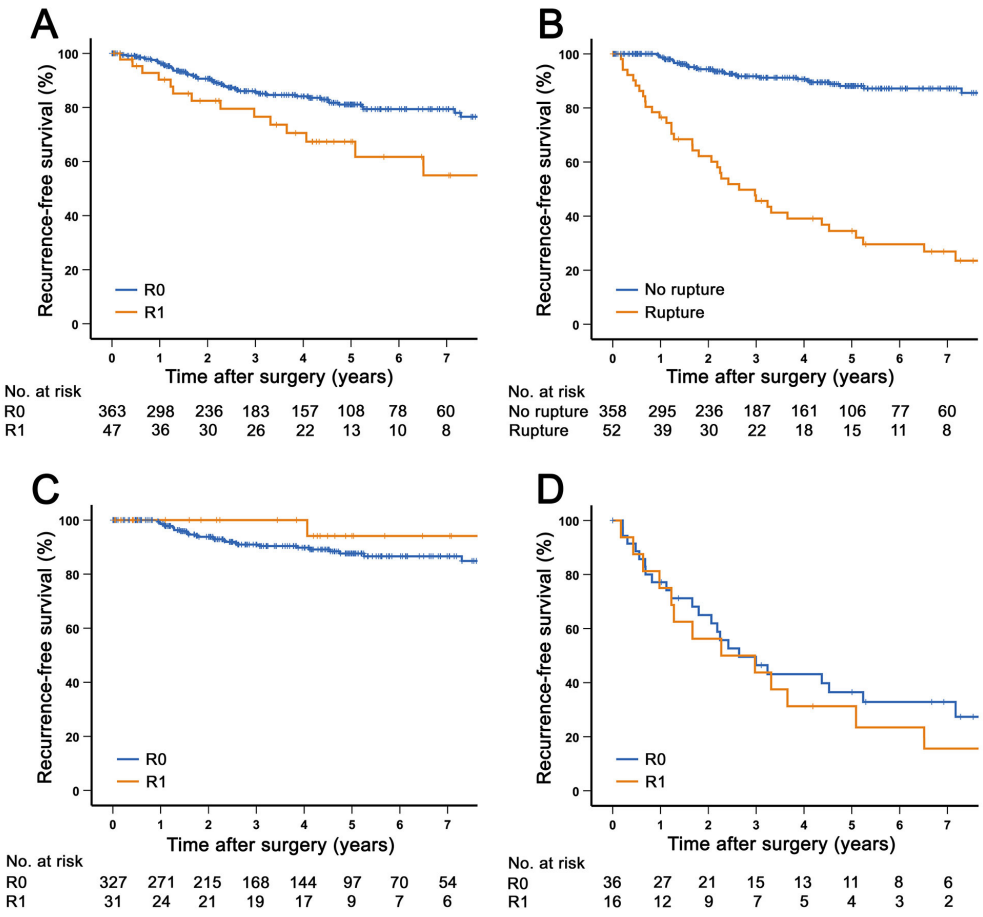

Figure 1.
Kaplan-Meier curves of recurrence-free survival after resection of primary non-metastatic GIST: **a** R0 *versus* R1 in the complete cohort, *P*=0.001; **b** no tumour rupture *versus* tumour rupture in the complete cohort, *P***c** R0 *versus* R1 in patients without tumour rupture, *P*=0.638; **d** R0 *versus* R1 in patients with tumour rupture, *P*=0.420.

Poster 194 3033347

AN INTEGRATED RNA AND MICRORNA PROFILING OF THE MALIGNANT EVOLUTION OF MINIGIST TO GIST

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Objective: Gastrointestinal stromal tumors (GIST) are rare neoplasms. Instead, miniGIST, i.e. small (< 2 cm), mitotically inactive GIST-like lesions that share with overt GIST the presence of activating KIT or PDGFRA mutations, can be detected in up to one third of adult individuals. This suggests that these premalignant precursors evolve to GIST only in a minute fraction of cases. What are the genetic determinants that sustain miniGIST evolution to GIST is still unclear. microRNAs represent a growing class of small RNAs that exert an epigenetic control over gene expression by targeting specific mRNAs for degradation or translation repression.
Here we sought to exploit transcriptional profiling to investigate the role of microRNA in the malignant progression of miniGIST.

Methods: microRNA and mRNA transcriptional profiling were performed by RNA-Seq on 47 cases, 19 miniGIST (< 2 cm;

ave MI <1) and 28 overt GIST (≥ 2 cm; ave MI 12). Profilings were integrated to identify microRNA/mRNA target pairs putatively associated with miniGIST malignant progression. In vitro validation was performed on a subset of candidates.

Results: The comparison of the transcriptional profiles of GIST vs miniGIST yielded to the identification of 110 differentially expressed microRNAs and 1786 differentially expressed mRNA.
Among these we identified a number of potential microRNA/target mRNA pairs with inverse correlation in expression. Validation of microRNA/mRNA interactions was performed in vitro on a set of candidates by ectopic expression of microRNA mimics.

Conclusion: Our study highlighted the existence of unprecedented microRNA/mRNA interactions possibly implicated in the malignant evolution of GIST.

Poster 195 3042862

NOVEL DIAGNOSTIC APPROACH FOR GASTROINTESTINAL STROMAL TUMOR USING AN ANTI-KIT DNA APTAMER

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Objective: Gastrointestinal stromal tumor (GIST) is the most common sarcoma. It is usually diagnosed by invasive tissue biopsy and KIT-positive immunostaining. At present, diagnostic methods rely on KIT antibodies that are expensive or require ongoing hybridoma production. An emerging class of detection molecules include aptamers, which are easily synthesized short, single-stranded oligonucleotides that selectively bind protein targets with high affinity and specificity. We hypothesized that a KIT-specific DNA aptamer can label GIST cells and can serve as a cost-effective, easily produced and highly accurate GIST diagnostic.

Methods: We investigated the capacity of a KIT DNA aptamer (Zhao *et al.*, *Biomaterials* 2015) to bind human and murine KIT. Cell lines included *KIT*-mutant GIST-T1 (heterozygous $KIT^{Val570\_Tyr578del}$) and GIST882 (KIT^{K642E}), as well as a control pancreatic cancer cell line (Panc1). Primary *KIT*-mutant human GISTs were collected (IRB #090401) and dissociated into single cell suspensions. Transgenic murine GISTs were similarly prepared for aptamer binding assays. Aptamers were synthesized with 5'-biotinylation and fluorescently labeled with streptavidin-phycoerythrin. All cell binding experiments compared KIT aptamer, scrambled control aptamer, and an anti-human KIT antibody (BioLegends). Using flow cytometry (FCM), cell binding was quantified by calculation of the geometric mean (GM) of fluorescence intensity. Cell killing was assessed by CellTiter-Glo assay. Confirmatory confocal immunofluorescence (IF) microscopy was performed using GIST-T1 and GIST882 cells.

Results: KIT aptamer bound human GIST-T1 cells (Geometric Mean, GM 249) with similarly high avidity to anti-KIT antibody (GM 226), whereas scrambled control aptamer bound with low avidity (GM 4.5) (Fig. 1A). Similar findings were observed in the GIST882 line (GM 145, 124 and 9.4, respectively), but not the Panc1 line (GM 9.9, 3.0 and 7.1, respectively). Treatment of GIST cells with KIT aptamer or scrambled control aptamer did not affect cell viability suggesting that the aptamers are non-toxic. Single cell preparations of primary human GIST demonstrated KIT aptamer binding (GM 389) was present and 2.4-fold higher than anti-KIT antibody (GM 168) (Fig. 1B). Single cell suspensions of primary KIT^{K641E} murine GIST cells also had 3-fold higher KIT aptamer binding (GM 35.2) than scrambled control (GM 11.9), suggesting that the aptamer cross-reacts with murine KIT. Using GIST lines, confirmatory confocal IF demonstrated plasma membrane and cytosolic binding of the KIT aptamer, which colocalized with the anti-KIT antibody (Fig. 1C).

Conclusion: For the first time, we report highly specific, but non-cytotoxic, KIT aptamer labeling of human and murine GIST cells, including primary human tumor cells. This KIT aptamer labeling is equivalent or superior to anti-KIT antibody and binds a similar distribution of KIT molecules. Taken together, these studies provide proof-of-principle for investigating the utility of KIT aptamers for developing novel GIST diagnostics.

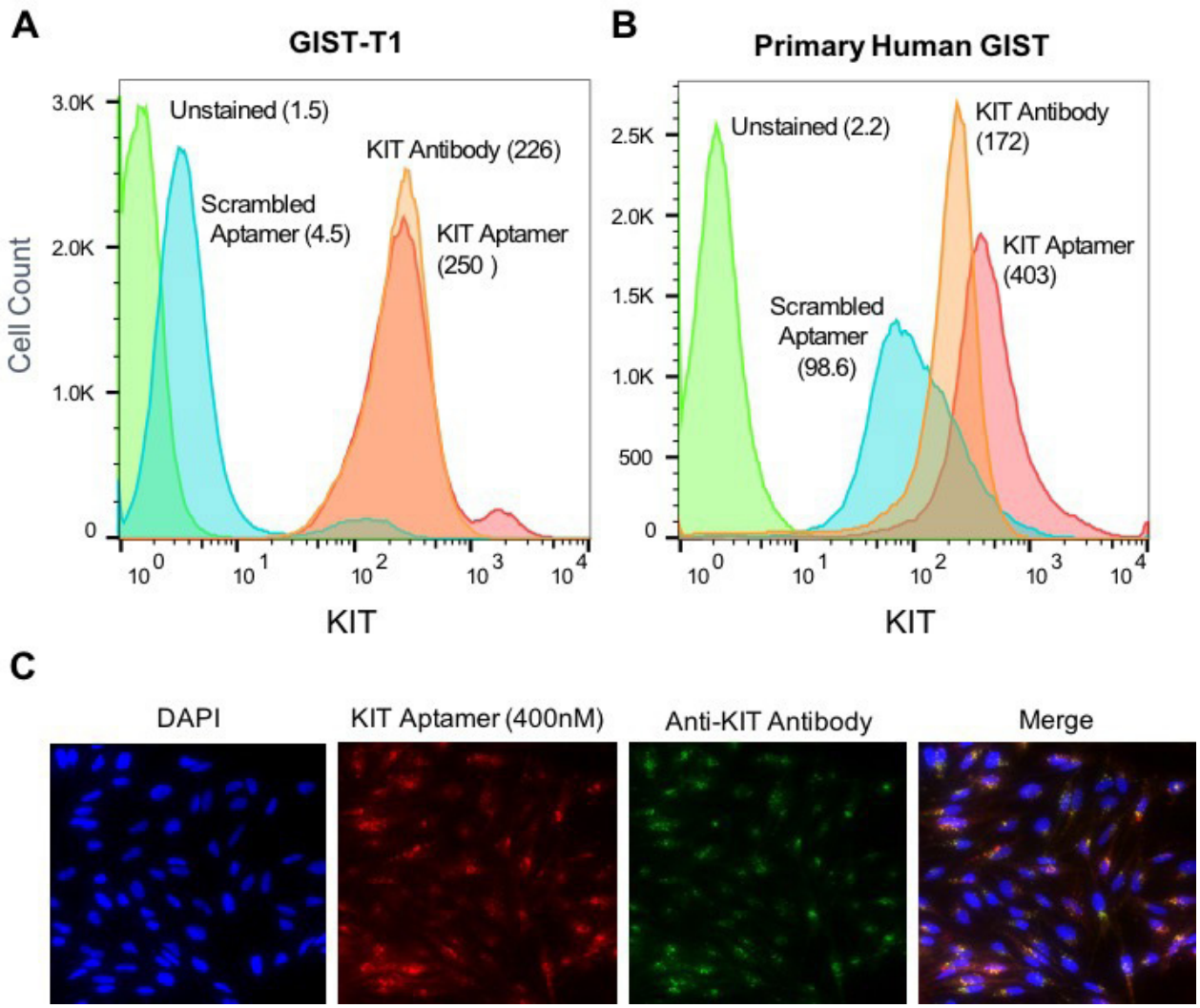

Figure 1: Anti-KIT aptamer has equivalent binding to anti-human KIT antibody in (A) GIST-T1 cells; (B) Primary human GIST; and (C) anti-KIT aptamer colocalizes with anti-human KIT antibody.

Poster 196 3009932

PLOCABULIN, A TUBULIN INHIBITOR, HAS ANTITUMOUR ACTIVITY IN PATIENT-DERIVED XENOGRAFT (PDX) MODELS OF GASTROINTESTINAL STROMAL TUMOUR (GIST)

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Objective: Advanced GIST is commonly treated with tyrosine kinase inhibitors (TKI) [e.g. imatinib (IMA)]. With time, the vast majority of patients develops TKI-resistance. GIST is resistant to chemotherapy with established cytotoxic agents. The aim of our study was to test plocabulin (PLO; PM060184, PharmaMar), a potent cytotoxic tubulin-dynamics modifier, in two PDX models of GIST, characterized by different sensitivity to IMA.

Methods: NMRI *nu/nu* mice (n=34) were transplanted bilaterally with human xenografts UZLX-GIST3^{sens} (*KIT* exon 11: p.W557_V559delinsF; IMA-sensitive) or -GIST9^{res} (*KIT* exon 11+17: p.P577del;W557LfsX5;D820G; IMA-resistant). Xenografted animals were randomly assigned to three treatment groups: control [vehicle, 5ml/kg/QW intravenously (i.v.)], IMA (50mg/kg/BID orally) and PLO (16mg/kg/QW, i.v.). Treatment lasted 22 days and the antitumour activity was assessed by tumour volume measurement, histopathology and KIT signalling pathway by Western blotting. Tumours with volumes smaller than 100mm^3 at start of experiment were excluded for tumour volume analysis. However, all tumours in which a

sufficient number of high-power fields could be evaluated were included in the histopathological assessment. Histological response (HR) was evaluated as previously described (Antonescu *et al.,* 2005). Mann Whitney U test was used for statistical analysis with p <0.05 considered as significant.

Results: PLO treatment resulted in a reduction of tumour volume to 64% and 61% of the baseline volume in GIST3^{sens} and GIST9^{res} respectively. Good HR (grade 3 and 4) was observed in 70% (GIST3^{sens}) and 50% (GIST9^{res}) of tumours. HR obtained with PLO was mainly characterized by central necrosis, while IMA induced mainly myxoid degeneration in the sensitive model. In addition, in GIST3^{sens} PLO decreased the microvessel area and increased apoptosis as assessed by immunohistochemistry, which was not observed in GIST9^{res}. PLO showed better activity than IMA in the latter model in terms of tumour volume reduction (61% *vs*. 169%, p=0.01) and HR (grade 3, 4 in 50% *vs.* 0%). PLO did not affect KIT signalling. The experimental drug was well tolerated throughout the experiment at the dose administered.

Conclusion: PLO is the first anti-tubulin agent showing antitumour activity in GIST PDX, in models sensitive or resistant to IMA. The drug induces cytotoxicity in GIST, mainly through necrosis, without affecting KIT signalling. Due to the different modes of action of PLO and established TKI our work provides a scientific rationale to combine PLO and IMA to overcome resistance to small molecule TKI.

Poster 197 3042635

MORE FREQUENT OCCURRENCE OF UNUSUAL CENTRAL NERVOUS SYSTEM METASTASES IN GIST PATIENTS

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Objective: Gastrointestinal stromal tumor (GIST) metastases occur in 20-47% of patients and most commonly involve the liver and peritoneum. Central nervous system (CNS) metastases are rare, with only limited single patient case reports available in the literature. We present three GIST patients who developed CNS metastasis in the past year and compare their clinical features and molecular profiles, to add to the current knowledge of these sanctuary sites.

Methods: We conducted retrospective chart review of the three patients treated at MD Anderson Cancer Center who developed CNS metastasis during their course of therapy in the past year, identifying demographics, mutation status, as well as clinical and pathologic characteristics at time of initial GIST diagnosis, initial metastatic diagnosis, and CNS metastasis.

Results: All three patients had received tyrosine kinase inhibitors (TKIs), with a range of 2-6 treatments, prior to CNS metastasis. The primary GIST was >5cm (9-26 cm) and the location was diverse (gastric, mesenteric, and rectal). Synchronous metastases, defined as metastatic disease within 3 months of initial GIST diagnosis, were seen in all three patients that ultimately went on to develop CNS metastases, which occurred 20-46 months following initial metastatic diagnosis. Two patients had c-KIT mutations in exon 11, while the third patient had a PDGFRA mutation in exon 18 (D842V). One patient died 4 days after diagnosis of CNS metastasis to the left inferior rectus muscle, while two patients remained alive with disease at time of last follow up. Further clinical characteristics for these three patients are detailed in Table 1.

Conclusion: CNS metastases have been rarely described in GIST patients, however increasing life expectancy with access to more TKIs to control systemic disease may lead to increased frequency of metastases to sanctuary sites as highlighted in these cases. Unusual symptoms should prompt CNS imaging. While mutations are known to be of significant importance in GIST, our data combined with available case reports in the literature suggests that the type of primary mutation does not seem to change the predilection for CNS metastases. Future data will help determine if there is differential penetration with the various TKIs. We plan to sequence available tissue obtained from metastases to evaluate for secondary mutations.

Table 1. Clinical Characteristics of Three Patients with Metastatic GIST to the CNS.

Age at Diagnosis (years)	Primary Tumor Site and Size	Time to Metastases and Site(s)	Treatment prior to CNS Metastasis (Best Response)	Time from Metastatic GIST to CNS Metastasis and Site	CNS Presenting Symptom	Treatment post CNS Metastasis (Best Response)	Primary Mutation	Status (Survival from initial diagnosis; from CNS metastasis diagnosis)
49	Mesenteric, 18.4 cm	77 days, lung	Imatinib (PD), Sunitinib (PD), Regorafenib (PD), Nilotinib (PD), Investigational TKI (PD), Dasatinib (SD)	39 months, epidural soft tissue mass at T7-T8	NA – noted on planned restaging	Radiation planned	PDGFRA exon 18, codon 842 (D842V)	Alive with disease (42 months; 11 days)
53	Gastric, 26 cm	0 days, liver	Imatinib (PR), Sunitinib (PR), Regorafenib (SD), Investigational TKI (PD)	46 months, left inferior rectus muscle	Vision changes	None (died 4 days after CNS metastasis diagnosis)	c-KIT mutation in exon 11	Deceased (46 months; 4 days)
55	Rectal, 9 cm	0 days, liver	Imatinib (SD), Investigational TKI (SD)	20 months, right skull base and epidural soft tissue disease spanning C3-C5	NA – noted on planned restaging	Radiation (PR), Sunitinib (PR)	c-KIT mutation in exon 11, TP53 mutation	Alive with disease (27 months since initial GIST diagnosis, 226 days since CNS metastasis diagnosis)

* PR: Partial Response, SD: Stable Disease, PD: Progressive Disease, TKI: tyrosine kinase inhibitor, NA: not applicable

Poster 198 3041762

NEW PROTOCOL FOR IMAGE GUIDED SURGERY OF GASTROINTESTINAL STROMAL TUMOUR

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Objective: Identification of Gastrointestinal Stromal Tumours during laparoscopic surgery can be difficult due to their location in the serosa of the stomach. Subsequently, conversion to laparotomy might be necessary. Intraoperative navigation using fluorescence guidance is an innovative technique enabling real-time identification of tumours. The objective of the current study was to evaluate the feasibility of detection of GIST by florescence guidance.

Methods: Patients undergoing laparoscopic and open resection of a GIST of the stomach are eligible for inclusion. Patients will receive standard of care, including preoperative CT. In addition, 10 mg indocyanine green will be intravenously administered one day prior to surgery. After introduction of the laparoscope, inspection and fluoroscopy will be performed.

Results: Our aim is to include 10 patients with a GIST of the stomach in the coming months. We hope to present the first results of this feasibility study during the CTOS 2018.

Conclusion: *not available yet*

Poster 199 3042866

PRIMARY SARCOMA OF THE VULVA AND VAGINA: OUTCOMES AFTER DEFINITIVE THERAPY

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Objective: Primary vaginal and vulvar cancers are rare with approximately 4600 and 6000 cases per year, respectively. Of those, < 3% are primary sarcoma histologies. There is little published data on how to treat primary vulvovaginal sarcoma as most consists of case reports. We report a series of 26 patients treated at our institution.

Methods: In an IRB approve retrospective review, we analyzed patients treated from 1973 to 2016 with primary sarcoma of the vulva and vagina. Demographics, clinopathologic characteristics, treatment details, oncologic outcomes, and toxicity were analyzed. Kaplan Meier analysis and Cox proportional hazards regression were used to analyze survival outcomes and prognostic factors.

Results: 25 cases of primary sarcoma of vulva and vagina were identified. No patients had prior radiation exposure. Median age at diagnosis was 48 years (range 21-83). Histologic subtypes included leiomyosarcoma (48%), dermatofibrosarcoma (12%), epithelioid sarcoma (12%), myxoid liposarcoma (8%), and 4% each of MFH, extra renal rhabdoid tumor, synovial sarcoma, and angiosarcoma. 20% was grade 1, 24% grade 2, and 54% grade 3. Median tumor size was 4 cm (range 1.3-16 cm). Nodal involvement was seen in 8%. Patients were treated with: surgery alone (40%), surgery followed by postoperative radiation therapy to a median dose of 53.9 Gy (RT, 24%), preop RT to a median dose of 47.5 Gy followed by surgery +/- postop RT (28%), RT alone (4%), IORT boost (4%) and brachytherapy boost to median of 20 Gy (8%). Median RT dose to the primary tumor was 54 Gy (26-70Gy). Pelvic lymph nodes (LN's) were treated in 3 patients (12%) to a median dose of 45 Gy and inguinal LN's were treated in 2 patients (8%) to a median dose of 50.8 Gy. At median of 70 months of follow up the 5 year OS is 78%, CSS is 84%, LC is 79%, and PFS is 67%. Use of RT was not associated with OS, CSS, PFS, or LC. Of the 14 patients receiving RT, 36% recurred: 21% distant and 15% local-reginal. Of the 10 patients (all N0) who received primary site RT only without any RT to inguinal or pelvic LNs, none failed in a regional lymph node. Of the 4 patients who received primary site and pelvic/inguinal RT (2 had positive LN on presentation), 75% still failed in regional lymph nodes and 50% also had local recurrence.

Conclusion: In this large single institution series of primary vulvovaginal sarcoma, leiomyosarcoma was the most common histology. The cancer-specific survival was high 84% and LC 79% (85% in those who received RT). Of patients treated with primary site only radiation therapy, there were no nodal recurrences, suggesting that nodal irradiation may not be indicated in vaginal and vulvar sarcoma in N0 patients, unlike in vaginal/vulvar squamous cell carcinoma. RT for N+ vaginal/vulvar sarcoma patients at the doses typically used for vaginal/vulvar carcinomas may not be sufficient. Larger series are needed to confirm these findings to further understand the pattern of recurrence and management in these rare sarcomas.

Poster 200 3038351

INTEGRATED MOLECULAR ANALYSIS OF UNDIFFERENTIATED UTERINE SARCOMAS REVEALS CLINICALLY RELEVANT SUBTYPES

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Objective: Undifferentiated uterine sarcomas (UUS) are rare, extremely deadly, sarcomas with no effective treatment. The goal of this study was to identify novel intrinsic molecular UUS subtypes using integrated clinical, histopathologic and molecular evaluation of a large, fully annotated, patient cohort.

Methods: Fifty cases of UUS with full clinicopathological annotation were analyzed for gene expression (n=50), copy number variation (CNV, n=40), and with computer assisted image analysis (n=39). Gene ontology (GO) and network enrichment analysis (NEA) was used to relate over- and underexpressed genes to pathways and relate these to clinicopathologic and phenotypic findings.

Results: Integrated molecular analysis identified four distinct RNA groups, which varied in their clinicopathologic

parameters. GO and NEA analysis revealed differential activation of pathways related to genital tract development, immune cell modulation, extracellular matrix (ECM) and muscle function. Potential therapies exist to many of these pathways. A multivariable, adjusted Cox proportional hazard model demonstrated that RNA group, in addition to mitotic index and hormone receptor expression, influence patient overall survival (OS). CNV arrays revealed characteristic chromosomal changes that were significantly associated with each group. Image analysis demonstrated that the most aggressive group, B2 ECM-associated, showed a significantly decreased cell density and increased nuclear area. Applying a cell density cutoff of 4,300 tumor cells per mm^2 could separate the B2 ECM tumors from the remaining cases with a specificity of 94% and a sensitivity of 83%.

Conclusion: Integrated molecular evaluation of UUS provides novel insights into the biology, prognosis, phenotype and possible treatment of these tumors.

Poster 201 3041759

TREATMENT OF RECURRENT AND METASTATIC UTERINE ADENOSARCOMAS

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Objective: Uterine adenosarcomas represents <10% of all uterine sarcomas. Uterine adenosarcoma with sarcomatous overgrowth has a high recurrence rate, approximately 70-80%. There is no standard treatment for recurrent or metastatic uterine adenosarcomas with regards to surgical resection or chemotherapy. We aimed to provide a descriptive summary of patients with recurrent and metastatic uterine adenosarcoma followed at a single institution.

Methods: Patients (pts) diagnosed with recurrent and/or metastatic uterine adenosarcoma from 1987 to 2017 were included in the study population. Radiographic response was determined using RECIST 1.1. Overall survival (OS) was defined from the time of relapse to the time of death or last follow-up. Progression-free survival (PFS) was defined from start of 1st line chemotherapy to progression, or death, or censored at time of last follow-up. Disease-free interval was defined as time from end of initial treatment to time of relapse. OS and PFS were calculated using the Kaplan-Meier method.

Results: There were 50 pts diagnosed with recurrent or metastatic uterine adenosarcoma from 1987 to 2017. Two pts were excluded for lack of follow-up, and 48 pts comprised the study population. Median follow-up was 7.5 years. Median OS for all pts with recurrent and/or metastatic uterine adenosarcoma was 29.1 months (mo). Recurrences were within the abdominal/pelvis in 32 pts (67%), distant in 7 pts (15%), and both abdominal/pelvic and distant in 8 pts (17%); one patient had metastatic disease on diagnosis (2%). Median OS did not differ based on site of recurrence abdomen/pelvic 25.6 mo, distant 34.3 mo, both 12 mo, p=0.27. For first recurrence, 34 pts (71%) underwent surgery, 26 (54%) received chemotherapy, and 6 (12.5%) received radiation (Table 1). Pts that underwent resection of abdominal/pelvic recurrence had an OS of 37 mo (95% CI 18.5 to 62.1) vs. no resection 13.2 mo (95% CI 6 to 24.6) months, HR 2.41, p=0.03. OS was not influence by 1st line systemic chemotherapy (23.9 mo) vs. no chemotherapy (49.5 mo), HR 0.55, p=0.13. Disease-free interval was significantly associated with surgical resection for disease recurrence 25.8 mo vs no surgery 2.5 mo, p<0.001. Twenty-five patients received >1 cycle of systemic chemotherapy for 1st recurrence and were included in the OS and PFS analysis for 1st line chemotherapy, Table 2. There was no statistically significant difference in OS or PFS for 1st line chemotherapy comparing doxorubicin and ifosfamide (AI) to other doxorubicin based regimens and non-doxorubicin based regimens. RECIST 1.1 best response was evaluable in 15 patients treated with 1st line chemotherapy. Objective response rate by RECIST 1.1 for 1st line doxorubicin based chemotherapy was 5/13, 38.5% (AI: 1 complete response, 3 partial responses; liposomal doxorubicin: 1 partial response). In addition, 5 of 13 pts, 38.5%, achieved stable disease as best response, (liposomal doxorubicin: 4, doxorubicin: 1), and progressive disease was seen in 3 of 13 pts, 23% (liposomal doxorubicin: 2, doxorubicin: 1). There were two non-doxorubicin based 1st line chemotherapy regimens evaluable for RECIST 1.1 response, carboplatin (stable disease) and gemcitabine/docetaxel (partial response).

Conclusion: Abdominal/pelvic recurrence for uterine adenosarcoma was more common than distant metastatic disease but pattern of recurrence did not influence survival in this series. Pts with a longer disease-free interval were more likely to have undergone surgical resection of recurrent disease and have a longer overall survival than pts with a shorter disease-free interval and did not undergo surgical resection of recurrent disease. For pts that required chemotherapy there was no statistically significant difference in OS or PFS comparing AI to other doxorubicin based regimens or to non-doxorubicin

based regimens. Objective responses were seen with AI, single agent doxorubicin, Ifosfamide, liposomal doxorubicin, and gemcitabine/docetaxel.

Treatment for 1st Recurrence

Therapy for 1st Recurrence	Surgery Alone	Surgery + XRT	XRT alone	Surgery + Chemo	Chemo Alone	Surgery + XRT + Chemo	No Treatment
N	18	1	1	11	11	4	2

XRT-radiation

OS and PFS 1st Line Systemic Chemotherapy

Chemotherapy Regimen (n)	Median OS (months)	HR	p value	Median PFS (months)	HR	p value
AI-Doxorubicin/Ifosfamide (5)	23.7	ref	0.37	8.4	ref	0.08
Other Doxorubicin based Regimens (13)	14.8	2.40	--	2.6	4.28	--
Non-Doxorubicin based regimens (7)	21	1.65	--	3.1	2.87	--

Poster 202 3042707

EFFICACY OF TRABECTEDIN IN METASTATIC UTERINE LEIOMYOSARCOMA: A RETROSPECTIVE MULTICENTER STUDY OF THE SPANISH OVARIAN CANCER RESEARCH GROUP (GEICO)

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Objective: Uterine leiomyosarcoma (uLMS) is a rare malignancy accounting for nearly 1% of all uterine tumors. Despite adequate surgical resection, uLMS patients have high risk of metastasis with poor prognosis. Trabectedin is an option in the treatment of metastatic uLMS. This study assessed the efficacy of trabectedin in relapsed/metastatic disease.

Methods: We retrospectively analyzed 36 advanced uLMS patients who received trabectedin (1.5 mg/m2 intravenous over 24h) after anthracycline regimen, in 11 Spanish hospitals.

Results: Between May 2008 and October 2016, 36 metastatic uLMS patients (median age 58 years) received a median of 6 trabectedin cycles (range: 3-25). The median number of previous chemotherapy regimens was 2 (range: 0-3). Sixty-one percent of patients received adjuvant therapy, while 89% received previous chemotherapy lines in advanced disease. Best overall RECIST responses to trabectedin were 3% CR, 25% PR, 50% SD, 22% PD, with objective response and disease control rates of 28% and 78% respectively. Median progression-free survival from trabectedin was 5.4 months (range: 3.5-7.3), and median overall survival was 18.5 (range: 11.5-25.6) and 46 months (range: 33.1-58.9) with respect to trabectedin initiation and initial diagnosis respectively. Trabectedin administered in first and second lines, ECOG performance status 0-1 at trabectedin start, and localized tumor extension at initial diagnosis were associated with improved survival. Toxicity was manageable in accordance with trabectedin known safety profile, being neutropenia the most common G3-4 adverse event (19%).

Conclusion: Trabectedin demonstrates important clinical benefit in patients with recurrent/metastatic uLMS with manageable toxicity. Best outcomes are observed when trabectedin is given in initial lines, in patients with good ECOG performance status at trabectedin administration, and localized disease at initial diagnosis.

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Poster 203 WITHDRAWN

Poster 204 3042769

PROGNOSTIC FACTORS IN ENDOMETRIAL STROMAL SARCOMA (ESS): A SUBGROUP ANALYSIS OF THE GEIS 26 STUDY (SPANISH GROUP FOR RESEARCH ON SARCOMAS)

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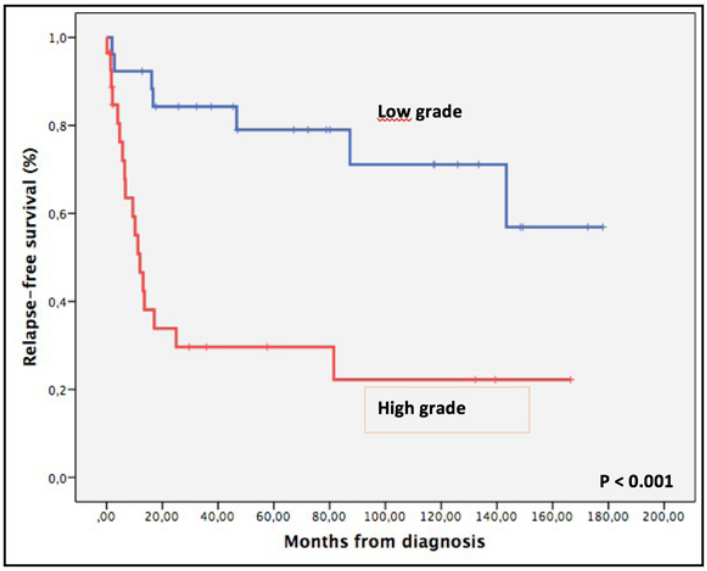
Objective: To analyze epidemiologic data, prognostic factors, molecular factors, response to treatment and prognosis in patients with endometrial stromal sarcoma included in GEIS 26 study.

Methods: An online registry on rare sarcomas (GEIS 26) was developed in 49 hospitals in Spain. Ethics Committee approval was obtained in all involved centers. We performed a subgroup analysis in endometrial stromal sarcoma. The evaluated variables were age and symptoms at diagnosis, tumour size, stage, grade, lymph node involvement, adjuvant treatment, progression-free survival (PFS) and overall survival (OS).

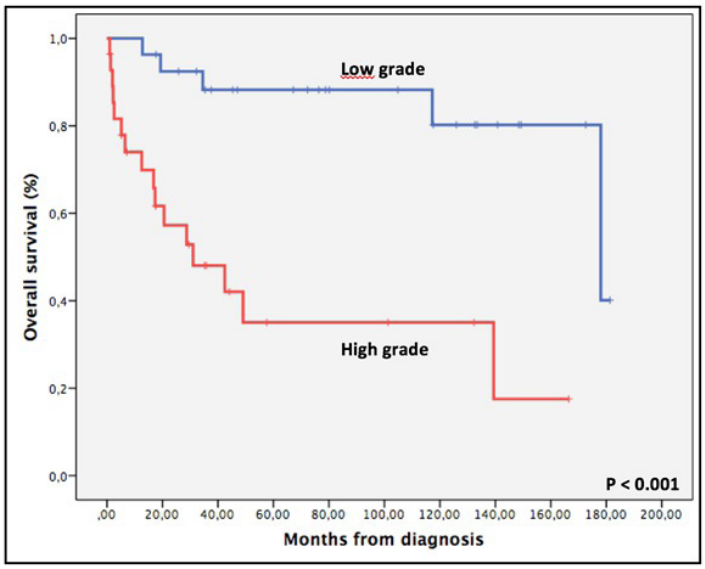
Results: 74 patients (pts) were included. Median age at diagnosis was 56 years. The most frequent symptoms at diagnosis were bleeding (59%) and abdominal pain (23%). Data on grade was included in 61 pts. 32 patients had low grade (LG) and 29 high grade (HG). FIGO stage was recorded in 58 pts (51% stage I/12% stage II/19% stage III and 17% stage IV). In 49/61 pts complete resection was performed. Adjuvant treatment was administered in 26 patients (15 pts received radiotherapy, 5 chemotherapy, 3 radiotherapy plus hormone therapy, 2 chemo and hormone therapy and 1 patient received radiotherapy plus chemotherapy). 62 patients have follow up data. With a median follow up of 60 months (range 1-274), 14/27 pts with low grade (LG) and 5/28 pts with high grade (HG) tumours are alive without disease. 7% of the patients with LG and 54% of those with HG have died due to progressive disease. Median PFS for LG was not reached vs 12 m for HG

(p<0.001). Median overall survival for LG was 178 m compared to 31 m for HG (p<0.001). Adverse prognostic factors for survival in univariate analyses were: age at diagnosis (>60y), high grade, presence of lymph node metastases at diagnosis and absence of adjuvant treatment. For LG tumours, the most important prognostic factor for PFS was complete surgical excision whereas for HG, the only significant prognostic factor was the stage at diagnosis.

Conclusion: ESS is a rare tumour with very little data on the literature. Efforts should be made for treatment advances in HG and LG ESS between working groups in sarcoma. HG and LG ESS are different diseases and future studies should separate these entities. This study is ongoing and pathology review and molecular assessment are underway. Updated analyses will be presented at the meeting.



Recurrence-free survival for HG and LG ESS.



Overall survival for HG and LG ESS.

Poster 205 3028803

UPFRONT ISOLATED LIMB PERFUSION (ILP) IN UNTREATED PATIENTS WITH UNRESECTABLE NON-METASTATIC PRIMARY SOFT-TISSUE SARCOMAS (STS) OF THE LIMB: A RETROSPECTIVE SERIES ON 41 PATIENTS

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Objective: Options for limb-preserving surgery in locally advanced (LA) STS include chemotherapy and/or radiotherapy (RT), or ILP with tumour necrosis factor-alpha (TNFa) + melphalan, if the tumour is confined to an extremity. The aim of this study is to evaluate the benefit of upfront ILP in untreated unresectable patients (pts).

Methods: All pts with an unresectable non-metastatic primary LA STS of the limb treated at Gustave Roussy with an exclusive ILP, as induction treatment between 2003 and 2016 were included in this study. Demographic, clinical and long-term characteristics were obtained from the electronic medical records and retrospectively analyzed.

Results: 41 pts were identified, with a median age of 51 years [range: 21-76]. Liposarcoma and undifferentiated pleomorphic sarcoma were the most common subtypes (27% and 22 % respectively) with tumors classified as FNLCC grade 3 in 11 pts, grade 2 in 16 and grade 1 in 13. Acute regional toxicities after ILP (Wieberdink classification) were grade 2 in 35 pts (85%), and grade 3 in 2 (5%). No grade IV-V were observed. Objective response rate and disease stabilization were observed in 22% (including 2 CR) and 65% respectively. 8 pts were not operated (4 had exclusive RT, 1 pt progressed, 2 pts were in CR and 1 pt died after 3 months after ILP of a massive pulmonary embolism). 1 patient had early amputation due to PD after ILP. Out of 41 pts, 32 patients had conservative resection (78%). 2 pts (6%) experienced pathological CR, 17 (53%) had pathological PR (≥ 50% necrosis) while 13 (41%) were considered refractory (< 50% necrosis). All but 5 pts (84 %) received post-operative RT. After a median follow-up (FU) of 43 months 18 pts (47%) relapsed; one locally, 13 at distance (62% in the lung) and 4 in both sites. The median disease-free survival was 6.7 yrs. The 1-yr, 5-yrs and 10-yrs DFS rates were 75%,

50% and 45% respectively. The median overall survival (OS) was not reached after a median FU of 6.3 yrs.1-yr, 5-yrs and 10-yrs OS rates were 90%, 63% and 55%.

Conclusion: This study suggests that upfront ILP in unresectable is a potentially curative limb saving procedure and is well tolerated without affecting OS.

Poster 206 3042668

SURVEILLANCE CHEST COMPUTED TOMOGRAPH (CT) IMAGING DURING CHEMOTHERAPY IN PEDIATRIC SARCOMA PATIENTS: IS THE RADIATION RISK JUSTIFIED?

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Objective: Intermittent chest CT imaging is recommended, or even required (for those on clinical research trials), throughout chemotherapy through the end of therapy to ostensibly monitor for progressive disease in pediatric sarcoma patients by the Children's Oncology Group and the National Comprehensive Cancer Network (NCCN, 2018). Despite the average of 2-3 chest CT scans ordered per patient during chemotherapy, there are little, if any, evidence to support this standard practice in sarcoma patients, especially pediatric and young adults.
Radiation exposure can range from ~0.2 mSv (chest X-ray) to ~7 mSv (chest CT) to 25 mGy for PET scans depending on the scan ordered. With over 4,000,000 CT scans performed on children every year, CT scans are now the highest non-accidental radiation exposure to children. Pediatric patients exposed to radiation present increased risks of acquiring radiation-induced cancers and systemic complications, in addition to the risk for developing a secondary cancer (see table 1). These risks are especially relevant for pediatric sarcoma patients who are predisposed to other cancers already and are very frequently treated with doxorubicin, a potent radio sensitized and multiplier of radiation damage to the heart. Radiation exposure to the chest of young girls and women is especially concerning given the known association of radiation and subsequent breast cancer.

Methods: We reviewed all new pediatric patients, under age 25, treated by our pediatric team over the last 10 years with a diagnosis of sarcoma, including osteosarcoma (OST), Ewing sarcoma (EWS), Rhabdomyosarcoma (RMS) and other. We reviewed the number of chest CT scans performed after initial workup and until end of therapy.

Results: Of the 47 patients identified, the average age was 10.3 years, the median age was 18 years. There were 19 males and 28 females. There were 26 OST, 8 EWS, 1 RMS and 12 other sarcoma, with a total of 112 CT chest scans performed during chemotherapy and after initial staging workup for an average of 2.4 CT scans per patient or ~16.8 mSv per patient. Of these, we did not find any examples of confirmed progressive disease, and two cases of 'possible progression,' requiring repeat CT of the lungs 6 weeks later where they had resolved, presumably from a resolved pneumonia. No one had a change or interruption of chemotherapy.

Conclusion: In our preliminary, single institution, investigation, we did not find benefit to our newly diagnosed pediatric sarcoma patients with routine CT scanning of the chest during chemotherapy. Although it's possible some patients or providers get psychologic benefit from a 'negative' scan, we did not investigate this. Two of our patients, in fact, got unnecessary second chest CT scans because of equivocal scans in the setting of likely viral pneumonia that, in fact, increased the psychologic distress for them and their providers. More institutions and more data are needed to further investigate the benefits, both medical and psychological to routine surveillance chest CT scans in young pediatric sarcoma patients and weigh this against the potential risks.

Table 1: Chest CT Radiation Exposure Risks

System	Chest CT Exposure Risks
Cardiac	Risk of radiation-induced cardiac disease (Darby, 2010) Radiation in combination with chemotherapy agents, like Doxorubicin, can trigger radiation recall (Howard, 2010)
Respiratory	Early onset pulmonary effects, leading to interstitial lung injury (Abid 2001) Late onset pulmonary effects, leading to pulmonary fibrosis (Abid, 2001) Radiation-induced lung cancer (Radford, 2015)
Lymphatic	Men and, more reportedly, women at risk for radiation-induced breast cancer from radiation exposure at younger age (Radford, 2015)
Endocrine	Risk of radiation-induced thyroid cancer (Sinnott, 2010)

Poster 207 3041924

ADVANCED IMAGING IS A COST-EFFECTIVE SURVEILLANCE STRATEGY FOLLOWING SOFT TISSUE SARCOMA RESECTION

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Objective: Following therapy for soft tissue sarcomas (STS) of the extremities, patients enter a surveillance phase where early detection of local and distant recurrence becomes the focus. While several guidelines for surveillance exist, the specific surveillance strategies for imaging the chest and extremities vary among orthopaedic oncologists. The purpose of this study was to evaluate the cost-effectiveness of various surveillance strategies for local and metastatic disease following primary STS resection. This societal-perspective analysis was based on measures of both quality of life and survival.

Methods: A discrete-time Markov chain decision model was constructed as a cost-effectiveness analysis comparing local and metastatic surveillance strategies. The model was run for ten years using a three-month cycle length. Local strategies included physical examination (PEx), magnetic resonance imaging w/w/o contrast (MRI), and positron emission tomography (PET). Metastatic surveillance strategies included watchful waiting (WW), chest radiograph (CXR), and chest computed tomography w/ contrast (CCT). Outcome probabilities, utilities, and diagnostic test sensitivities were queried from the literature. Costs were collected from the CY 2018 Medicare database. Surveillance strategies were compared with the incremental cost-effectiveness ratio (ICER). Willingness-to-pay (WTP) was set to $ 50,000/quality-adjusted life year (QALY).

Results: Distant recurrence surveillance strategies incorporating CT and CXR showed a survival benefit over WW. The combination of MRI and CCT for local and metastatic surveillance was considered to be cost-effective at a WTP of $ 50,000/QALY. The ICER for MRI and CCT was $ 38,464. At a WTP below $ 38,464, the combinations of PEx with CCT and PEx with CXR were preferred with ICERs of $ 3,302 and $ 1,331, respectively. Using one-way sensitivity analysis, at high physical exam sensitivity, >0.60, the combination of PEx with CCT was preferred over MRI and CCT, as the latter's ICER increased to $ 72,591/QALY. The combinations of WW/PEx, CXR/MRI, and PET were not cost-effective.

Conclusion: At a three-month surveillance interval, local and metastatic surveillance with MRI and CCT respectively were preferred at a WTP of $ 50,000/QALY. With increased physical examination sensitivity, PEx with CCT became cost effective. As expected, strategies with increased sensitivity in detection of metastatic disease demonstrated improved survival.

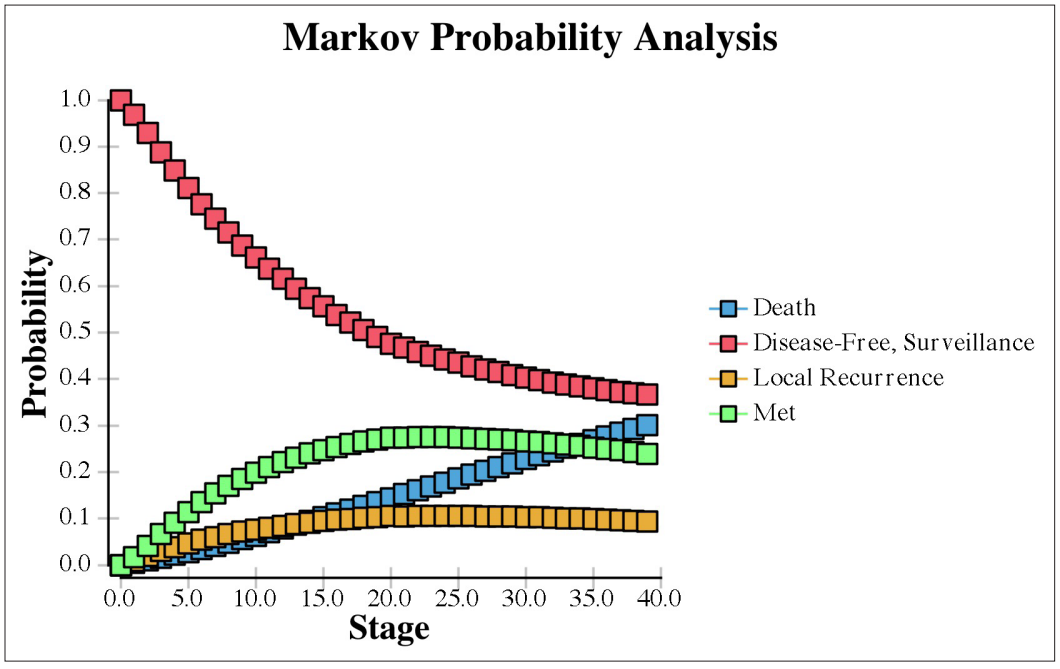

FIGURE 1. Markov state probability changes over stage progression.

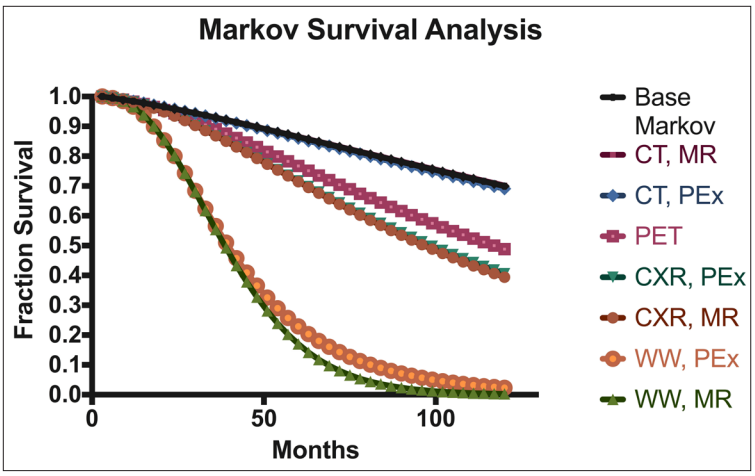

FIGURE 2. 10-year Markov survival analysis with and without diagnostic sensitivity.

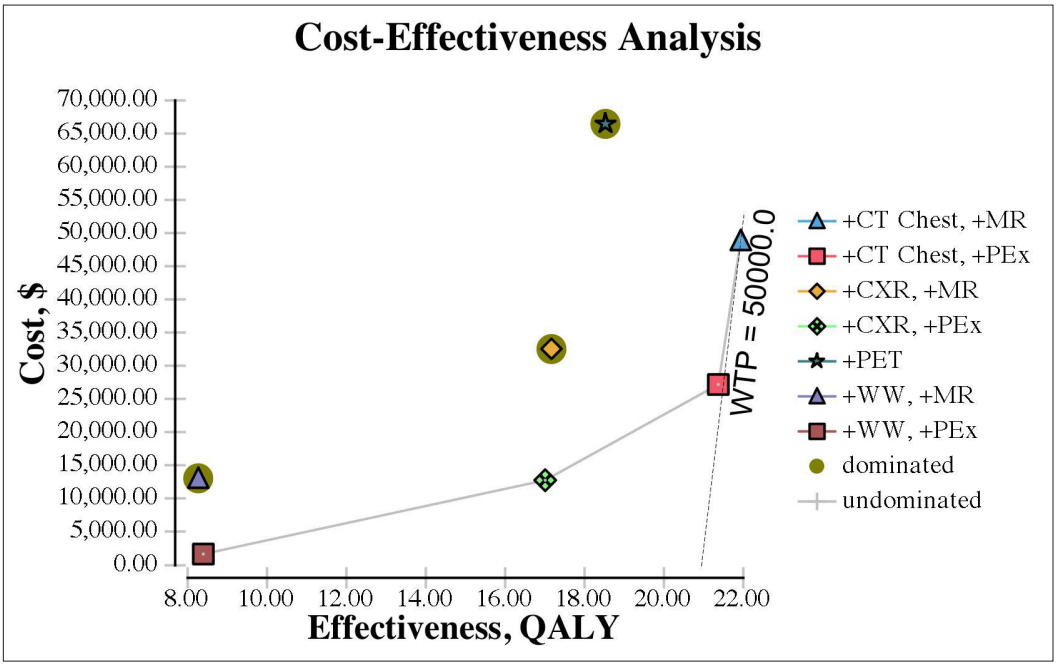

FIGURE 3. Base-case cost-effectiveness analysis with a WTP of $ 50,000.

Poster 208 3042664

RADIATION EXPOSURE IN PEDIATRIC SARCOMA PATIENTS RECEIVING INITIAL CHEMOTHERAPY

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Objective: To question the risks/benefits of ionizing radiation imaging during initial systemic chemotherapy for children with sarcoma.

Regular imaging scans are routinely used in newly diagnosed pediatric sarcoma patients during initial chemotherapy ostensibly to detect the progression of disease and the need to alter therapy. The *National Comprehensive Cancer Network* (NCCN) and the Children's Oncology Group (COG) recommend or require (for those on COG protocols) lung CTs or CXR at checkpoints during chemotherapy for the most common pediatric sarcomas: Osteosarcoma (OST), Ewing (EWS), and Rhabdomyosarcoma (RMS) (NCCN, 2018).

Pediatric sarcoma patients are already at increased risk of secondary cancers, especially those with genetic predispositions, a not uncommon finding in pediatric sarcoma. There is an increased risk of secondary sarcomas after radiation exposure greater than 10Gy in childhood, and likely at much lower doses as found in Japanese atomic bomb survivors exposed to < 5Gy (Gonzalez, 2012).

Standard chest X-rays deliver approximately 0.1 mGy per view and lung CT about 7mGy (Harvard Health, 2018). Studies of 400,000 radiation workers with an average of 40 mGy exposure showed increased risk of cancer (Brenner, NEJM, 2007). There is a consensus that this level of exposure creates an even higher risk for children. Children exposed to radiation therapy had 3.3 x higher risk of secondary sarcoma compared to adults, thought to be due of higher cell turnover at younger ages and more time for manifestation of deleterious effects (Gonzalez, 2012). In 2013, Miglioretti, et al, estimated 4870 future cancers attributable to the approximately 4,000,000 CT scans performed every year on children in America (JAMA Pediatrics 8:700-707).
Besides secondary cancers, lung irradiation also increase the risk of heart disease (especially in those receiving doxorubicin which is standard for OST, EWS and RMS), lung disease, and thyroid disease. Breast cancer in young girls and women exposed to radiation is an especially serious concern.

Methods: We reviewed all published data from the last 15 years from the COG for the diagnoses of OST, EWS and RMS. We recorded the number of chest X-Rays, lung CTs, bone scans, and PET scans required for each patient during chemotherapy for each protocol and calculated the total radiation exposure based on chest x-rays delivering 0.2mGy per scan (.1 mGy per view), lung CTs delivering 7.0mGy per scan, bone scans delivering 6.3mGy per scan, and PET delivering 25 mGy per scan (Harvard Health, 2018) (Radiological Society of North America, 2018). Additionally, we documented the number of patients who were removed from protocol during chemotherapy (induction or consolidation) because of new or progressive disease detected on required imaging.

Results: Overall, combining all of the sarcoma protocols, a total of 53428 imaging scans during chemotherapy were done and the average patient received 42.7 mGy of radiation, while only 3.2% of the patients were found to have progressive disease. For EWS, 3048 chest X-rays, 6427 lung CTs, and 3467 bone scans were performed on 2048 patients with an average radiation exposure per patient of 32.9 mGy. For OST, 16765 chest X-rays, 11120 lung CTs, and 8860 bone scans were done on 3179 patients, totaling 43.1 mGy of radiation exposure per patient. For RMS, 1902 lung CTs, 667 bone scans, and 1136 PET scans were performed on 634 patients, exposing them to 72.4 mGy per patient. The percentage of patients found to have progressive disease was .2% for EWS, 5.5% for OST, and 1.1% in RMS.

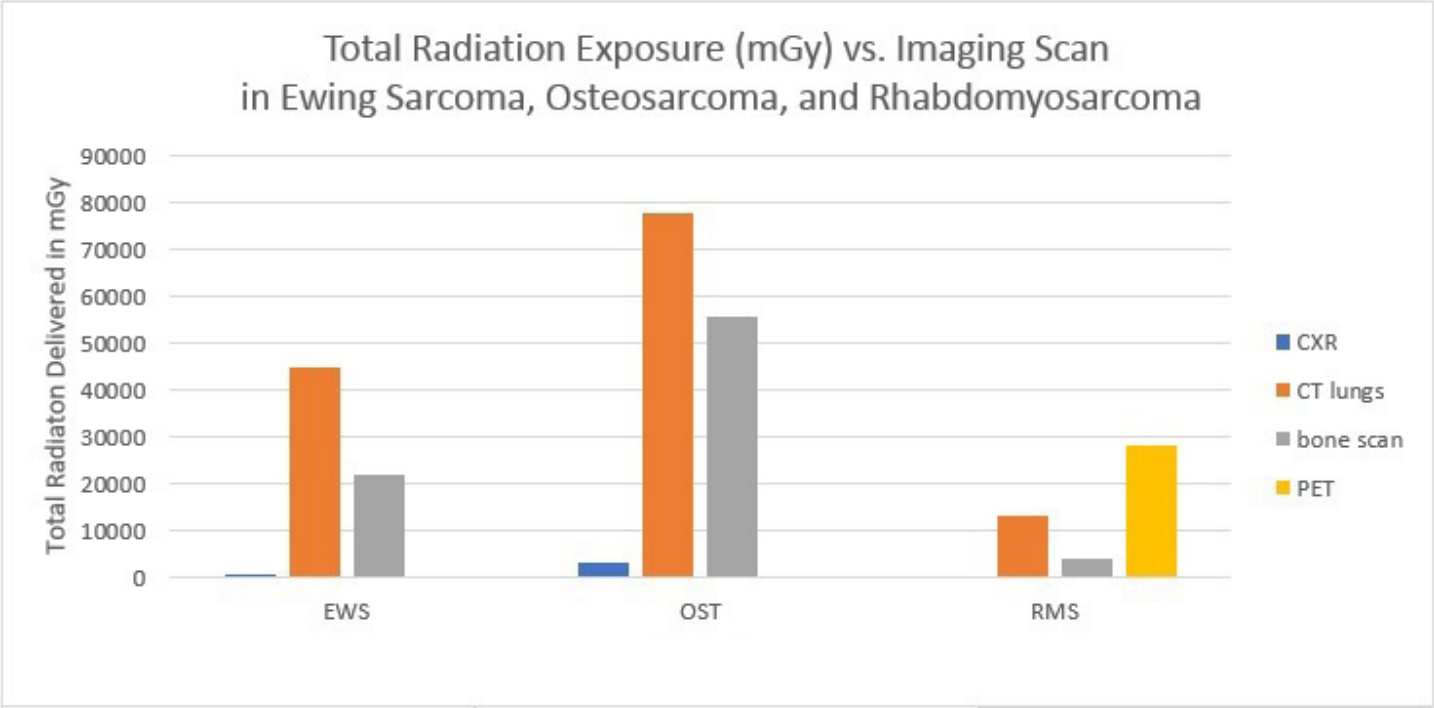
Conclusion: In our preliminary meta-analysis early progressive or relapsed disease was only detected 3.2% of the time, while 6048 patients were exposed to ionizing radiation. These chemotherapy protocols exposed a child to an average radiation dose of 42.7 mGy. Decreasing or eliminating these exposures during chemotherapy or replacing those deemed necessary with non-ionizing modalities may tip the risk benefit ratio back towards a benefit.

Total Radiation Exposure (mGy) vs. Imaging Scan in Ewing Sarcoma, Osteosarcoma, and Rhabdomyosarcoma

	Chest X-Ray (Radiation exposure (mGy))	CT Lungs (Radiation exposure (mGy))	Bone Scan (Radiation exposure (mGy))	PET (Radiation exposure (mGy))	Total Radiation Exposure (mGy)	Number of Patients	Average Radiation Exposure per patient (mGy)
EWS (AEWS1031, AEWS0031, AEWS0331)	616.8	44989	21842.1	0	67447.9	2048	32.9
OST (7921, AOST0331, P9754)	3353	77840	55818	0	137011	3179	43.1
RMS (ARST 0331, ARST0531, ART0431)	0	13314	4202.1	28400	45916.1	634	72.4
Total	3969.8	136143	81862.2	28400	250375	5861	42.7

Patients with Progressive Disease Detected on Chemotherapy vs. No Progressive Disease in Ewing Sarcoma, Osteosarcoma, and Rhabdomyosarcoma

	Progression Detected while on chemotherapy	No Progression	% (Patients with Progression Detected while on Chemotherapy/Total Patients in Protocol)
EWS (AEWS1031, AEWS0031, AEWS0331)	4	2048	0.2
OST (7921, AOST0331, P9754)	176	3179	5.5
RMS (ARST 0331, ARST0531, ART0431)	7	634	1.1
Total	187	5861	3.2



Poster 209 3042864

ACCURACY OF FDG-POSITRON EMISSION TOMOGRAPHY (PET) SCAN IN DESMOPLASTIC SMALL ROUND CELL TUMOR

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Objective: Desmoplastic small round cell tumor (DSRCT) consists of small round blue cells embedded in a desmoplastic stroma. Disease is often disseminated at diagnosis, and miliary peritoneal seeding and omental caking are common. Anatomical scans therefore have limitations in extent of disease evaluation and in assessing response to chemotherapy. The objective of this study was to assess the accuracy of FDG- PET scan in detecting viable DSRCT.

Methods: After IRB approval, a retrospective review was conducted on patients undergoing resection of disease at Memorial Sloan Kettering Cancer Center between January 2013 and December 2017. Patients with positive FDG-PET scans immediately prior to surgery were analyzed. FDG avidity on PET scan was corelated to disease status on corresponding lesions based on pathology reports and operative notes. Intensity, assessed by standard uptake value (SUV) of FDG was also noted.

Results: Twenty-seven patients (26 male, 1 female, median age at surgery 20 years) with a total of 107 discrete lesions reported on PET scan were identified. All patients had previously received neoadjuvant chemotherapy. Median SUV in PET-positive lesions was 4 while median background SUV in the liver was 1.7. All had at least one positive finding on pre-operative PET scan report. Of 107 lesions detected on PET, 82 lesions had pathological findings reported on histopathology. Out of the 82 lesions with histologic correlates available, active DSRCT was confirmed by histopathology in 79, leading to lesion-specific positive predictive value of 96%. Twenty-six patients with positive FDG-PET had evidence of active DSRCT,

resulting in patient-specific positive predictive value of 96%. Three FDG-positive lesions (respective SUVs of 5.7, 8.6 and 10.8) in 2 patients did not have histological evidence of DSRCT. These showed inflammatory changes. All 26 patients with positive histology, had positive pre-operative PET scans yielding patient-specific sensitivity of 100%.

Conclusion: FDG-PET has high positive predictive value in detecting DSRCT even when evaluated after neoadjuvant chemotherapy, and can guide the surgeon to areas of disease at resection. Lesion-specific sensitivity of PET in detecting active disease in lesions that are measurable on CT scan was not formally assessed for this report, but is ongoing.

Poster 210 3042859

COMPLIANCE OF RADIOLOGICAL FOLLOW-UP FOLLOWING RESECTION OF PRIMARY INTRAABDOMINAL SOFT TISSUE SARCOMA WITH ESMO/ESNWG GUIDELINES: A 10-YEAR AUDIT OF PRACTICE FROM A UK QUATERNARY REFERRAL CENTRE

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Objective: ESMO/European Sarcoma Network Working Group guidelines (2014) provide pragmatic protocols for radiological follow-up of operated intra-abdominal sarcoma. This study aimed to evaluate the compliance of radiological follow up for these tumours with ESMO guidelines at a single, quaternary soft tissue sarcoma unit (Queen Elizabeth Hospital, Birmingham, UK).

Methods: Retrospective audit. Adult patients undergoing primary resection of intraabdominal liposarcoma or leiomyosarcoma over a ten year period were identified (1 January 2005 to 31 December 2015), and radiological follow-up was recorded up to date of discharge, death or last seen alive up to 1 June 2018. The primary outcome measure was ESMO guidleline compliance, stratified by high-grade versus low-grade histology, and date of surgery (prior to 2014 versus after 2014).

Results: 273 patients were included (51% male: 49% female) with a mean age of 65 years (range: 38–86). Overall ESMO guideline compliance was 58.9%. This was higher after introduction of the guideline than before 2014 (72.2% versus 36.1%), and higher in low grade than high grade tumours (78.9% versus 43.8%). For high grade tumours, median scanning interval within the first two years was 6 months (range: 1-15), and 11 months between 2-5 years (range: 3-18). CT was the most common scanning modality (97.4%). For low grade tumours, mean scanning interval within the first five years was 11 months (range: 3-36). CT was performed for 96.4% of follow-ups, and chest radiographs in 3.6%. 16.7% of those alive beyond five years postoperatively had ongoing follow-up.

Conclusion: Our current practice in radiological follow-up of operated soft tissue sarcomas is moderately compliant with ESMO guidelines. Introduction of ESMO guidelines for follow-up has increased intensity of follow-up to 5-years for both high and low-grade disease. An international, multicentre, prospective evidence base to support follow-up protocols in this setting is urgently required.

Poster 211 3041967

DIFFERENTIATING WELL-DIFFERENTIATED LIPOSARCOMAS FROM LIPOMAS USING A RADIOMICS APPROACH – PRELIMINARY RESULTS

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Objective: Well-differentiated liposarcomas (WDLPSs) can be difficult to distinguish from lipomas. Distinction between lipomas and WDLPSs is made by testing for *MDM2* amplification, using fluorescence in situ hybridization (FISH). This amplification is absent in lipomas and present in WDLPSs. Therefore, patients need to undergo an invasive biopsy for pathological examination, with the risk of sampling error and risk of complications, in particular for those cases with a tumor difficult to access. Radiomics is a non-invasive technique where quantitative medical imaging features are correlated with underlying biological information, such as *MDM2* amplification. The aim of this study is to predict the presence or

the absence of *MDM2* amplification, thereby differentiating between lipomas and WDLPSs, based on MRI scans using a radiomics approach.

Methods: Patients with a pathologically confirmed *MDM2*-negative lipoma or *MDM2*-positive WDLPS and a pre-treatment T1-weighted MRI scan were included from 2009-2017. The MRI scans were obtained during routine diagnostic workup. Segmentation of the tumors was performed semi-automatically and independently by two different persons, using state-of-the-art software. A single, representative slice was manually annotated. Next, deformable image registration was used to warp the segmentation to a neighboring slice. The result was manually corrected and again warped to the next slice. This process was repeated until the full lesion was correctly segmented in 3D-context. Radiomics features describing intensity, shape, orientation and texture were extracted from the tumor segmentations. Age, gender and the manually scored depth of tumor (above or beneath superficial fascia) and its location were added, resulting in a total of 415 features. Classification was performed using a Support Vector Machine (SVM). For performance evaluation, a 50x random-split cross-validation was used. In each of the 50 iterations, the data set was randomly split in a training set (80%) and test set (20%). Feature selection was performed by using an exhaustive search among the feature groups. The parameters for this selection and the SVM hyperparameters were optimized on the training set in each iteration using 5-fold cross-validation. The 95% confidence intervals of the classification performances on the test set were calculated using the corrected resampled t-test.

Results: In total, 88 patients were identified: 42 patients with a lipoma and 46 patients with a WDLPS. The data set originated from multiple clinical centers, resulting in heterogeneity in the data set. The scans differ for example in manufacturer (Siemens: 37, Philips Healthcare: 31 and GE Medical Systems: 20 scans), magnetic field strength (1T: 8, 1.5T: 73 and 3T: 7 scans) and slice thickness (mean: 5.61 mm and standard deviation: 1.49 mm). The most optimal radiomics approach to differentiate between WDLPSs and lipomas resulted in 95% confidence intervals of the AUC of [0.74, 0.93](figure 1), accuracy [0.67, 0.85], sensitivity [0.59, 0.86] and specificity [0.67, 0.92].

Conclusion: The preliminary results show that radiomics is a promising, non-invasive approach for the classification of WDLPS and lipomas. However, further optimization and validation is needed before it can be used in daily clinical practice.

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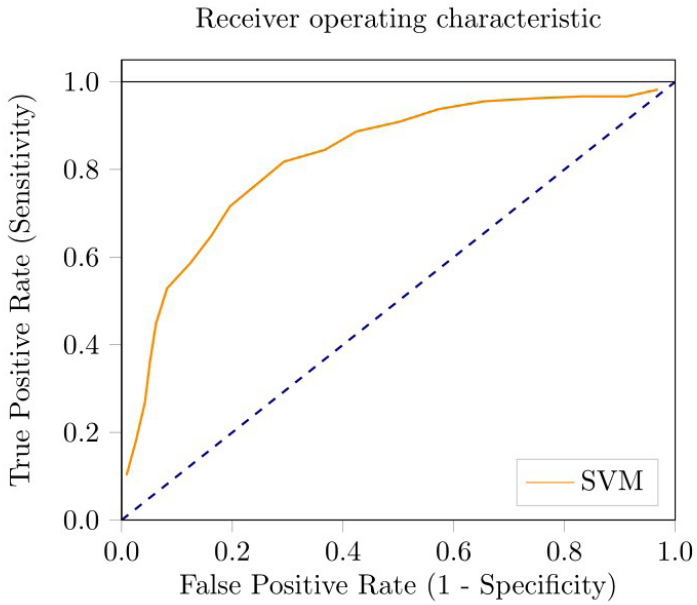

Figure 1: Receiver operating characteristic (ROC) curve of the proposed radiomics approach to differentiate between lipomas and well-differentiated liposarcomas, showing an area under the curve (AUC) of 0.84 (95% CI [0.74,0.93]).

Figure 1: Receiver operating characteristic (ROC) curve of the proposed radiomics approach to differentiate between lipomas and well-differentiated liposarcomas, showing an area under the curve (AUC) of 0.84 (95% CI [0.74,0.93]).

Poster 212 3037023

SIGNAL INTENSITY OF MRI COULD PEDICT THE EFFICACY OF MELOXICAM TREATMENT IN PATIENTS WITH DESMOID-TYPE FIBROMATOSIS

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Objective: Desmoid type fibromatosis (DF) is a benign neoplasm of mesenchymal origin that shows local aggressive nature, but do not metastasize. There are few factors reported to well predict the efficacy of conservative treatment for DF. This study aimed to determine the clinical significance of signal intensity of MRI as a possible predictor for responsiveness of meloxicam treatment in patients with extra-peritoneal DF. In addition, correlation between CTNNB1 mutation status and signal intensity of MRI during meloxicam treatment was analyzed.

Methods: Between 2003 and 2017, 46 patients with extra-peritoneal sporadic DF were consecutively and prospectively treated with meloxicam as a systemic medical therapy. The maximum transvers section of DF on T2-weighted MRI (T2) before initiation of therapy and the last visit during the meloxicam treatment was evaluated. Low intensity area (LIA) on T2-weighted MRI, which is defined as compared with muscle intensity surrounding the tumor, was calculated using Image J software. Tumor DNA was extracted from tumor frozen tissue or FFPE obtained by biopsy, and subjected to the CTNNB1 mutation analysis by Sanger method. Efficacy of meloxicam treatment was evaluated according to RECIST with MRI findings.We divided patients into 2 groups, Good Responder group (GR group; CR, PR, and SD) and Poor Responder group (PR group; PD). Correlation of the efficacy of meloxicam with the LIA was statistically analyzed. Relationship between CTNNB1 mutation status and LIA was also investigated.

Results: The mean age at the first visit was 42.4 years (range 10-79 years), and the mean tumor size before the initial treatment was 84.5 mm (range 23-220 mm). The median period of meloxicam administration was 15 months (range 1.4-102 months), the median follow up period was 57 months (range 7.7-151 months). RESCIST criteria showed 11 patients with PR, 17 patients with SD and 18 patients with PD. The mean LIA ratio (LIA/total area) before treatment was 37% in GR group and 11% in PR group, which was significantly higher in GR group ($p < 0.001$). For predicting efficacy of meloxicam, sensitivity was 68%, specificity was 89% if setting the cut-off value as 20% for LIA. Mean changes in the LIA ratio before and after treatment were 14.1% in GR group and -0.6% in PR group. There is a significant more increase in GR group ($p = 0.01$) compared with that in PR group. In the CTNNB1 mutation analysis, the S45F mutation tended to be higher in PR group (PR group, 4/18 patients; GR group, 1/28 patients; $p = 0.07$). Additionally the mean LIA ratio before treatment was 8% in S45F mutation group and 29% in other mutation group, which was significantly lower in S45F mutation group ($p < 0.001$). Mean changes in the LIA ratio were not significant in the mutation analysis (S45F, 2%; others, 9%; $p = 0.35$). In multivariate analysis, LIA ratio before treatment was a significant predictor for responsiveness to treatment ($p = 0.02$).

Table 1. Univariate and multivariate analysis for factors correlated with efficacy of meloxicam treatment

Variables	Good prognosis Group (CR, PR, SD)	Poor prognosis Group (PD)	Univariate (P value)	Multivariate (P value)
Gender				
male	12	5	0.360	0.449
female	16	13		
Age (mean= 42.4 ys)				
<40	13	12	0.232	0.415
≥40	15	6		
Size (mean= 84.5mm)				
<80	16	10	1.00	0.803
≥80	12	8		
Mutation				
others	27	14	0.068	0.260
S45F	1	4		
LIA on T2-WI				
≥20%	19	2	<0.001	0.018
<20%	9	16		
Change of LIA ratio				
≥0%	24	8	0.007	-
<0%	4	10		

Conclusion: Several previous studies reported that MRI intensity, particularly on T2-weighted image, was a useful predictor for DF behavior. However, these studies analyzed the DF with cohort of wait and see or multiple treatment modality. In this study, we investigated the usefulness of MRI intensity in the identical cohort, treated with meloxicam. Results of this study suggested that the signal pattern of MRI was a useful predictor in patients treated with meloxicam. We may predict the prognosis more accurately in combination with other factors, such as CTNNB1 mutant status.

Poster 213 3037261

THE UTILITY OF FLUORINE-18-FDG PET/MRI FOR DIAGNOSING BONE AND SOFT TISSUE MALIGNANCIES SECONDARY TO PREEXISTING BENIGN CONDITIONS

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Objective: Fluorine-18-FDG PET imaging is now widely used for evaluating malignant tumors including musculoskeletal tumors. Although whole-body ^{18}F-FDG PET/MRI is sensitive for detecting abnormality in bone marrow as well as soft tissues, the utility for detecting malignant transformed lesion from preexisting benign condition is still obscure because of reality of those cases. We herein describe the utility of ^{18}F-FDG PET/MRI for detecting malignant transformation from benign musculoskeletal condition.

Methods: From March 2013, ^{18}F-FDG PET/MRI became clinically available in our hospital, and 4 cases (male : female = 3 : 1) of malignant transformations from benign musculoskeletal conditions were detected by ^{18}F-FDG PET/MRI to date. We retrospectively investigated the utility of the ^{18}F-FDG PET/MRI for detecting malignant transformation secondary to benign musculoskeletal condition.

Results: Secondary malignant musculoskeletal tumors composed of 3 cases of high-grade and 1 case of low-grade tumors. Secondary malignant tumors and preexisting benign conditions were as follows; case 1, undifferentiated high-grade sarcoma from synovial chondromatosis; case 2, fibroblastic osteosarcoma from diaphyseal medullary stenosis-like osteosclerotic lesion (non-hereditary); case 3, malignant melanoma from traumatic scar; and case 4, secondary low-grade chondrosarcoma from multiple osteochondromatosis.

In 3 cases of high-grade malignancies, abnormal ^{18}F-FDG uptakes were corresponded with histopathologically malignant-transformed lesions of the surgical specimens. Although secondary chondrosarcoma was low grade malignancy, ^{18}F-FDG PET/MRI findings of high FDG uptake as well as thick cartilaginous cap comparing with other preexisting osteochondromas helped to diagnose malignant transformation.

Conclusion: FDG PET/MRI was thought to be useful tool for diagnosing of malignant musculoskeletal tumors secondary to preexisting benign condition.

Poster 214 3042206

THE UTILITY OF PET/CT VERSUS BONE SCAN FOR DIAGNOSIS AND MONITORING OF PEDIATRIC SARCOMA PATIENTS

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Objective: Osteosarcoma and Ewing sarcoma are the most common primary pediatric bone cancers. Although the prognosis of pediatric sarcomas has greatly improved due to multimodal therapy, metastatic disease continues to cause significant mortality, with overall survival <30%. Thus, it is imperative to accurately detect primary disease and metastases. Imaging modalities are an essential part of the diagnostic and therapeutic plan in sarcoma patients; results of these studies will guide risk classification, prognosis, choice of chemotherapy, type of surgery, and foci of radiation to achieve maximal remission and prevent recurrence. Current guidelines for osteosarcoma and Ewing sarcoma from the Children's Oncology Group for initial imaging evaluation include conventional radiographs, CT, and MRI for primary tumor evaluation and CT chest and whole body MDP bone scintigraphy +/- SPECT for metastatic evaluation. FDG PET/CT (PET) is not mandatory and there are no strict guidelines for its use. However, in recent years PET has become more common for diagnostic evaluation and follow up after chemotherapy; in fact, some institutions pursue both, which adds to cost and radiation exposure. We aim to descriptively compare the identification of metastases using bone scan (BS) versus PET in our patient population. We hypothesize that PET is more likely to detect osseous metastases of primary bone sarcomas both at diagnosis and relapse, and may be able to replace BS altogether in disease evaluation.

Methods: We performed retrospective chart reviews of patients treated for pediatric sarcoma at the Children's Hospital at Montefiore from 2008-2018. Paired BS and PET scans were reviewed by pediatric nuclear medicine physicians and imaging

modalities were compared for evaluation of disease and presence of osseous metastases at diagnosis and multiple time points during treatment.

Results: Of the patients reviewed, 31 patients had paired BS and PET during diagnosis or treatment. 25 patients were evaluated at initial diagnosis; 18 presented with localized disease, 2 had multifocal osteosarcoma, and 5 had distant osseous metastases. 17 patients had osteosarcoma (OS) and 14 patients had Ewing Sarcoma (ES). In the OS cohort, 5 patients had osseous metastases; 100% of these patients were detected on PET but only 60% of these patients were detected on BS (n=3). 14 bony lesions were seen on imaging in OS patients; 100% of these were identified on PET but only 36% on BS (n=5). In the ES cohort, 4 patients had osseous metastases; 100% of these patients were detected on PET but only 75% of these patients were detected on BS (n=3). 14 bony lesions were seen on imaging in ES patients; 100% of these were identified on PET but only 50% on BS (n=7). Five of all patients with bony metastases had confirmatory pathology for true disease. 1 patient with concerning imaging for bony metastasis had follow-up pathology consistent with a bone cyst.

Conclusion: Patients in our institution with OS or ES undergoing both PET and BS were more likely to show osseous metastases on PET. Lesions detected on BS were always visualized on PET. There was one instance of a false positive finding on PET, underscoring that radiologic or histologic confirmation is important. While these findings echo previous reports that find PET more sensitive than BS, the current study illustrates that all lesions detected via BS were also detected by PET, suggesting that BS may in fact be redundant and unnecessary in the setting of PET-proven localized disease. Given the rarity of pediatric sarcoma and the difficulty in obtaining large cohorts, our findings add strength to the previous literature, and taken in conjunction, aid in demonstrating that PET/CT may be useful as a first-line imaging study and obviate the need for bone scan in future diagnosis and monitoring of sarcoma patients. This approach may provide for better detection of distant disease while minimizing cost, radiation exposure and resource utilization.

Osteosarcoma

	Number	Percent (%)
Total no. of patients	17	
Patients with osseous metastases	5	
Patients with mets detected on bone scan (BS)	3	60%
Patients with mets detected on PET	5	100%
Total no. of bony lesions	14	
No. of lesions detected on BS	5	36%
No. of lesions detected on PET	14	100%

Ewing Sarcoma

	Number	Percent (%)
Total no. of patients	14	
Patients with osseous metastases	4	
Patients with mets detected on bone scan (BS)	3	75%
Patients with mets detected on PET	4	100%
Total no. of bony lesions	14	
No. of lesions detected on BS	7	50%
No. of lesions detected on PET	14	100%

Poster 215 3041981

COMBINING ONCOLYTIC VIROTHERAPY AND PD-1 INHIBITION IN AN ANIMAL MODEL OF ISOLATED LIMB PERFUSION TO IMPROVE LOCAL AND DISTANT DISEASE CONTROL IN ADVANCED EXTREMITY SOFT TISSUE SARCOMA

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Objective: Isolated Limb Perfusion (ILP) with melphalan and Tumour Necrosis Factor α (TNFα) for extremity soft tissue sarcoma (ESTS) can be used as a stand-alone treatment for irresectable disease or as induction therapy to downsize locally advanced tumours prior to limb conserving surgery. ILP is limited by a short duration of response and an inability to prevent systemic progression. TNFα in ILP serves to increase the concentration of melphalan within the centre of bulky tumours.

Oncolytic virotherapy (OV) exerts tumoricidal effects by direct tumour lysis but also can have an immune priming effect in non-immunogenic tumours such as ESTS. Intravenous OV treatment is limited in effect because of reticulo-endothelial sequestration, first pass hepatic metabolism and a failure to penetrate into bulky tumour. Therefore there is a theoretical advantage for OV delivery by ILP as all three of those barriers are circumvented. We sought to develop an animal model of limb sarcoma treated by ILP in order analyse the addition of OV and PD-1 inhibitors in combination with melphalan and TNFα. Local and distant response rates were assessed.

Methods: An immune- competent model of ILP was developed using Brown Norway rats and the BN175 sarcoma cell line. An oncolytic vaccinia virus (GLV-1h68) and PD-1 inhibitor (J43) were combined individually and together with a melphalan and TNFα in the ILP model. Therapeutcis were given as a single treatment without surgical resection (palliative ILP model) or prior to surgical rescetion and radiotherapy (induction ILP model).

Results: An animal model of ILP with an advanced ESTS treated with melphalan and TNFα, which was reproducible and well tolerated with minimal systemic side effects, was developed. The addition of OV, melphalan and TNFα (viral ILP) in a palliative ILP model significantly delayed tumour growth and prolonged survival compared with standard ILP (35 vs 23 days, $p<0.001$) but local control was not achieved with all tumours continuing to progress. Viral plaque assays on homogenised tumor, liver, spleen and skin demonstrated almost complete localisation of virus within the tumour and minimal systemic distribution. When OV was delivered in the induction model of ILP, long term disease control was achieved within the limb in 33% of treated animals although systemic metastases still developed in all cases. The addition of PD-1 inhibitors to palliative viral ILP without surgery resulted in complete regression of limb tumours in 33% of treated of animals($p<0.001$) but treatment resistance rapidly developed and survival was not improved. PD-1 inhibitors were unable to induce tumour regression as a monotherapy, indicative of a sensitising effect of viral ILP to these agents. The addition of PD-1 inhibitors to an induction viral ILP, in which the tumours were resected and irradiated after the ILP, cured local disease in all animals treated (Figure 1) and, furthermore, subsequent *post mortem* analysis of the lungs showed that no surviving animals had developed pulmonary metastases. *Ex vivo* analysis of tumours showed that the combination of PD-1 inhibitors with viral ILP promoted an inflammatory micro-environment with significantly increased numbers of CD3+ tumour infiltrating lymphocytes, T helper cells and activated natural killer cells in the centre of the tumour, consistent with immune activation.

Conclusion: In an animal model of advanced ESTS treated by ILP the addition of OV and PD-1 inhibitors resulted in improved local response rates in palliative model, and in an induction model resulted both in local cure and the prevention of the development of systemic metastases. The mechanism of action includes a promotion of an immunogenic micro-environment within the tumour. This encouraging laboratory data will be translated into a forthcoming phase 1/2 clinical trial (ClinicalTrials.gov Identifier: NCT03555032)

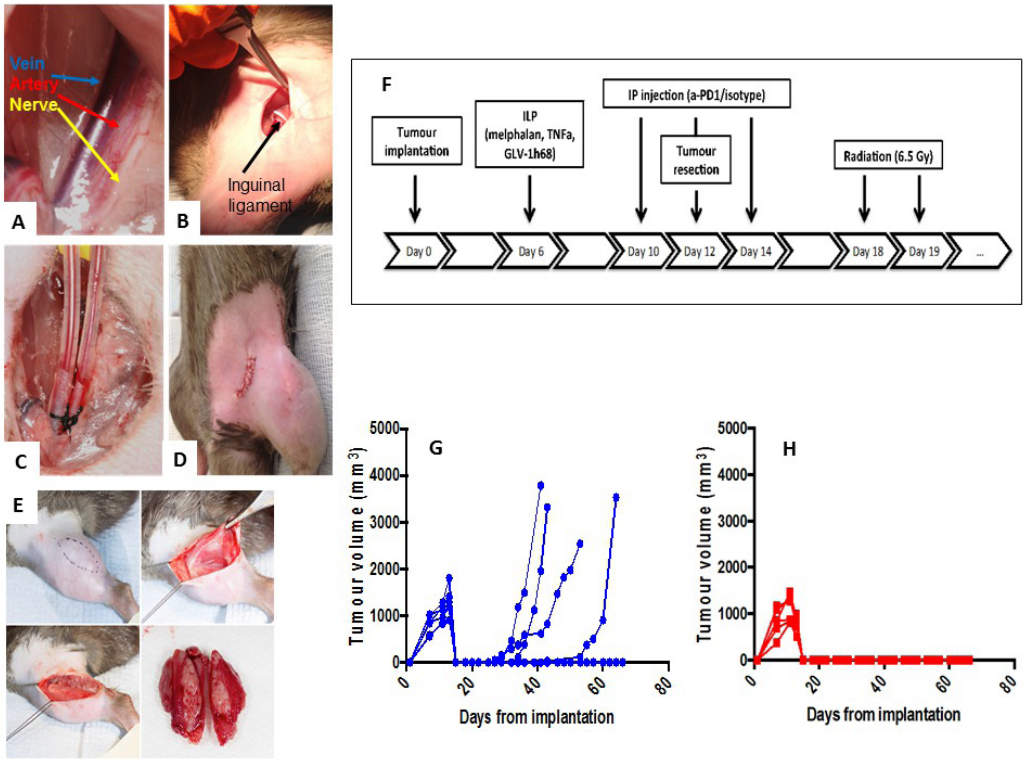

Figure 1. Induction ILP model treated with OV with and without PD-1 inhibition. Panel A- D Clinical photographs of ILP. Panel E Surgical resection of tumours post ILP. Panel F Schematic of treatment regime shown with the addition of PD-1 inhibitors. Panel G and H. Tumour growth curves without and with PD1 inhibitors – Panel G is viral ILP without PD-1 inhibition in which local control was achieved in 33% of cases but all surviving animals developed pulmonary metastases whereas in Panel H the addition of PD-1 inhibitors resulted in local and systemic cure in all animals.

Poster 216 3014823

NEOADJUVANT THERAPY INDUCES A POTENT INFLAMMATORY AND CORRESPONDING REGULATORY RESPONSE WITHIN THE SARCOMA IMMUNE MICROENVIRONMENT

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Objective: Following curative intent resection, half of patients with large, high-grade soft tissue sarcomas (STS) will recur with incurable disease. Adjuvant radiation improves local control but does not impact overall survival. Recent trials have demonstrated efficacy of anti-PD-1 immunotherapy in a subset of patients with advanced STS. Preliminary genomic studies suggest a heterogeneous infiltration of immune cells within STS, but a comprehensive understanding of the immune landscape is lacking. We sought to better define the immune response to STS and the mechanisms by which preoperative radiotherapy alters the tumor immune microenvironment (TIME).

Methods: Retrospective review of an institutional database was performed to identify STS patients who underwent neoadjuvant radiation followed by curative intent resection from 2007-2014. Tumor infiltrating leukocytes (TIL) were measured by multiplex immunohistochemistry (mIHC), using a tyramide-based secondary antibody system allowing for simultaneous 6-color staining (OPAL, PerkinElmer). Images were digitized for quantitative analysis.

Results: Twenty-two patients with adequate tissue for comprehensive immunoprofiling were identified, comprising a spectrum of relevant histologic subtypes: 14 undifferentiated pleomorphic sarcomas (UPS), 5 translocation-associated sarcomas (3 myxoid/round cell liposarcomas [MRCL], 2 synovial sarcomas [SS]), and 3 leiomyosarcomas (LMS). Notably, 82% of patients were also treated with anthracycline-based chemotherapy prior to radiation and resection. The most prevalent TIL across the cohort were CD68/CD163$^+$ macrophages (6.5%) and CD3$^+$ T lymphocytes (3.7%) (Fig. 1, Table 1). About 20% of T cells expressed the inhibitory checkpoint receptor PD-1, and 60% of macrophages expressed CD206, a marker of M2-like, suppressive phenotype. LMS was most infiltrated by T cells, whereas UPS was most infiltrated by suppressive TIL, including CD3$^+$FOXP3$^+$ regulatory T cells (Treg) and macrophages (Fig. 1C-E). Neoadjuvant treatment exerted heterogeneous and paradoxical effects (Table 1). Intratumoral T cell frequency increased across histologies (Fig. 1C), while the proportion of Treg decreased, most notably in UPS (Fig. 1D). Macrophages nearly doubled (Fig. 1E). T cell expression of PD-1 increased, but only in non-UPS tumors.

Conclusion: Preoperative radiation induces infiltration of both effector and suppressive immune cells into an already complex sarcoma microenvironment. Future neoadjuvant trials should investigate the combination of standard cytotoxic treatments with immune-activating therapies targeting the regulatory response.

Table 1. Summary of the most prevalent immune cell types infiltrating soft tissue sarcoma, pre- and post-neoadjuvant radiotherapy.

Immune Cell Frequency (Mean % of total cells)		Entire Cohort (n = 22)			UPS (n = 14)		MRCL/SS (n = 5)		LMS (n = 3)		P (2-way ANOVA)
		Pre	Post	P	Pre	Post	Pre	Post	Pre	Post	
T cells	CD3+	3.7	5.8	0.073	3.5	5.1	1.8	3.5	7.5	12.9	0.009*, 0.050
Treg^	CD3+FoxP3+	10.5	5.5	0.020*	13.1	6.0	5.6	3.1	6.6	7.2	0.518, 0.229
Mac	CD68/CD163+	6.5	11.9	0.042*	8.9	12.7	2.1	7.7	2.4	14.9	0.587, 0.028*

*Statistically significant difference ($p < 0.05$). 2-way ANOVA p-values represent effect of histologic subtype and pre- versus post-neoadjuvant treatment status, respectively. ^Treg expressed as % of total CD3+ T cells. Abbreviations: Histo: histologic subtype; Treg: regulatory T cells; Mac: macrophages; UPS: undifferentiated pleomorphic sarcoma; MRCL/SS: myxoid/round cell liposarcoma/synovial sarcoma; LMS: leiomyosarcoma.

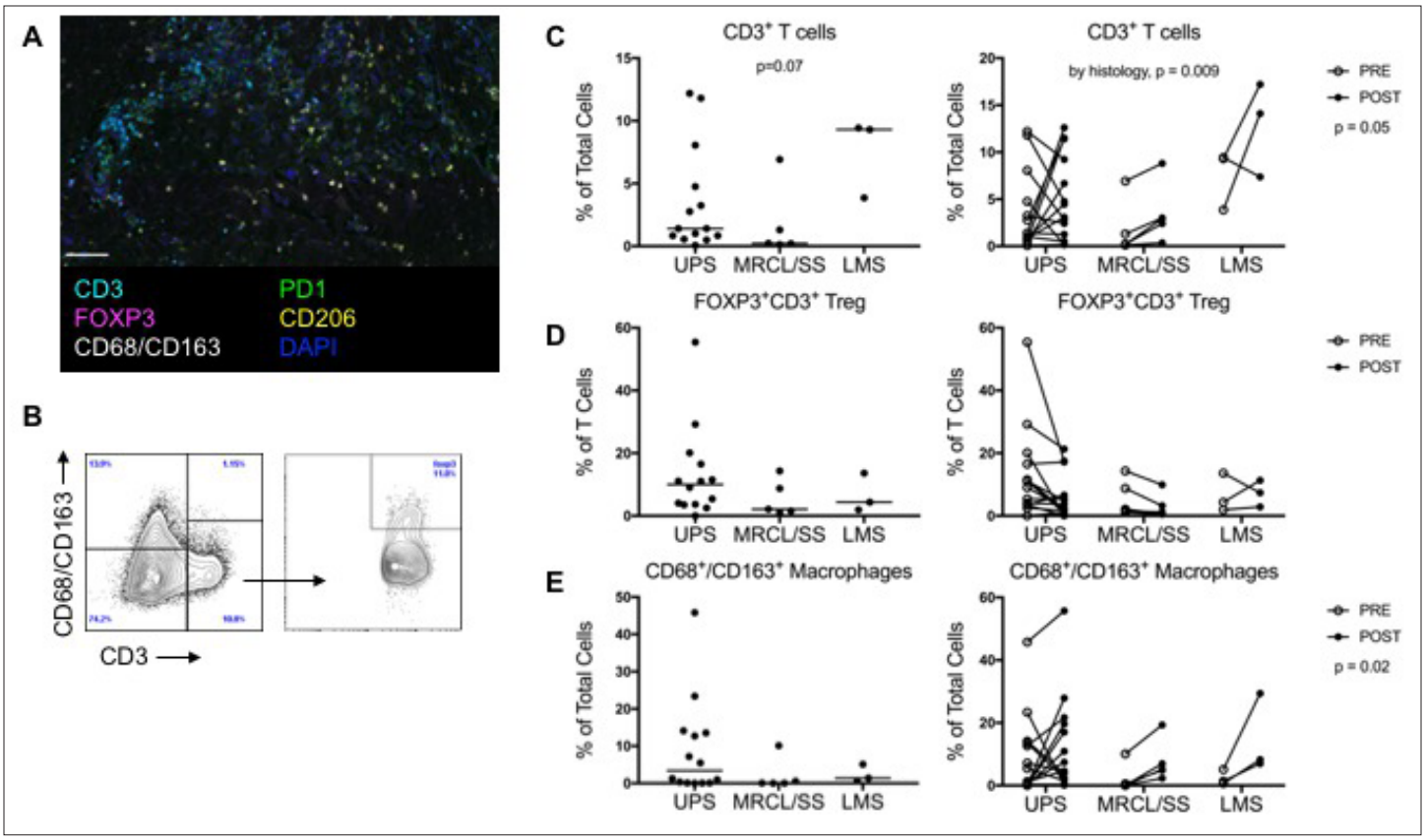

Figure 1. T cells and macrophages predominate the immune microenvironment in soft tissue sarcoma. (**A**) Representative multiplex immunohistochemistry (mIHC) of a pre-treatment UPS tumor. Scale bar, 100 mm. (**B**) Following mIHC image digitization and spectral unmixing, the fluorescence intensity of each cell marker within each cell was quantified using image cytometry, with representative gating demonstrated for CD68/CD163$^+$ macrophages, CD3$^+$ T cells, and CD3$^+$FOXP3$^+$ Treg. (**C-E**) Quantification of intratumoral immune cell frequencies by histologic subtype and pre/post-neoadjuvant treatment status (n = 14 UPS, 5 MRCL/SS, 3 LMS). Bars represent the median.

Poster 217 3015167

PD-1 BLOCKADE COMBINED WITH ONCOLYTIC HERPES HSV1716 VIROIMMUNOTHERAPY ENHANCES SURVIVAL IN AN IMMUNOGENIC MURINE OSTEOSARCOMA MODEL

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Objective: (1) To determine whether oHSV therapy enhances respond to PD-1 inhibition in immunocompetent murine models of osteosarcoma, (2) to quantify and characterize the anti-tumor T-cells infiltrating after treatment with oHSV and PD-1 inhibition individually and in combination and (3) to compare the mutanomes between two murine models of osteosarcoma.

Methods: We utilized an immunocompetent transplantable murine model using a cell line derived from a spontaneous metastatic osteosarcoma (K7M2, Balb/C background) and a transgenic mouse model with a mutant p53 (F420, C57/B6 background). We transplanted established tumor wedges subcutaneously or inoculated tumor cells ($5x10^6$ tumor cells) and monitored tumor volume by caliper measurement. Once tumors reached 200-400mm^3, we administered intratumoral injections of HSV1716 ($1x10^8$ plaque-forming units) every other day for a total of 3 injections. We then gave intraperitoneal injections of 250ug anti-PD-1 or control antibody twice weekly, up to 4 weeks, starting from the last dose of virus treatment. We monitored tumor growth via calipers twice weekly until tumors reached 2500mm^3. We quantified and characterized innate and adaptive immune cell infiltrates in tumors using flow analysis. We utilized RNAseq and PvacSeq data to compare mutanomes of the two models and determine MCH Class I binding capacity of each models neoantigens. Utilizing flow on cell lines of both models, we assessed the expression of MCH Class I.

Results: We found significantly prolonged survival with our combination therapy group compared to all other groups in the K7M2 but not the F420 model. We found that anti-PD-1 by itself had little impact on T cell recruitment while the virus infected groups had higher influx of CD8+ cells with a reduced amount of T-regulatory cells (CD4+Foxp3+CD25+). We found an increase in CD44+ effector memory cells in our virus infected groups. In our mutanome analysis, we found the 2 models had similar mutations and MHC Class I binding capacity. K7M2 exhibited a higher number of fusion genes (9) compared to none in F420. We also found that K7M2 had higher expression of its specific MCH Class I compared to F420.

Conclusion: Osteosarcoma is one of the deadliest cancers in the pediatric population with little progress in morbidity and recurrence rates since the 1980's. Oncolytic Herpes Simplex-1 virus (oHSV) is an attenuated virus that has shown encouraging results against certain solid tumors. Programmed cell death protein (PD)-1-mediated T cell suppression via engagement of its ligand, PD-L1, is also of particular interest due to recent successes in selected cancers, especially those with high genetic mutational loads. Most pediatric cancers do not have a wide variety of mutations; however, osteosarcoma has a chaotic genome, prone to genetic mutations. It has been shown through numerous other studies that PD-1 inhibition alone is not sufficient treatment to result in statistically significant tumor growth delays in osteosarcoma models and patients. The combination of PD-1 inhibition and oHSV injection prolonged survival of mice bearing K7M2 osteosarcoma xenografts. Virotherapy treatment changed the microenvironment to be more inflammatory in the K7M2 model. The lack of response of F420 in likely due to the lower expression of MCH Class I and its absence of fusion genes present. Our data support further preclinical and clinical studies.

Poster 218 3025852

DECREASED T CELL INFILTRATION IN UNDIFFERENTIATED PLEOMORPHIC SARCOMA (UPS)—MEDIATED BY WNT, TGF-β AND MEX3B—PREDICTS POOR SURVIVAL

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Objective: Undifferentiated pleomorphic sarcoma (UPS) was the most responsive soft tissue sarcoma (STS) to anti-PD1 immunotherapy in SARC-028. Still, 60% of patients with UPS did not respond to anti-PD1 therapy. T cell infiltration is a biomarker for response to anti-PD1 therapy in other malignancies. We sought to characterize T cell infiltration in UPS, define its impact on clinical outcome, and identify molecular signatures associated with poor T cell infiltration.

Methods: Using matched genomic and clinical data from The Cancer Genome Atlas (TCGA), we estimated the prevalence of tissue-infiltrating immune cells with transcriptome-based approaches: Microenvironment Cell Populations (MCP) counter and Cytolytic Activity (CYT). We compared groups using the Wilcoxon rank sum test, assessed gene correlations with Spearman's rank correlation, and performed survival analyses using the Kaplan-Meier method and the log rank test. We analyzed differential gene expression using a negative binomial distribution model (DESeq2). These data informed an exploratory analysis to assess candidate gene sets associated with immune signature using the Kyoto Encyclopedia of Genes and Genomes (KEGG), with evaluation of overlap between gene sets using hypergeometric probability.

Results: In 254 sarcomas spanning several histologies, cytotoxic T lymphocyte (CTL) infiltration was highest among UPS (n = 74), dedifferentiated liposarcoma (n = 57), and malignant peripheral nerve sheath tumors (n = 9). These MCP counter findings were validated with CYT score. Notably, mutational burden was low across histologic subtypes (mean = 81 mutations per patient) and did not correlate with CTL infiltration.

CTL score was strongly associated with improved overall and disease-free survival (OS, DFS) in UPS but not in other sarcoma subtypes (for top third vs. bottom third of CTL scores, UPS median OS 40.6 months vs. not reached, p = 0.011; median DFS 16.6 months vs. not reached, p = 0.036). Given this survival difference, we evaluated differential gene expression in patients with high vs. low CTL infiltration in UPS. To understand drivers of immunologically 'cold' UPS tumors, we identified 672 GSEA-annotated transcripts with two-fold higher expression in low-CTL samples (false discovery rate, FDR 0.05). These 672 genes were significantly enriched in 12 of 186 KEGG gene sets, including two cooperative pathways: Wnt signaling ($p = 1.5 \times 10^{-5}$) and TGF-β ($p = 4.8 \times 10^{-6}$), both of which are implicated in tumor immune evasion.

We observed a particularly strong inverse relationship between CTL infiltration and expression of *MEX3B* (rho = -0.408, p = 0.00035), which encodes an RNA-binding protein that destabilizes *HLA-A* transcripts and predicts

poor response to anti-PD1 therapy in melanoma. Across all TCGA tumors, *MEX3B* is most highly expressed in sarcoma ($p < 0.001$). Expression of *MEX3B* was strongly inversely correlated with antigen presentation in UPS, including immunoproteasome genes *PSMB8-10,* and 28 HLA class I and II genes ($p < 0.05$ for each gene).

We hypothesized that the Wnt or TGF-β pathways may regulate *MEX3B* expression. The 1956 genes differentially expressed with *MEX3B* in UPS (FDR 0.00001) were enriched for the TGF-β (14 of 86 genes, $p < 1x10^{-5}$), and Wnt (42 of 235, $p < 1x10^{-14}$) pathways, including described Wnt/β-catenin reporter *AXIN2*.

Conclusion: Poor CTL infiltration is associated with markedly worse overall survival in UPS. Genes in the Wnt and TGF-β pathways, both of which have been implicated in tumor immune privilege, were enriched in poorly infiltrated tumors. We identified *MEX3B,* a negative regulator of antigen presentation, among individual genes most correlated with poor CTL infiltration in UPS. Our findings suggest that MEX3B may be an effector of Wnt and TGF-β mediated immune exclusion in UPS through its negative impact on antigen presentation.

Poster 219 3041781

THE IMMUNE MICROENVIRONMENT IN LEIOMYOSARCOMA, DEDIFFERENTIATED LIPOSARCOMA AND UNDIFFERENTIATED PLEOMORPHIC SARCOMA

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Objective: There are limited data on the immune-tumour interaction in sarcomas. Provisional clinical trial data indicate that immune checkpoint inhibitors may be active in genomically complex sarcomas. This study aims to (i) characterise the immune microenvironment in three clinically aggressive soft tissue sarcoma subtypes associated with genomic complexity (leiomyosarcoma (LMS), dedifferentiated liposarcoma (DDLPS) and undifferentiated pleomorphic sarcoma (UPS)) and (ii) assess the association of immune factors with disease-free and overall survival.

Methods: Patients who had undergone surgical resection of treatment-naïve primary tumours at a single specialist sarcoma centre were retrospectively identified from a departmental database. Patient baseline clinicopathological variables and outcome data were collected by retrospective notes review and formalin-fixed paraffin-embedded tissue blocks were retrieved. . Areas of viable tumour were sampled from a single block per specimen for inclusion in tissue microarray (TMA) and extraction of tumour RNA. Sections from TMA were stained for a panel of immune-related markers (CD3, CD8, CD4, CD68, PD-L1). Tumour expression profiles of 21 immune-related genes were obtained using NanoString nCounter PlexSet. Multivariable Cox regression analyses were used to study the association of immune features with disease-free and overall survival. Machine learning approaches were used to identify immune response related subtypes across tumours.

Results: There were 121 LMS, 70 DDLPS and 73 UPS included in the study. The average number of tumour infiltrating T lymphocytes (TIL) was comparable across all 3 sarcoma subtypes **(Table 1).** 10-20% of tumours contained very high TIL numbers (>400 CD3+ TIL/mm^2). UPS and DDLPS had a greater degree of infiltration with CD68+ histiocytes than LMS. Tumour cell expression of PD-L1 for LMS, DDLPS and UPS are summarised in **Table 1** – fewer UPS (42%) had entirely absent tumour cell PD-L1 staining than LMS or DDLPS (55% and 53%). Higher CD68+ infiltration and PD-L1 expression was associated with higher number of TILs.

Analysis of immunohistochemical data suggested that there are subgroups of tumours that share common immune profiles across the 3 STS subtypes. However, the correlation between levels of immune factors and disease-free and overall survival was dependent upon histological subtype – for example, high levels of CD68+ infiltration were associated with significantly worse outcome in LMS, but with no significant association with outcomes in UPS or DDLPS cohorts. These observations indicate a potential deterministic interaction between subtype-specific tumour biology and immune response.

Conclusion: Presence of immune cells and immune gene expression levels were equivalent across the 3 subtypes examined. A minority of 10-20% of tumours from each subtype had high levels of immune factors, potentially representing a subset of T-cell inflamed tumours that would be potential candidates for immune checkpoint inhibition therapy. Association of immune factors with survival outcome was limited to specific subtypes. These results should inform patient selection and stratification of future trials of immunotherapies in STS. Meanwhile, further research is required to gain an understanding as to the factors that determine the immune phenotype of STS at individual and subtype level

Table 1. Overview of IHC data on T lymphocyte infiltration and tumour cell expression of PDL1

	T lymphocyte infiltration			Tumour PDL1 staining score (0-6): Intensity score: **0**: Absent **1**: Weak **2**: Moderate **3**: Strong Frequency score: **0**: <1% **1**: 1-10% **2**: >10-50% **3**: >50%			
	Cohort median (IQR) lymphocytes per mm^2			Average tumour PDL1 score			
	CD3	CD4	CD8	0	≤1	≤3	>3
				Number of cases (%)			
LMS N=121	86 (29-236)	20 (6-63)	65 (19-175)	66 (55%)	32 (26%)	17 (14%)	6 (5%)
DDLPS N=70	107 (62-210)	33 (18-61)	79 (45-134)	37 (53%)	19 (27%)	9 (13%)	5 (7%)
UPS N=73	105 (32-323)	26 (11-77)	89 (20-250)	31 (42%)	24 (33%)	13 (18%)	5 (7%)

Poster 220 3030228

KRAS/P53 MEDIATED MURINE MODEL OF RHABDOMYOSARCOMA HAS AN IMMUNE INERT MICROENVIRONMENT AND IS AN IDEAL MODEL TO TEST NOVEL IMMUNOTHERAPIES.

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Objective: Soft tissue sarcomas (STS) have not demonstrated favourable clinical responses to emerging immunotherapies such as checkpoint inhibitors. Studies in carcinomas and melanoma have demonstrated that tumours lacking T-cell infiltrates are associated with poor responses to immunotherapies. It is postulated that STS lack tumour asscoiated lymphocytes which renders these tumours insensitive to checkpoint inhibitors. Our objective was to develop a novel syngeneic mouse model of STS and characterize the immune phenotype of these tumours. Additionally, we sought to evaluate the therapeutic responses of these sarcomas to checkpoint inhibitors and a Type I interferon agonist.

Methods: K-ras mutagenesis and p53 deletion was induced using a Lenti-Cre-recombinase injection into the hindlimb of 3 week old C57BL/6 mice. Tumours were harvested and characterized using standard histopathology techniques and whole trascriptome sequencing (RNAseq). Full body necrospy and histopathology was performed to identify metastases. Flow cytometry and immunohistochemistry was used to evaluate tumour immune phenotypes. Tumours were implanted into syngeneic C57BL/6 mice and the therapeutic responses to anti-CTLA4, anti-PD1 and DMXAA (Type I interferon agonist) were performed. Tumour responses were evaluated using bioluminescent imaging and caliper measurements.

Results: Soft tissue sarcomas developed in mice within 2-3 months of Lenti-Cre injection with 90% penetrance. Histologic analyses of tumours was consistent with a high-grade myogenic sarcoma characterized by smooth muscle actin, Desmin and Myogenin D positive immunostaining. Using crossplatform normalization protocols, gene expression signatures of the mouse tumours most closely correlated with human embryonal rhabdomyosarcoma (ERMS) gene expression signatures. Collectively, gene expression signatures of this murine sarcoma correlated with all muscle-derived human sarcomas (ERMS, ARMS, Synovial sarcoma, UPS). No lung or other visceral metastases were observed in all mice who developed spontaneous tumours. Immune phenotyping demonstrated a paucity of tumour-infiltrating lymphocytes (TILs; <1% of all cells) and relative enrichment of tumour-associated macrophages (TAMs). 50% of identified TILs in these murine sarcomas expressed PD-1, yet tumours were not responsive to anti-PD1 therapy or anti-CTLA4 therapy. A single intra-tumoural (i.t.) injection of the Type I interferon agonist, DMXAA resulted in 80-90% tumour necrosis 72 hrs post-injection, decreased tumour viability up to 2 weeks post-injection and a marked infiltration of CD8+ T-cells and anitgen presenting dendritic cells and macrophages. Additional longitudinal experiments demonstrate a sustained and progressive anti-tumour effect in 83% (5/6) mice up to 6weeks following a single i.t. injection of DMXAA. All control treated mice (6/6) reached humane endpoint within 14 days.

Conclusion: We have characterized a new orthotopic and syngeneic mouse model of a myogenic soft tissue sarcoma.

Like most human STS sub-types, these tumours have an immune inert tumour microenvironment and are not sensitive to checkpoint inhibitors. This model, syngeneic to C56BL/6 mice will enable future opportunities to investigate how various branches of the immune system can be targetted or manipulated to unearth new immunotherapeutic strategies for sarcoma. Using this model we have demonstrated that a single, intra-tumoural injection of a Type I interferon agonist can result in anti-tumour effects and recruit cytotoxic lymphocytes and antigen presenting cells into the the tumour microenvironment. Future work is needed to determine if upregulation of Type I inferferon pathways can be used as a therapeutic strategy for sarcoma or as a sensitization strategy for checkpoint inhibitors.

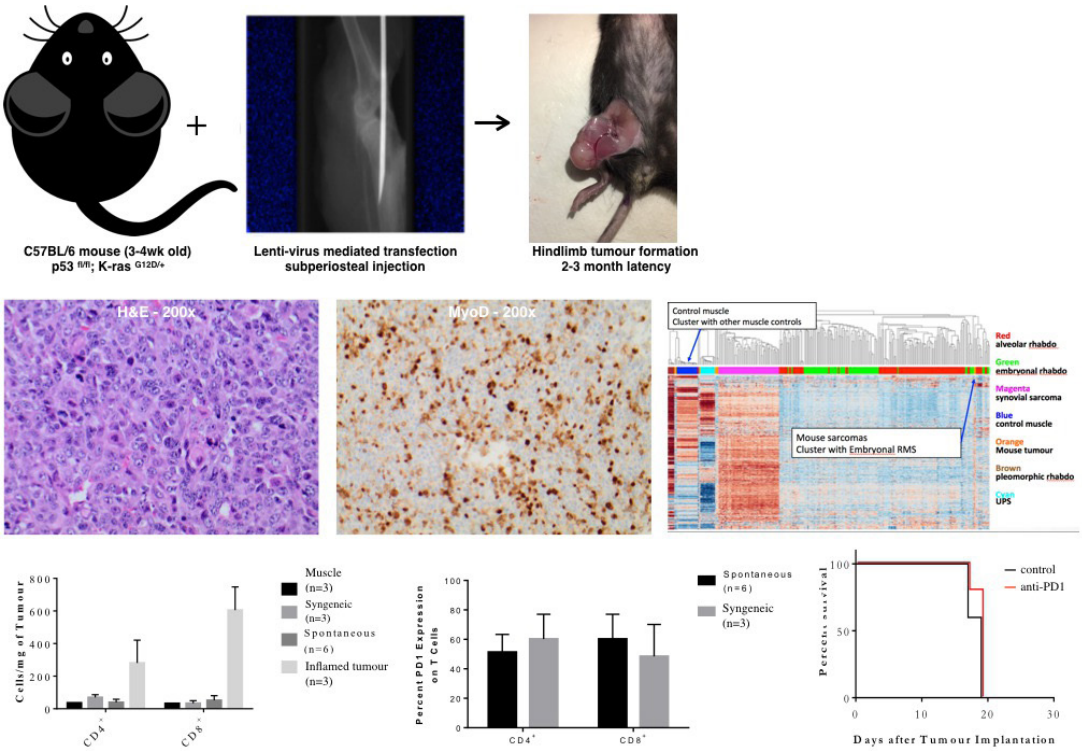

Figure 1: Sarcoma model development and characterization.

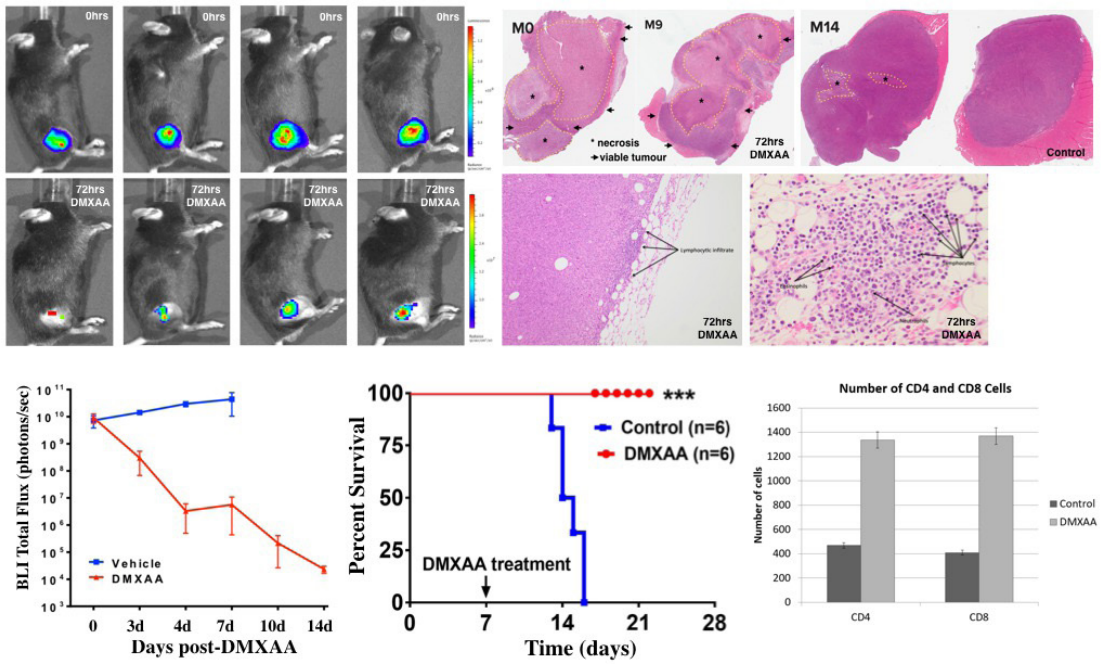

Figure 2: The immunotherapy, DMXAA induces tumour necrosis and T-cell infiltration in murine RMS tumours.

Poster 221 3042164

HOST IMMUNE RESPONSE IN UNDIFFERENTIATED PLEOMORPHIC SARCOMA - A 10-YEAR RETROSPECTIVE ANALYSIS

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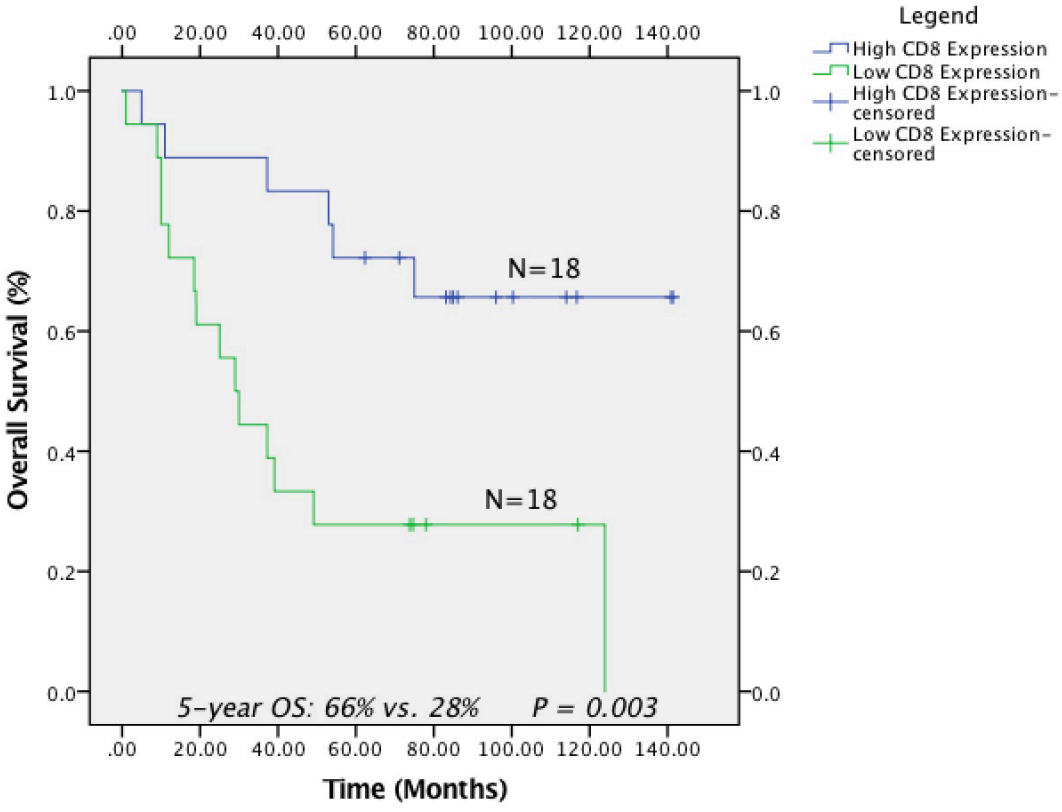
Objective: Which patient characteristics and clinicopathologic parameters correlate with improved survival in UPS patients? What is the host immune response observed in UPS tumors? Do the presence or absence of specific tumor infiltrating lymphocytes (TILs) influence disease progression or survival?

Methods: Thirty-six clinically annotated UPS patients collected over 10 years at a single institution with minimum five-year follow-up and available tumor specimens were included in this retrospective study. A univariate cox regression analysis was used to determine clinicopathologic factors associated with overall survival (OS) and disease-free survival (DFS). Using primary tumor specimens, we performed a targeted immunohistochemical analysis of the UPS microenvironment. We quantified expression of lymphocyte markers (CD8, CD20, CD68) and immune checkpoint protein (PD-L1) in all 36 UPS tumors using automated image analysis. The median percentage of positive cells for each subpopulation was used to define high expression vs. low expression. The Kaplan-Meier method was used to analyze OS and DFS; the association of specific TILs with OS and DFS was analyzed using the Log Rank Test.

Results: Factors that correlated with improved overall survival in our UPS cohort included localized disease (p=0.015), and use of intraoperative radiation therapy (IORT) or adjuvant radiation therapy (p=0.01). There was also a trend toward worse survival with tumors greater than 5 cm at diagnosis (p=0.09). Our immunohistochemical analysis revealed the presence of TILs (CD8, CD20, CD68) and expression of immune checkpoint protein (PD-L1) in UPS tumors. Patients with a greater population of CD8+ TILs had a 5-year OS of 66% compared to those with lower levels of 28% (p=0.003, Figure 1). CD8+ T-cell expression in UPS tumors inversely correlated with local recurrence (p=0.04), suggesting CD8+ T-cell mediated immune surveillance. Interestingly, we also observed an increase in metastatic events in patients whose tumors harbored low CD8 expression compared to high CD8 expression (59% vs. 41%).

Conclusion: Through our quantitative immunohistochemical (IHC) analysis of immune cell subsets in UPS tumors, we identified improved survival in patients with increased infiltration of CD8+ T-Cells. Our study demonstrates that patients with low levels of CD8+ TILs are at increased risk of local (and potentially metastatic) recurrence. These findings underscore the importance of immune mediated tumor surveillance in UPS. Our results are consistent with other non-mesenchymal tumors and provide clinical and biological rationale to further investigate STS to identify subtype specific prognostic biomarkers that can potentially influence the development of novel therapeutic strategies. Recent advancements in systemic immunotherapy further highlight the immunogenicity of UPS tumors and demonstrate the clinical impact of targeting the tumor microenvironment to improve outcomes for UPS patients.



Poster 222 3042484

TUMOR INFILTRATING LYMPHOCYTES MAY PREDICT FOR DISTANT METASTASIS IN SOFT TISSUE SARCOMAS TREATED WITH PREOPERATIVE RADIATION THERAPY

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Objective: The presence of tumor infiltrating lymphocytes (TILs) has been shown to be prognostic in malignancies such as breast, ovarian and colorectal cancer. Moreover, hypofractionated radiation therapy (RT) has been shown to improve tumor control and lead to an increased number of TILs in tumors. However, the significance of TILs in soft tissue sarcoma (STS) remains to be determined. In this study, we aim to determine if TILs are prognostic in patients undergoing pre-operative RT for STS of the extremity and chest-wall, and to evaluate if hypofractionated RT is associated with increased TILs when compared to standard fractionation.

Methods: H&E slides from resected specimens of extremity and trunk STS patients who underwent pre-operative standard fractionation at 2 Gy/fx or hypofractionation at 7 Gy/fx were reviewed by a blinded pathologist to quantify TILs. All hypofractionated patients were enrolled on an institutional clinical trial. TILs were defined as lymphocytes infiltrating in areas of viable tumor cells. TILs were quantified utilizing 40x and 10x objectives lens (Olympus BX40 microscope) at the tumor hot spots (areas of tumors with highest concentration of TILs) and expressed as a percentage; TILs%/ 40x and TILs%/ 10x. Receiver-operating curve (ROC) analysis was performed to assess the best cut-off that predicted for distant metastasis (DM) in patients undergoing pre-operative RT. Distant metastasis-free survival (DMFS) was calculated using Kaplan-Meier survival analysis. A t-test was performed to assess the difference in means between the 2 groups.

Results: 79 patients with stage I-III STS of the extremity and chest-wall were analyzed, 61 who underwent standard and 18 who underwent hypofractionated RT. Median overall age was 56. Median overall tumor size was 9.8 cm. Median dose of the standard and hypofractionated groups were 50 Gy and 35 Gy, respectively. 30% of patients developed DM in the standard fractionated group vs 11% in the hypofractionated group (p=0.07).
The median overall % TILs at 10x and 40x was 20% and 25%, respectively. The mean % TILs at 10x and 40x for the standard and hypofractionated RT was 19.68% vs 31% (p=0.06) and 26.2% vs 42.8% (p=0.03), respectively. ROC analysis revealed that % TILs (10x and 40x) ≤10 was associated with increased risk of distant metastasis (p<0.0001). Median DMFS for patients with % TILs ≤10 was 44.3 months vs >54 months for % TILs > 10% (p=0.0009).

Conclusion: In localized STS of the extremity and chest-wall, increasing %TILs was associated improved DMFS. Hypofractionated RT appears to be protective with these patients demonstrating higher % TILs and a decreased rate of developing DM. A cut-off ≤10 % TILs of was shown to be associated with poorer DMFS in this study for all patients treated with pre-operative RT. Further validation of the clinical utility of TILs in this context is warranted.

Poster 223 3042550

IMMUNE PROFILING OF INTRATUMORAL TERTIARY LYMPHOID STRUCTURES IN DEDIFFERENTIATED LIPOSARCOMA

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Objective: The immune response plays a critical role in shaping the tumor microenvironment in many cancers. Tertiary lymphoid structures (TLS) are organized aggregates of immune cells that may be sites of antigen presentation within tumors. TLS have been described in several solid tumor types and we have previously reported their presence in well differentiated / dedifferentiated (WD / DD) liposarcoma (Tseng et al., Sarcoma 2015; Tseng et al., Front Oncol 2016). We sought to further characterize TLS in this disease by analyzing patterns of gene expression.

Methods: Archived, representative H&E slides were retrieved from cases of DD liposarcoma resected at Keck Hospital of the University of Southern California (USC) and National Taiwan University Hospital (NTUH) between 2011-2016. H&E slides were thoroughly surveyed for TLS. For study cases, additional unstained slides were sectioned from corresponding FFPE blocks, RNA was extracted and then sent for multiplex gene expression analysis using the Nanostring PanCancer Immune Profiling Panel. Gene expression levels in study cases with TLS versus without TLS were tested for statistical significance using two-tailed t-tests on log-transformed normalized data. A macro scale analysis was also conducted on all 770 genes in the panel to identify biological processes represented amongst the genes, using the Gene Ontology enRIchment anaLysis and visuaLizAtion tool (GOrilla) (Eden et al., BMC Bioinformatics 2009).

Results: In total, 13 DD liposarcoma cases were studied, 9 from USC and 4 from NTUH. The presence of TLS was noted in 77% of all cases between 2 institutions. 86 genes out of the panel of 770 genes had significantly different expression levels ($p<0.05$) between cases with TLS and without TLS (Figure 1). The genes with the largest fold change are shown in Table 1. These genes are all mediators of lymphocyte activity, including chemotaxis, activation, or response to antigens. All of these immune-related genes were more highly expressed in cases with TLS versus those without TLS, except for COLEC12, a scavenger receptor expressed on myeloid cells (e.g. macrophages) which had lower relative expression. Tumor-related genes that were differentially expressed at significant levels are shown in Table 2. These genes were all found to have lower expression in cases with TLS versus those without TLS. Several of these genes have been reported to play a role in cancer stem cells. Based on the GOrilla analysis, biological processes found to be significantly different between cases with TLS versus those without TLS included immunological synapse formation, lymphocyte polarity and costimulation, regulation of calcium ion sequestration and transport, and response to prostaglandin E.

Conclusion: TLS are found in the majority of cases of DD liposarcoma and likely play a significant role in disease biology. The combined immune profiling data from 2 institutions in this study begins to elucidate the potential immune-tumor cell interactions via TLS in this disease. Further collaborative investigation of the intratumoral immune response in WD / DD liposarcoma is needed, as this may also uncover potential clinical biomarkers and therapeutic targets.

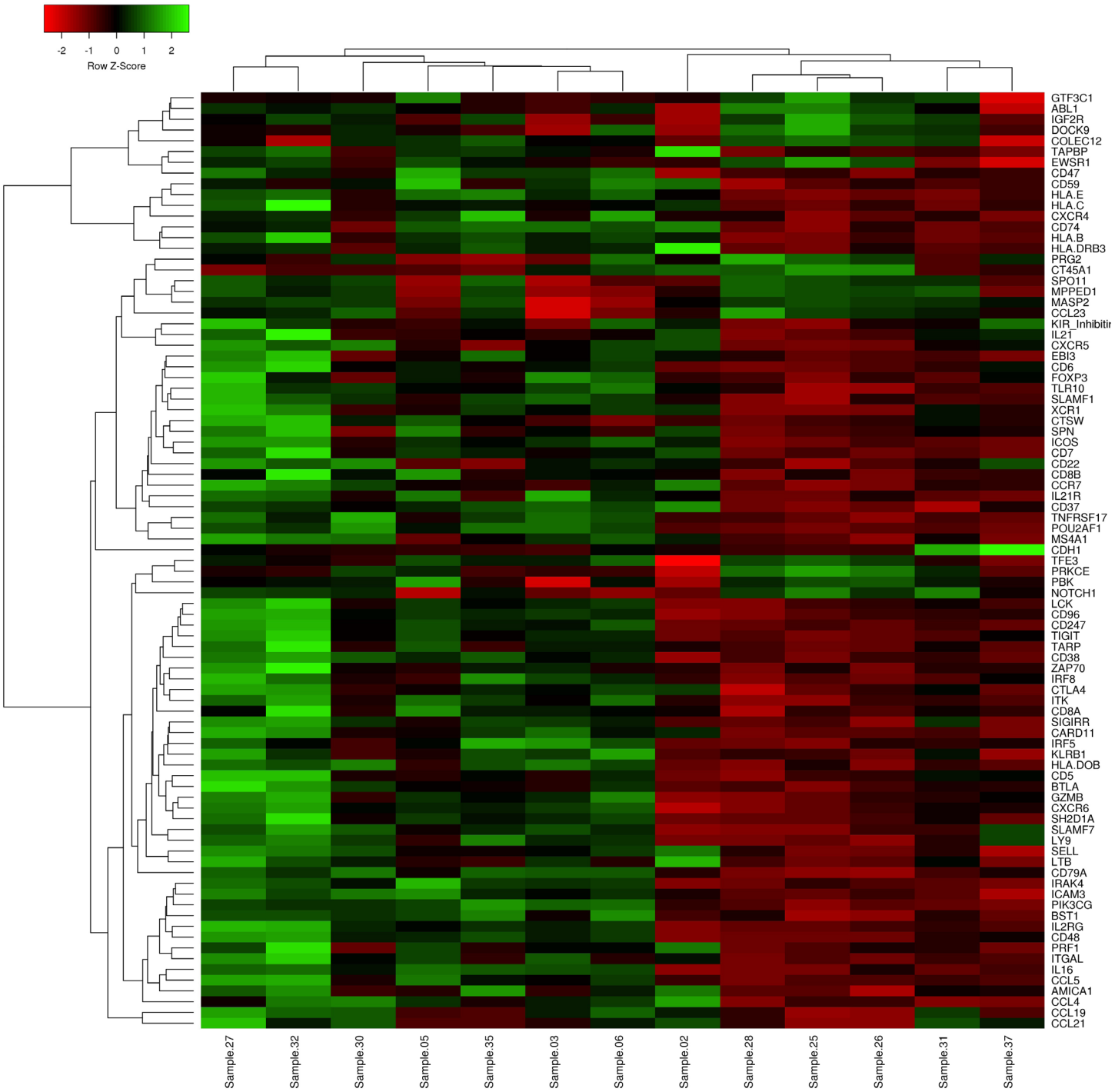
Genes with Largest Fold Change for Cases with TLS vs without TLS

Gene	Fold Change	P-Value
CCL21	16.50	0.0130
CD79A	11.73	0.0000
CCL19	7.94	0.0196
MS4A1	6.06	0.0052
TNFRSF17	5.08	0.0041
LY9	4.97	0.0002
POU2AF1	4.97	0.0010
SLAMF7	4.45	0.0051
CD8A	3.72	0.0400
COLEC12	-3.91	0.0059

Tumor-Related Genes with Significant Fold Change for Cases with TLS vs without TLS

Gene	Fold Change	P-Value
PBK	-2.46	0.0278
ABL1	-2.45	0.0022
CT45A1	-2.36	0.0005
IGF2R	-2.04	0.0226
NOTCH1	-2.00	0.0302
PRKCE	-1.97	0.0001

Figure 1. Z-scores of log-transformed normalized expression levels for 86 genes with significantly different expression levels (p



Poster 224 3042552

COMPREHENSIVE GENOMIC PROFILING IDENTIFIES A POTENTIAL IMMUNOTHERAPEUTIC OPPORTUNITY IN GASTROINTESTINAL STROMAL TUMORS

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Objective: While some patients with solid tumors, have benefited from immune checkpoint inhibitors (ICPI), the clinical utility of these inhibitors in sarcomas is still under investigation. Since tumor mutational burden (TMB), which acts as a surrogate for neoantigen burden (NAB), has become a well-established marker for ICPI responsiveness, we sought to evaluate TMB and NAB in sarcomas.

Methods: Hybrid capture-based comprehensive genomic profiling was performed on more than 5800 cases of sarcomas

using the FoundationOne® or FoundationOne®Heme platform to sequence exons and select introns of 395 or 465 genes, respectively. On the FoundationOne®Heme platform, additional fusion detection was performed using targeted RNA-seq for 265 genes. TMB, HLA typing, and neoantigen prediction was determined as previously described (Chalmers ZR, 2017, Hartmaier RJ, 2017).

Results: Immune evasion genes (*CD274*, *CD70*, *B2M*, *CD58*, and *CIITA)* are wildtype in 93.4% of sarcomas. Sarcomas have a median TMB of 2.4 mutations/mb with an interquartile range (IQR) of 3.2. The sarcomas that were most frequently TMB high (>=20 mutations/mb) were skin sarcomas, lung sarcomas, and angiosarcomas. TMB and NAB are broadly correlated across all sarcomas (ρ=0.74). Sarcomas have a median NAB of 2 with an IQR of 2 and a range of 0-118. While sarcomas are more likely to be TMB low (TMB-L; <6 mutations/mb) (p<1e-27, OR=0.22) than carcinomas, a subset of these TMB-L sarcomas still have high NAB (NAB-H; >=5 predicted neoantigens or frameshifts). In particular, GIST cases are significantly overrepresented in this category (p<0.02, OR=1.42). GIST specimens have a median TMB of 1.7 mutations/mb (IQR = 1.7), which is notably lower than the remainder of sarcomas. Despite this, GIST specimens had a similar NAB to all other sarcomas (median = 2; IQR = 2). 12% of GIST cases fall into the TMB-L/NAB-H category, whereas 8.7% of all other sarcomas are TMB-L/NAB-H. Fitting this, TMB and NAB are less correlated in GIST (ρ=0.28). Short variants (SVs) in GIST cases are more likely to generate a neoantigen relative to SVs in all other sarcomas (p<3.5e-9). Moreover, predicted neoantigens in GIST are more likely to stem from SVs that were previously described to be oncogenic (p < 2.2e-16). SVs in KIT and PDGFRA are particularly neoantigenic (p<1.2e-25, p<4.2e-4, respectively), each with 43.7% and 38% of variants being predicted to generate a neoantigen, respectively. Lastly, 92% of neoantigenic KIT SVs have been previously characterized as oncogenic.

Conclusion: There is an overall strong correlation between TMB and NAB in sarcomas, consistent with linkage of TMB to clinical benefit from ICPI. However, the TMB-L/NAB-H GIST population suggests that the addition of NAB may expand our ability to identify ICPI responders in this disease. In GIST, we propose that the low correlation between TMB and NAB is linked to oncogenic alterations KIT alterations, which are highly neoantigenic. In tandem, predicted neoantigens in GIST are more often found in oncogenic drivers. Taken together, these results provide evidence that NAB can highlight sarcoma types that are disproportionately driven by neoantigenic alterations, since NAB encompasses alterations regardless of driver status. These data, alongside our observation that GIST lack alterations in immune evasion genes, also support ICPI as a novel avenue to target GIST, particularly in KIT-altered, TKI-resistant cases. Finally, our data enhances the rationale behind ongoing trials investigating ICPI in GIST and suggests that supplementing these trials with biomarker analyses, such as TMB and NAB, may be warranted to stratify patients.

Poster 225 3042554

INTERLEUKIN-13 IN THE SARCOMA MICROENVIRONMENT PROMOTES EXPRESSION OF THE INTERLEUKIN-13 RECEPTOR ALPHA-2

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Objective: The T helper type 2 (Th2) inflammatory response has been implicated in promoting the progression of a variety of solid tumors. Interleukin-13 (IL-13) is one of the primary Th2 cytokines, and binds to either the IL-13 receptor alpha-1 (IL-13Rα1) or IL-13 receptor alpha-2 (IL-13Rα2) on the cell surface. The IL-13 receptors are upregulated on a variety of solid tumors, including soft tissue sarcomas. Interleukin-13 receptor alpha-2, in particular, has been implicated in promoting tumor cell invasion and distant metastasis. Furthermore, novel therapeutic strategies such as toxin-conjugated antibodies and chimeric antigen receptor (CAR) T-cells against IL-13Rα2 are currently in development to capitalize on the specificity of tumor cell IL-13Rα2 expression. The objective of the current study is to explore the expression patterns and regulation of IL-13Rα2 in a variety of murine and human sarcomas.

Methods: Multiple murine soft tissue sarcoma cell lines, including two from murine models of undifferentiated pleomorphic sarcoma (UPS) expressing mutant K-ras and null for p53 (KP) or mutant K-ras and with INK4a/ARF deletion (KIA), as well as a carcinogen induced (methylcholanthrene) sarcoma cell line (B6PRG), and a cell line from a murine model of synovial sarcoma (Rosa-SSM2 $Myf5^{Cre}$) were used to investigate the effect of IL-13 treatment on IL-13Rα2 expression. KP, KIA, B6PRG, and Synovial sarcoma cell lines as well as human liposarcoma and fibrosarcoma cell lines were treated with either IL-13 or control for 48 hours, followed by RNA extraction, cDNA generation, and quantitative real time polymerase chain reaction (qRT-PCR). Cell lines stably expressing shRNAs against IL-13Rα1 were generated to investigate the role of IL-13Rα1 in regulating the expression of IL-13Rα2. Cell lines expressing shRNAs targeting IL-13Rα1 or non-targeting controls were treated with IL-13 or control and IL-13Rα2 expression was quantified by qRT-PCR. Fluorescence-activated cell sorting (FACS) was used to sort CD45+ leukocytes and CD45- tumor and stromal cells from murine flank tumors to investigate the

expression of IL-13 and IL-13 receptor subunits in leukocytes and tumor cells by qRT-PCR.

Results: Both murine and human soft tissue sarcoma cell lines demonstrated a significant increase in IL-13Rα2 mRNA expression after treatment with IL-13 compared to control ($p<0.05$). IL-13 treatment of cell lines expressing shRNAs targeting the IL-13Rα1 showed a significant decrease in induction of IL-13Rα2 compared to cell lines expressing a non-targeting control hairpin construct ($p<0.05$). qRT-PCR analysis of sorted murine tumors demonstrated that IL-13 is produced almost exclusively by CD45+ leukocytes in the tumor microenvironment ($p<0.001$). There is a 1.5 fold increase in IL-13Rα1 expression in CD45+ leukocytes compared to control cells ($p<0.05$), while IL-13Rα2 is almost exclusively expressed in CD45- tumor and stromal cells ($p<0.0001$).

Conclusion: Interleukin-13 upregulates IL-13Rα2 in murine and human sarcoma cells. IL-13 produced by leukocytes in the tumor microenvironment may be an important regulator of IL-13Rα2 *in vivo*. Given that expression of IL-13Rα2 is largely restricted to tumor cells, it is a promising target for the treatment of soft tissue sarcomas. Future studies will aim to identify mechanisms regulating the expression of IL-13Rα2 as well as the downstream effects of IL-13Rα2 activation.

Poster 226 3042690

IMMUNOMODULATORY ROLE OF PAZOPANIB IN ADVANCED SOFT-TISSUE SARCOMAS

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Objective: Pazopanib is a multi-tyrosine kinase inhibitor approved for the treatment of advanced non-adipocytic soft-tissue sarcoma (STS). Pazopanib efficacy in STS is limited, due to lack of predictive biomarkers, whereas the underlying mechanisms related to pazopanib activity are slightly studied in-depth. Interestingly, changes in cytokines were correlated with activity of pazopanib in renal and non-small cell lung cancer (NSCLC), suggesting a potential role of Pazopanib in immunomodulation. Furthermore, the pivotal trial of pazopanib in STS did not detected any significant correlation between angiogenic factors and pazopanib activity. Altogether, we hypothesize that pazopanib activity might be mediated by immunogenic factors. We have explored genes involved in immunomodulation in paired tumor samples of pazopanib-treated patients, as a discovery phase of research.

Methods: Eleven patients diagnosed with STS that were treated with pazopanib, at any line of advanced disease, and with available paired formalin-fixed paraffin-embedded (FFPE) samples from the diagnostic time and immediately after pazopanib treatment were included in the study. Clinical characteristics and outcome were collected. Gene expression profiling was performed with HTG EdgeSeq technology (HTG Molecular Diagnostics, Tucson, AZ, USA) using the Immuno-Oncology (IO) HTG Assay panel. For HTG IO data processing, one demultiplexed FASTQ file per sample was retrieved from NGS sequencing. Validation by immunohistochemistry (IHC) was tested on FFPE paired samples using CD68 (790-2931; Ventana, Roche, Basel, Switzerland), PAI-1 (C-9, sc-5297; Santa Cruz Biotechnology, Inc.; Dallas, TX, USA) and C1q (ab71089; Abcam, Cambridge, UK). All samples were collected with the written consent signed by the patients.

Results: This exploratory study included 6 males and 5 females with a median age at diagnosis of 41 years (range: 21-65). The median follow-up of the series was 73 months and a total of 7 events of metastases were registered. STS subtypes were the following: solitary fibrous tumor (n=3), synovial sarcoma (n=3), leiomyosarcoma (n=2), liposarcoma (n=2) and pleomorphic sarcoma (n=1). Primary tumours median size was 10.15 cm (ranging from 4 to 30 cm) and primary tumour locations were: extremities (n=3), retroperitoneum (n=2), trunk wall (n=2), eye orbit (n=1), superior maxilla (n=1) and uterus (n=1). HTG IO assay was planned with 11 paired tumor samples; however, 3 tumor blocks at diagnosis did not have enough tissue for gene expression profiling. Bioinformatics' analyses of HTG IO data, determined that 38 genes were significantly and differently expressed between diagnostic and post-pazopanib tumor samples. Of these 38 genes, only 4 had a False discovery rate (FDR) adjusted p-value < 0.05: *CD68* (logFC=-1.51; FDR=0.007); *SERPINE1* (logFC=-2.07; FDR=0.016); *C1QA* (logFC=-1.56; FDR=0.027) and *CXCL8* (logFC=-1.19; FDR=0.044). All the genes were overexpressed after pazopanib treatment, comparing to the diagnostic time. The differential expression of *CD68* and *C1QA* was successfully validated by IHC, in paired samples.

Conclusion: *C1QA* and *CD68* expression levels seem to be consistently modulated by pazopanib. Further studies are

necessary to understand the mechanisms underlying *CD68* or *C1QA* increase after pazopanib treatment, as well as to validate their prognostic and/or predictive value in larger cohorts of STS cases. Of note, these genes have a direct role in macrophages differentiation, polarization and function that deserves to be explored.

Poster 227 3042754

SOX2/OCT4-HIGH SUBGROUP OF RELAPSED AND METASTATIC OSTEOSARCOMA HAS HIGH PD-L1

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Objective: Despite the high levels of point mutations, rearrangements, and other genomic instability events, immune checkpoint inhibitors have shown limited clinical activity in osteosarcoma (OS). SOX2 has been shown to be a contributor to OS development and proliferation.[1] In hepatocellular carcinoma cells, SOX2 binds to a motif within the PD-L1 promoter in order to enhance expression.[2] Thus, SOX2 expression in OS may contribute to low immunogenicity of OS patients through PD-L1. We completed in-depth genomic and immune profiling in parallel for a cohort 48 patients with primary, relapsed and metastatic high-grade osteosarcoma to identify strategies to improve immunogenicity.

Methods: Sequencing of the whole genome (average = 75X), RNA, and T-cell, with reverse phase protein array (RPPA) and immunohistochemistry of immune markers were used to characterize the genomic associations, composition and activation of the immune infiltrate in a clinically annotated set of primary, relapsed, and metastatic OS tumor specimens with matched normal tissue.

Results: Overall, low T-cell productive clonality (average = 0.09) was present in all samples despite some having higher immune infiltrate. Unsupervised hierarchical clustering of RPPA results revealed two subgroups (SG1 and SG2) that were not different in tumor purity, mutation, copy number, and rearrangement burdens. SG1 (N = 9) that included largely lung metastases (6/9) and ultra-young pediatric patients (age <12) was enriched in muscle-like expression patterns as compared to SG2. SG2 (N = 13) (mixture of primary, relapse, and metastatic specimens) had higher levels of SOX2 ($P < 0.0001$), OCT4 ($P < 0.001$), RAS-MAPK activation ($P < 0.05$), and PD-L1 levels ($P < 0.001$), with lower immune infiltrate and lower T-cell activation markers.

Conclusion: Multiple pathways exist to inhibit immune targeting of osteosarcoma, possibly based on the differentiation state of tumor cells. Concurrent high levels of stem cell markers SOX2/OCT4, RAS-MAPK activation and PD-L1 may identify a subset of osteosarcomas in need of T-cell activation prior to anti-PD-L1 immunotherapy regardless of tumor specimen type.

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Poster 228 3042756

INDUCTION OF ANTI-TUMOR IMMUNITY AND EFFECTS ON SURVIVAL OF NEOADJUVANT ONCOLYTIC VIROTHERAPY IN DOGS WITH OSTEOSARCOMA: AN UPDATE OF THE VIGOR CLINICAL TRIAL

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Objective: Oncolytic viruses, such as vesicular stomatitis virus (VSV), selectively replicate in and destroy tumor cells, exposing tumor antigens and activating an anti-tumor immune response. The aim of this study is to determine the anti-tumor immune response induced by oncolytic VSV in canine osteosarcoma.

Methods: Dogs with osteosarcoma are randomized to receive neoadjuvant oncolytic VSV or placebo followed by amputation and carboplatin chemotherapy. Pre- and post-treatment tumor biopsies and serial peripheral blood mononuclear cells are obtained to assess anti-tumor immunity by histopathology, RNA and DNA sequencing, and lymphocyte effector functions.

Results: Twenty-four dogs have been enrolled, of 30 dogs planned. The VSV safety profile is excellent, with mild, transient changes in body temperature and evidence of acute cytokine responses. Preliminary analyses show survival outcomes exceed the expectation for standard-of-care alone. Focal tumor necrosis that is potentially treatment-related has been observed. Assessment of naïve and treatment-associated gene cluster expression summary scores from RNA sequencing is ongoing, as is massive parallel sequencing of lymphocyte antigen receptors to describe clonal expansion and attrition.

Conclusion: Neoadjuvant VSV treatment is well-tolerated and shows preliminary evidence of biological activity and clinical efficacy. Updated results describing anti-tumor immunity that is attributable to oncolytic VSV, and its effects on patient outcomes will be presented.

Poster 229 3042851

RESPONSE TO SUBSEQUENT THERAPY IN NY-ESO-1 POSITIVE SOFT TISSUE SARCOMA PATIENTS TREATED WITH CMB305 THERAPY

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Objective: CMB305 is an active immunotherapy regimen designed to generate and expand anti-NY-ESO-1 T cells. It consists of LV305, a dendritic cell targeting lentiviral vector encoding NY-ESO-1, and a boost with G305, an NY-ESO-1 recombinant protein plus GLA-SE, a TLR-4 agonist. This first-in-human study of CMB305 examined safety, immunogenicity, and efficacy in patients (pts) with NY-ESO-1 positive (+) solid tumors. Previous results reported at ASCO 2017 demonstrated induction of anti-NY-ESO-1 T cells in soft tissue sarcoma (STS) pts with 12 months overall survival rate 83%. These STS pts have been followed for long term survival and evidence of clinical benefit from subsequent therapy in pts with anti-NY-ESO-1 immune induction with CMB305.

Methods: Adults with previously treated NY-ESO-1+ STS were enrolled in a Phase 1b study. The CMB305 regimen included 4 intradermal injections of LV305, alternating with 3 intramuscular G305 injections for 3 months, then bimonthly G305 injections up to 1 yr. A review of immune response (IR) data to determine potential impact on tumor response to subsequent therapy after progression on CMB305 was performed.

Results: As of 01June2018, 45 STS pts with recurrent locally advanced/metastatic STS were evaluable for tumor efficacy on subsequent therapy after CMB305 discontinuation. An induction of IR while on CMB305 therapy was evaluated in the majority of pts: 21/34 (61.7%) developed NY-ESO-1 specific T antibodies and 13/29 (44.8%) anti-NY-ESO-1 T cells. Partial responses were seen on subsequent therapy in 4 pts (doxorubicin n=1, ifosfamide n=1, radiation n=1, and trabectedin n=1) with 3 of these pts demonstrating induction of anti-NY-ESO-1 IR prior to progression on CMB305 therapy.

Conclusion: CMB305 is safe, well tolerated, and demonstrates a survival rate that is favorable when compared with approved agents for recurrent STS. Treatment after progression on CMB305 resulted in 4 STS pts responding to subsequent therapy with evidence of anti-NY-ESO-1 IR induction on CMB305 therapy in 3 pts. These data warrant further post progression monitoring for responses with CMB305 immunotherapy. A randomized study of CMB305 in the maintenance setting is ongoing.

Poster 230 3042145

IMMUNE RESPONSE, SAFETY, AND OVERALL SURVIVAL OF NY-ESO-1+ SOFT TISSUE SARCOMA PATIENTS TREATED WITH CMB305 THERAPY

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Objective: CMB305 is an active immunotherapy regimen designed to generate and expand anti-NY-ESO-1 T and B cells. It consists of priming with a dendritic cell-targeting lentiviral vector encoding NY-ESO-1, and a boost with NY-ESO-1 recombinant protein plus TLR-4 agonist. This first-in-human study of CMB305 examined safety, immune response (IR), and efficacy in pts with NY-ESO-1 positive (+) solid tumors. At ASCO2017, median overall survival (OS) for soft tissue sarcoma (STS) was not reached (12 mos OS rate 83%).

Methods: Adults with previously treated NY-ESO-1+ solid tumors were enrolled in a 3+3 dose-escalation with an expansion phase 1b study. The CMB305 regimen included 4 intradermal injections of the prime, alternating with 3 intramuscular boost injections over 3 months, then bimonthly boost injections up to 1 yr. An updated STS survival analysis was performed.

Results: As of 06 April 2018, 25 pts with STS (15 synovial (SS), 8 myxoid/round cell liposarcoma (MRCL), 2 other) were evaluable for safety; 24 pts were evaluable for IR and efficacy. All pts received prior therapy for advanced disease, 67% >=2 prior chemo regimens. No dose limiting toxicities were observed. Most treatment related adverse events were Grade 1 or 2; one Grade 3 (prostatic pain); no grade 4 or 5 events. Best tumor response was stable disease in 8/15 (53%) SS pts and 6/8 (75%) MRCL pts with evidence of tumor growth arrest. The median progression free survival (PFS) was 3.9 mos (2.1, 7.5) for STS and 3.7 mos (2.1, 7.8) for SS. Median OS was 23.7 mos (15.5, NR) for STS and 29.2 mos (12.2, NR) for SS. Presence of anti-NY ESO 1 antibodies (Ab) at baseline (25.0% pts) was associated with longer survival. Anti-NY-ESO-1 specific T cells and Ab developed in 46% and 67% STS pts, respectively. Pts with baseline and induced anti-NY-ESO-1 IR (T-cells and/or antibodies) had a trend to improved clinical outcomes. T cell receptor sequencing indicated increased clonality and antigen spreading was observed.

Conclusion: CMB305 is well tolerated, broadly immunogenic, and impacts patient survival favorably when compared with approved agents for recurrent STS. These results support a randomized phase 3 trial evaluating CMB305 in the maintenance setting after 1st line therapy in SS patients.

Poster 231 3034622

MACROPHAGES DOMINATE THE IMMUNE LANDSCAPE ACROSS MOST SARCOMA SUBTYPES

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Objective: As early trials for single agent immune checkpoint inhibitors in sarcomas deliver mixed results, efforts to improve outcomes look to combinatorial strategies with novel immunotherapeutics, including some that target macrophages. However, lacking a strong systematic understanding of the immune microenvironment of sarcomas, these trials largely repurpose protocols tested in other cancers. To enhance our understanding of the sarcoma immune landscape, this study aims to quantify and characterize tumor-associated macrophage infiltration across sarcoma subtypes, to complement our previously presented data on sarcoma lymphocyte infiltrates.

Methods: We surveyed CD68 and CD163 expression by immunohistochemistry in tissue microarrays of 1360 sarcoma specimens (spanning 23 subtypes) and 245 benign bone and soft tissue tumor specimens. Markers were scored by the number of positive-staining macrophages per mm^2 of tumor tissue. Subgroups were compared by a Kruskal-Wallis 1-way ANOVA test and a related-samples Wilcoxon signed rank test. Outcomes analysis was performed by Log-rank (Mantel-Cox) survival analysis.

Results: Pleomorphic sarcomas demonstrated the greatest numbers of CD68+ and CD163+ macrophages, particularly undifferentiated pleomorphic sarcoma (median CD68=481/mm^2, CD163=510/mm^2, n=84) and dedifferentiated liposarcoma (median CD68=356/mm^2, CD163=490/mm^2, n=81). As a group, pleomorphic sarcomas had significantly higher ($p<0.001$) macrophage counts (median CD68=148/mm^2, CD163=182/mm^2) than translocation-associated sarcomas (median CD68=39/mm^2, CD163=63/mm^2) or benign mesenchymal tumors (median CD68=30/mm^2, CD163=52/mm^2). Across nearly all sarcoma subtypes investigated, macrophage infiltrates outnumber tumor-infiltrating lymphocytes ($p<0.0001$). This macrophage predominance is particularly evident in undifferentiated pleomorphic sarcoma, myxofibrosarcoma, leiomyosarcoma, and angiosarcoma.

Using the ratio of CD163 to CD68 to assess M2- vs M1-polarized macrophages, we observed that sarcomas as a group tend to have a higher proportion of CD163+ (M2) macrophages, particularly synovial sarcoma (median CD163/CD68=1.8, n=144), myxoid liposarcoma (median CD163/CD68=3.0, n=41), and alveolar soft part sarcoma (median CD163/CD68=6.2, n=8). The highest relative M1 macrophage infiltration was observed in embryonal rhabdomyosarcoma (median CD163/CD68=0.4, n=12) and low-grade fibromyxoid sarcoma (median CD163/CD68=0.3, n=11).

For osteosarcoma, progression-free survival (PFS) was enhanced in cases high in CD68 (above median score of 95/mm^2; HR 5.6, p=0.018) or CD163 macrophages (above median score of 130/mm^2; HR 5.3, p=0.021), increasing median PFS from 13.4mos to 17.2mos and from 11.7mos to 17.2mos, respectively. Similarly, in undifferentiated pleomorphic sarcoma, progression-free survival was enhanced in cases high in CD163 macrophages (above median score of 508/mm; HR 3.5, p=0.05), increasing median PFS from 8.7mos to 13.5mos. No significant associations with overall survival were observed.

Conclusion: Tumor-associated macrophages outnumber tumor-infiltrating lymphocytes in nearly every sarcoma subtype and tend to be biased toward M2 (immunosuppressive) polarization, both to a greater extent than is observed in lung cancer or melanoma. Macrophage-focused immunomodulatory agents, such as CD47 or IDO-1 inhibitors, may be particularly worthwhile to pursue in sarcomas, alone or in combination with lymphocyte-focused agents.

Poster 232 3034818

SOLUBLE PD-L1 IN PATIENTS WITH SOFT TISSUE TUMORS

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Objective: PD-L1 (B7-H1 or CD274), a 40-kDa transmembrane glycoprotein, is known as a primary ligand of PD-1. The interaction of PD-L1 and PD-1 can induce T cell immunosuppression, leading to evasion of the host immune response and tumor aggravation. Some studies reported that high PD-L1 expression in tumor tissues was related to a poor prognosis in various malignant tumors including soft tissue sarcoma. The soluble form of PD-L1 (sPD-L1) in blood has also attracted much attention. High sPD-L1 is related to a poor prognosis in various cancers. Although membrane type of PD-L1 expression in tumor tissues has been studied, the role of circulating sPD-L1 have not been fully elucidated. The purpose of the present retrospective study was to analyze serum sPD-L1 levels in soft tissue tumor patients.

Methods: A total of 139 patients with primary soft tissue tumors from 2009–2016 were enrolled in this study. The histopathological diagnosis and histological grade were verified by independent pathologists. The serum samples were obtained from all patients before biopsy or treatment and stored at -80°C. sPD-L1 levels were measured quantitatively using a commercially available sandwich enzyme-linked immunosorbent assay (Human PD-L1 ELISA Kit, Abcam, Cambridge, MA).

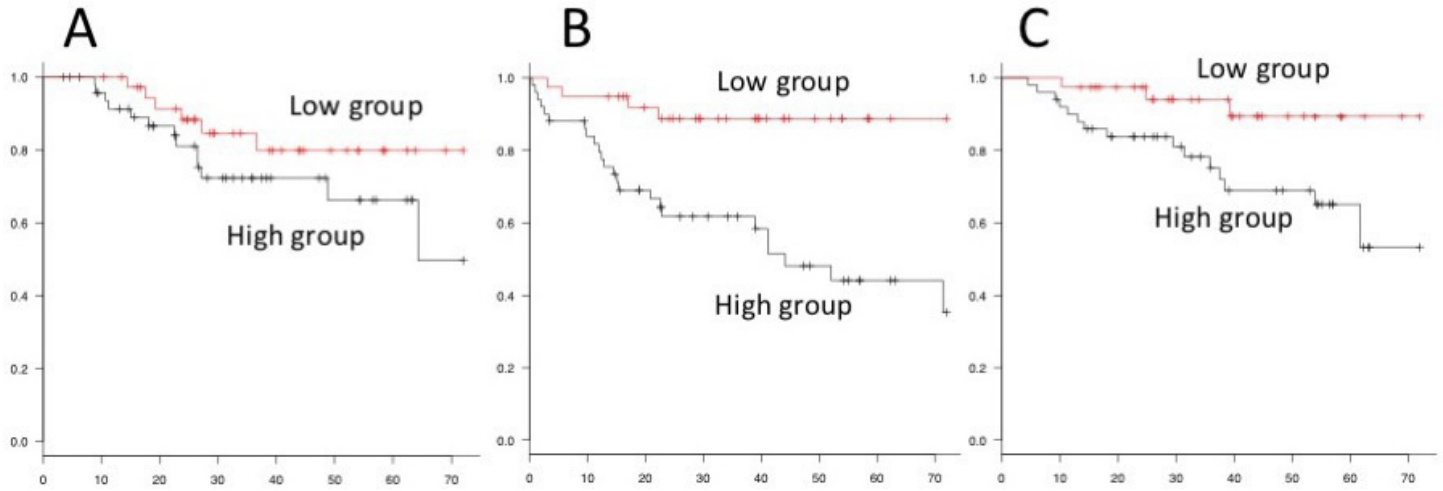
Results: Patients over 60 years old, those with STS, and those with history of other malignant tumors had higher sPD-L1 levels, but the differences were not significant. The sPD-L1 concentrations in STS patients were higher in those over 60 years old, with tumors over 10 cm, or with histopathological high-grade tumor, but the differences were not significant. According to the UICC classification, patients with higher stages showed higher sPD-L1 concentrations than those with lower stages, but the difference was not significant. The recurrence showed no significant difference. The metastasis group (28patients) and the died of disease (DOD) group (19patients) had significantly higher sPD-L1 concentrations than the no metastasis group and the no DOD group, respectively. From ROC analysis, using an sPD-L1 threshold of 44.26 pg/ml, the

sensitivity and specificity for identifying metastasis were 85.7% and 56.7% with AUC 0.696. A cut-off value of 44.26 pg/ml was used to divide the groups into low (≤44.26 pg/ml) and high (>44.26 pg/ml) sPD-L1 groups. Recurrence free survival showed no significant difference (5 years: low 79.9%, high 66.3%, P=0.174) (Figure 1A). The high group had significantly lower MFS (metastasis-free survival) (5 years: low 88.7%, high 44.1%, p=0.00477) (Figure 1B). For OS (overall survival), the high group had a significantly worse prognosis (5 years: low 89.3%, high 64.1%, P=0.00657) (Figure 1C). Furthermore, to adjust for the imbalance in prognostic factors among patients, Cox proportional hazard analysis was used. For MFS, only the high group showed significant differences on both univariate and multivariate analyses. For OS, the high group, in addition to age, showed significant differences on univariate and multivariate analyses (Table).

Conclusion: The reported source of sPD-L1 is proteolytic cleavage of membrane PD-L1 and spliced variants that lack the transmembrane domain. sPD-L1 was able to be detected by PD-1-Ig fusion protein for capturing sPD-L1. Spliced variants of sPD-L1 show inhibitory functions on T-cell activation and proliferation. Since sPD-L1 can bind to PD-1 and affect T cell biological activity, circulating sPD-L1 has the potential to induce systemic immune suppression. In this study, sPD-L1 had a strong relationship with metastasis and DOD in STS patients. Once the environmental combination of high sPD-L1 and malignancy occurred, it led to poorer MFS and OS in the high-sPD-L1 group than in the low-sPD-L1 group. The present study showed that sPD-L1 concentrations could predict future metastasis and prognosis; thus, sPD-L1 may have a potential as a biomarker for using checkpoint inhibitors.

Multivariate COX proportional analysis

	MFS		OS	
	HR	p-value	HR	p-value
Male	0.78	0.487	0.89	0.7934
Age	1.02	0.0602	1.05	0.0086
Size	0.96	0.1081	0.99	0.963
Superficial	0.98	0.9686	0.80	0.778
Trunk	0.97	0.9411	1.63	0.3089
sPD-L1>44.2	3.51	0.0014	5.77	0.0069



Poster 233 3036245

PROGNOSTIC ROLE OF NEUTROPHIL-TO-LYMPHOCYTE RATIO (NLR) IN PATIENTS WITH SARCOMA TREATED WITH IMMUNOTHERAPY

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Objective: The pro-tumoral effect of neutrophils in chronic inflammation and carcinogenesis is well reported in the literature[1]. Elevated NLR at baseline has been associated with worse clinical outcomes in various solid tumors treated with immunotherapy. In addition, early decline in NLR has been associated with improved outcomes in patients treated with checkpoint inhibitors[2]. We investigated its role in sarcoma patients treated with checkpoint inhibitors.

Methods: We retrospectively evaluated 43 patients from Sylvester Comprehensive Cancer center who were treated with

immunotherapy in the context of clinical trials (NCT02636725, NCT02694822) or off label. NLR was calculated prior to treatment as well as after three weeks of therapy. Cox regression analysis and log-rank tests were performed to evaluate the correlation between NLR below and above 4.1, prior to therapy and three weeks after, with progression free survival (PFS) and overall survival (OS).

Results: Median follow-up was 11.6 months. Median age was 47.7 years old (range 15-80), median number of prior therapies was 2 (range 0-7), and median number of immunotherapy doses was 8 (range 2-33). There were 11 patients with alveolar soft part sarcoma (ASPS), 7 patients with pleomorphic fibroblastic sarcoma, 5 patients with dedifferentiated liposarcoma (DDLPS) and 20 with other sarcoma subtypes. Treatments included pembrolizumab + axitinib (n=31), pembrolizumab alone (n=10), nivolumab alone (n=1), and anti-CTLA4 antibody alone (n=1). The median OS was 13 months, not reached for the ASPS, 10 months for pleomorphic fibroblastic sarcoma, and 11 months for DDLPS, respectively. The overall mPFS was 5months, 22 months for ASPS, 8 months for pleomorphic fibroblastic sarcoma, and 2 months for DDLPS. Pretreatment NLR<=4.1 was correlated with better PFS (p=0.035) and there was a trend towards better OS without statistical significance (p=0.206). The NLR three weeks after treatment, as well as the difference between NLR at baseline and right before the second treatment was not associated with neither OS nor PFS. However, NLR<=4.1 at progression time was strongly associated with improved OS (HR 3.09, 95%CI 1.265-7.585, p=0.013) and PFS (p=0.026, HR 2.3, 95%CI 1.111-5.181).

Conclusion: Limited number of patients from our institution with various types of sarcomas treated with immunotherapy, showed consistent results as reported in different cancers. Persistently low NLR showed favorable outcomes. High baseline or increase of NLR may serve as marker for impending resistance, hence, limited response to checkpoint inhibition and warrants further investigation.

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Poster 234 3041760

DISULFIRAM INDUCES IMMUNOGENIC CELL DEATH AND ENHANCES ANTI-PD-1-MEDIATED TUMOR SUPPRESSION IN OSTEOSARCOMA

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Objective: Osteosarcoma (OS) is the most prevalent bone malignancy in childhood and adolescence with highly aggressive and early systemic metastases. New therapeutic approaches are urgently needed. Therapeutics targeting the immune system have become a major treatment modality in cancer. Monoclonal antibodies targeting immune checkpoints, such as programmed cell death-1 (PD-1) and programmed cell death ligand-1 (PD-L1), has demonstrated remarkable success in the clinic for the treatment of cancer; however, a majority of tumors are resistant to anti-PD-1 monotherapy. Recent studies found that immunogenic cell death (ICD) improves T cell responses against different tumors, thus indicating that ICD may further augment antitumor immunity elicited by anti-PD-1.

Methods: The effects of Disulfiram (also known by the trade name Antabuse) were evaluated on human osteosarcoma cells growth and apoptosis. Signaling pathways were analyzed by Western blotting. The immunocompetent mouse tumor models were used to determine antitumor activity following combinatorial therapy with anti-PD-1Ab and disulfiram in osteosarcoma.

Results: Our results showed that disulfiram markedly suppressed the growth and induced apoptosis in osteosarcoma cells. We observed antitumor activity following combinatorial therapy with anti-PD-1Ab and disulfiram in immunocompetent tumor-bearing mouse model. Tumor cells treated with disulfiram showed the hallmarks of ICD including enhanced expression of calreticulin and heat-shock protein 90 on the cell surface, a decrease in intracellular ATP, and the release of HMGB1. Mice treated with combination of anti-PD-1 and disulfiram showed increased T cell infiltration and DC activation within the tumor, indicating that this combination improves the overall quality of the immune response generated.

Conclusion: These findings identify a potential mechanism for the observed benefit of combining disulfiram and anti-PD-1, in which disulfiram induces ICD, thereby converting the tumor cell into an endogenous vaccine and boosting the effects of anti-PD-1.

Poster 235 3042362

CHARACTERIZING THE IMMUNE LANDSCAPE IN ALVEOLAR SOFT PART SARCOMA

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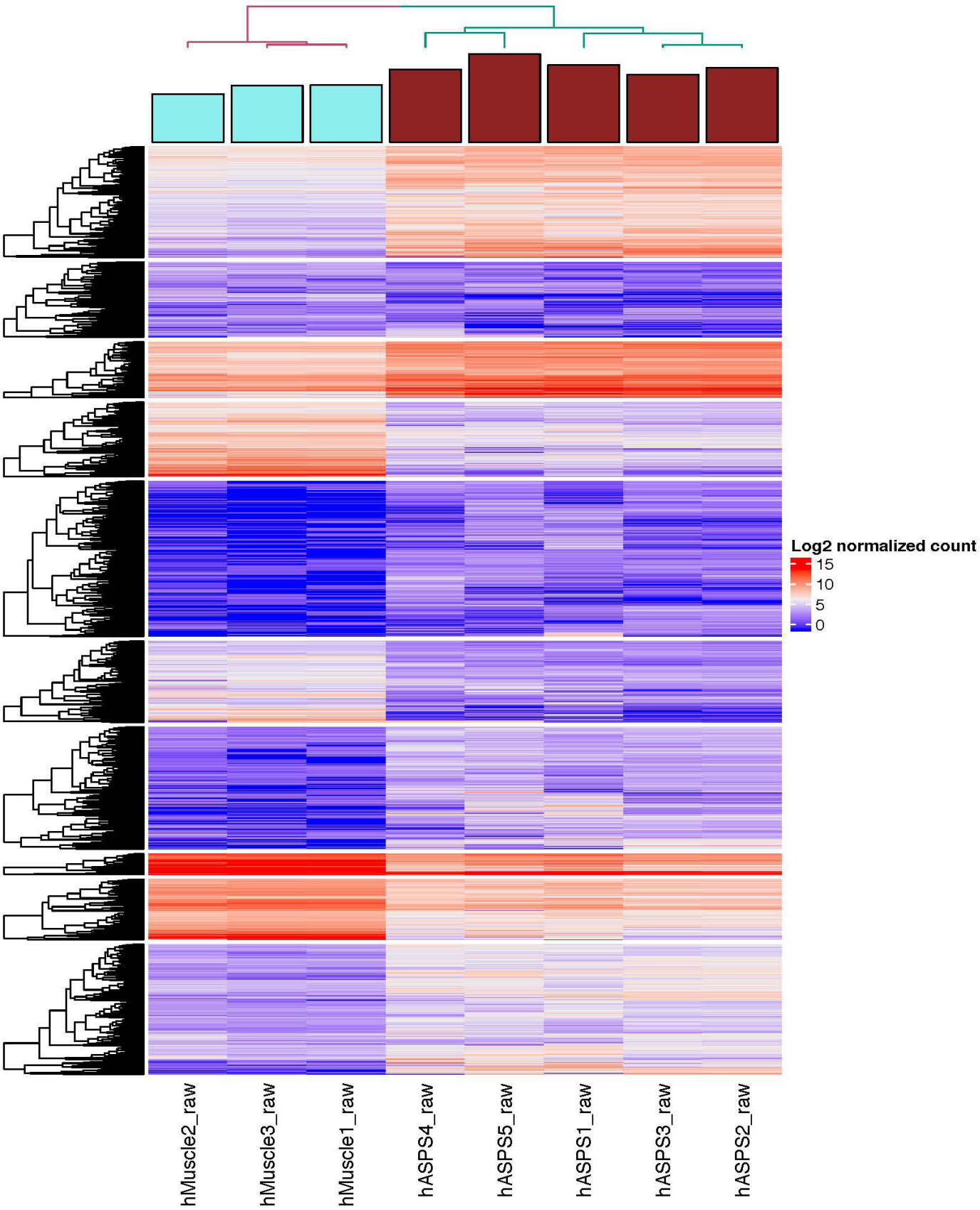
Objective: Alveolar soft part sarcoma (ASPS) is a rare soft-tissue sarcoma characterized by an unbalanced t(X; 17) translocation, resulting in the formation of the ASPSCR1-TFE3 fusion gene. Although the disease displays a relatively indolent course, prognosis remains poor due to its high metastatic potential to the lung and brain. While the cell of origin has yet to be defined in ASPS, prior studies have shown that these tumors may have skeletal muscle origins. Here, we compare transcriptomic data from five ASPS and three skeletal muscle samples to better characterize the immunogenic landscape of ASPS.

Methods: RNA sequencing data was obtained from the Gene Expression Omnibus (GEO) database under ID number GSE54729. Data was normalized and outliers and low read count genes were excluded. The data was processed through our in-house pipeline and the most variable genes between the ASPS and muscle samples were analyzed. The most differentially expressed genes were used to build pathway analysis. Expression data was overlaid on the most significant KEGG pathways using Pathview. Immune scores were calculated using ESTIMATE. All statistical analyses were conducted in R.

Results: Differential expression between the ASPS and skeletal muscle groups were primarily associated with genes related to cell proliferation and angiogenesis. ASPS samples had significantly upregulated levels of midkine(MDK) and downregulation of DEP Domain containing MTOR interacting protein(DEPTOR). These samples had significant upregulation in the autophagy pathway, including HIF-1a and the ULK family of genes. Phospholipase A2(PLA2G7) and prostaglandin D2 synthase(PTGDS), involved in eicosanoid signaling, were also significantly upregulated in ASPS. Increased expression of HLA-A, HLA-C and TAP-binding protein, genes involved in antigen processing and presentation, were also noted. Clustering identified two major subgroups of differentially expressed genes between ASPS and skeletal muscle: ASPS-intermediate and ASPS-high. Gene Set Enrichment Analysis (GSEA) of the ASPS-high group showed significant gene overlap in pathways associated with the immune system, toll-like receptor cascades, cell-adhesion molecules, and the innate immune system.

Conclusion: In ASPS, the ASPSCR1-TFE3 fusion protein is thought to be the primary driver of cell proliferation and angiogenesis through c-Met. Additionally, our data shows increased expression of MDK, a secreted protein that also promotes proliferation and angiogenesis. Increased expression of PLA2G7 and PTGDS in ASPS may mediate immune evasion by promoting a Th2 bias. While immune deviation has traditionally been described as TGF-beta or IL10-mediated, upregulation of PTGDS may also accomplish a similar result. This, combined with the upregulation of genes involved in antigen processing and presentation, may help explain how ASPS, a low mutation burden tumor, could be immunogenic and responsive to anti-PD1 immunotherapy.

Top 5000 Most Variable Genes



Poster 236 3042557

EXPRESSION OF PROGRAMMED DEATH LIGAND 1 (PD-L1) AND EFFECT OF IMMUNOTHERAPY IN MALIGNANT SOFT TISSUED SARCOMA

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Objective: Manipulation of immune checkpoints such as CTLA-4 or PD-1 with targeted antibodies has recently emerged as an effective anticancer strategy in several malignancies. Sarcomas are a heterogeneous group of diseases in need of more effective drugs. We aim to show that express PD-1 ligand in different subtypes of soft tissue and bone sarcomas.

Methods: We examined expression of PD-1 in 49 patients with soft tissue sarcoma including malignant peripheral nerve sheath tumors, leiomyosarcomas, angiosarcoma and Ewing sarcoma. We performed IHC staining of FFPE tissue sections for PD-1 receptor protein and its ligand (PD-L1) using by an anti-PD-1 antibody and anti-PD-L1 antibody. Quantitative real-time PCR for PD-L1 was performed using by whole sections from FFPE tissue of PD-L1 positive cases.

Results: Immunohistochemically, PD-L1 expression was present in 8 of 49 (16.3%) sarcomas. 4/15 (26.6%) malignant peripheral nerve sheath tumors, 1/8 (12.5%) angiosarcoma, 1/7 (14.2%) ewing sarcoma and 2/11(18.1%) leiomyosarcomas showed PD-L1 expression. Epithelioid sarcomas, desmoplastic round cell tumor and synovial sarcomas were all negative in PD-L1 expression. Among the 8 patients who showed PD-L1 expression, 3 patients had no additional option of standard chemotherapy. They were treated with nivolumab, a fully human monoclonal antibody blocking PD-1, One (1/3, 33%) patient have received nivolumab with response of stable disease.

Conclusion: We have shown PD-L1 expression in a subset of sarcomas, both at the protein and mRNA level. Most frequent PD-L1 expression was Malignant peripheral nerve sheath tumors. Clinical trials are necessary to further assess the effect of anti PD-L1 drugs on sarcomas showing PD-L1 expression.

Poster 237 3042637

THE SAINT: INITIAL RESULTS OF A PHASE 1/2 STUDY OF SAFETY/EFFICACY USING SAFE AMOUNTS OF IPILIMUMAB, NIVOLUMAB AND TRABECTEDIN AS FIRST LINE TREATMENT OF ADVANCED SOFT TISSUE SARCOMA

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Background: Sarcoma cells are most immunogenic earlier in the disease course and prior to treatment when the immune system can recognize and destroy them (Schreiber 2011). We hypothesize that immune checkpoint inhibitors would be most effective when given together with a pro-apoptosis immune modulator as first line therapy for advanced soft tissue sarcoma.

Objectives: (1) To evaluate the safety of ipilimumab (**I**), a CTLA4 inhibitor, nivolumab (**N**), a PD-1 inhibitor, and escalating doses of trabectedin (**T**), a marine- derived natural alkaloid with pro-apoptosis and immune modulator properties, in advanced soft tissue sarcoma (STS), (2) To investigate the disease control response rate (DCR), objective response rate (ORR), progression free survival (PFS) and overall survival (OS), and (3) to correlate response with immune cell trafficking in the tumor microenvironment.

Patients/Methods: This is an IRB-approved dose-seeking phase 1/2 protocol using defined doses of **I** (1 mg/kg i.v. q 12 weeks), **N** (3 mg/kg i.v. q 2 weeks) and escalating doses of **T** (1.0, 1.3, 1.5 mg/m^2 i.v. q 3 weeks), employing the "cohort of three" design. Twenty-two to 28 previously untreated patients will then receive the **S**afe **A**mounts of **I, N, T** until disease progression or unacceptable toxicity occurs.

Results: The Phase 1 part of the study has been completed and nine patients were enrolled at two dose levels. **Safety analysis:** At Dose 1: Grade 3 treatment related adverse events (TRAEs) include fatigue (n=1), increased TSH (n=1). At Dose 2, Grade 4 TRAEs include thrombocytopenia with bleeding, DLT (n=1), increased CK (n=1); Grade 3 TRAEs include anemia (n=1), myalgia (n=1), increased TSH (n=1), decreased TSH (n=1), increased AST (n=1).

Efficacy analysis (evaluable patients): At Dose 1: Disease Control Rate (DCR = CR, PR, SD) was 67%, median PFS, >18 weeks; median OS, >39 weeks; At Dose 2: DCR was 80%, median PFS, >18.5 weeks; median OS, >24 weeks.

Conclusion: Taken together, these data suggest that the **SAINT** protocol is safe with manageable adverse events and with no additive toxicity. The Phase 2 part of the study is on-going.

Poster 238 3042673

ACTIVITY OF TREMELIMUMAB AND DURVALUMAB IN ADVANCED SARCOMAS: PRELIMINARY RESULTS OF A SIGNAL-SEEKING PHASE 2 TRIAL

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Objective: The Molecular Screening and Therapeutics (MoST) program enables patients with pathologically confirmed, advanced or metastatic rare cancers access to precision medicine trials. We hypothesized that these patients may benefit from a combination of Tremelimumab (T: anti-cytotoxic T-lymphocyte associated antigen-4; CTLA4) and Durvalumab (D: anti-programmed cell death ligand 1; PD-L1). Within the MoST program, the clinical activity of DT was assessed in 64 patients with advanced rare cancers grouped post-hoc on the basis of tumor expression of PD-L1 and tumor infiltrating lymphocytes (TILs). Patients were treated with 1500mg D and 75 mg T q4w for up to 4 doses/cycles, followed by 1500 mg Durvalumab q4w *i.v.* starting on Week 16 for up to 9 doses. Clinical activity was measured by objective tumor response, progression-free and overall survival. Correlative studies were undertaken to investigate response to D+T.

Methods: Panel sequencing was used to assess tumor mutation burden (TMB), arbitrarily categorized into low to medium burden (≤20 mutations/Mb) and high (>20 mutations/Mb). PD-L1 expression on tumor infiltrating immune cells or on cancer cells was assessed by immunohistochemistry. Other correlative studies profiled expression of 128 genes, including predictors of immune response, as well as biomarkers for newer drugs that could benefit patients. Investigation of inflammatory cytokines in blood pre- and post- treatment, immune cell infiltration of lymphocytes, and T and B cell receptor sequencing was also conducted.

Results: Overall, 64 patients were treated with DT, including 33 patients with bone or soft tissue sarcomas (including 10 Leiomyosarcomas (LMS), 4 Undifferentiated pleomorphic sarcoma (UPS), 3 Dedifferentiated liposarcoma (DDLPS), 2 Ewings, and 2 Synovial sarcomas (SS). Preliminary data shows that adult-type sarcomas had a median event-free survival (EFS) of 223 days compared to 49 days for those with pediatric-type sarcomas (HR 0.172, *P*<0.0001) and 117 days for those with other cancer types. Fifteen (45%) subjects with sarcomas were progression-free at 6 months or greater (14 soft-tissue), with 5 partial responses by RECIST. Histologically, 3/3 DDLPS either experienced a partial response or disease stabilization >6 months, compared to 3/9 LMS and no patient with UPS. Taking all cancers, 58 patients were evaluable for TMB (high TMB: 11 patients; low-med TMB: 47 patients). Preliminary data shows high TMB trends with better outcomes: 54.5% EFS at 6 months, compared to 31.9% for low-med TMB (HR 0.468, *P*=0.0326). Neither PDL1 expression, mismatch repair gene mutation or expression, nor immune cell infiltration predicted response.

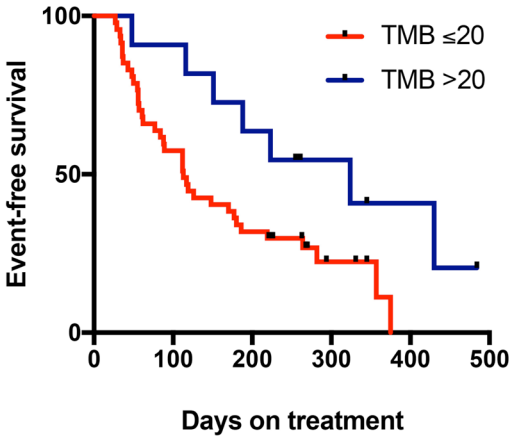

Fig 1 Kaplan-Meier Curves for PFS correlated with TMB (TMB Low: n=47; TMB High: n=11).

Conclusion: Based on EORTC historic data, a 6-month progression-free rate of 30-56% to experimental therapy suggests clinical activity in advanced soft-tissue sarcomas. Our preliminary data suggest D+T has clinical activity in an end-stage population with adult-type sarcomas. Interesting activity of D+T was observed in adult soft tissue sarcomas. High TMB also appears to predict response. Additional correlative studies are underway and will be reported.

Poster 239 3042804

ACTIVITY OF SINGLE-AGENT PD-1 INHIBITOR (PD-1I) THERAPY IN ADVANCED SARCOMA: A SINGLE-CENTER RETROSPECTIVE ANALYSIS

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Objective: Sarcomas constitute a heterogeneous group of tumors of mesenchymal origin with different clinical behaviors and limited responses to systemic therapies. Recent PD-1i immunotherapy studies show promising results with use in certain soft-tissue sarcomas, however, clinical and molecular features which best predict response to PD-1i remain unclear. In this study, we explore responses to PD1i in a cohort of patients treated off-trial as stratified by tumor subtype and patient demographics.

Methods: Demographic, imaging, histologic, and genetic sequencing data was collected for sarcoma patients who initiated single-agent nivolumab or pembrolizumab (PD1i) treatment at our institution between January 1st 2015 and March 31st 2017. The primary objective was to determine progression-free survival (PFS) in patients with advanced sarcomas receiving PD1i per immune-related Response Evaluation Criteria in Solid Tumors (irRECIST 1.1). Secondary objectives included determining overall survival (OS) and assessment of characteristics associated with response to PD1i.

Results: 29 patients met inclusion criteria for this study; these patients were pretreated with a median number of 2 prior therapies. Representative histologies included liposarcoma (n = 9), leiomyosarcoma (n=4), synovial sarcoma (n=2), osteosarcoma (n=1), spindle cell sarcoma (n=4) and others (n=9). Objective radiographic responses were seen in 2 patients; no complete responses were observed (ORR 6.9%). The median PFS of all patients was 16 wk, with 6 mo PFS of 39% and 12 mo PFS of 30%. Median OS was 47 wks, with 6 mo OS of 71% and 12 mo OS of 46%. There was no association between PD-1 expression and PFS, though patients with PD-1 positive tumors trended towards longer OS (p=0.09). Compared with patients who received <3 cycles, patients that received ≥3 cycles PD1i had a longer median PFS (35 vs 7 wk, p=0.0013) and OS (NR vs 17 wk, p=0.0001). Trends toward increased PFS and OS were also noted in patients of male gender and those aged ≥56 yr.

Conclusion: This retrospective study confirms the activity of single-agent PD1i in a pretreated cohort of advanced sarcoma patients. Our results highlight the importance of further research to better identify the optimal target population.

Poster 240 3042810

INTERFERON GAMMA MAKES "COLD" SYNOVIAL SARCOMA AND MYXOID/ROUND CELL LIPOSARCOMA "HOT": RESULTS OF A PHASE 0 TRIAL

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Objective: Synovial sarcoma (SS) and myxoid/round cell liposarcoma (MRCL) cells homogeneously express high levels of cancer/testis antigens, and consequently, potentially good candidates for vaccine and cellular immunotherapy. However, these tumors demonstrate a "cold" microenvironment, with low cell surface expression of human leukocyte antigen (HLA) molecules and few infiltrating T cells. Interferon gamma (IFNγ) has been used both as a single agent and in combination with other immunotherapies in cancers with comparatively "hot" i.e., highly inflamed tumor microenvironments such as melanoma. To test the impact of IFNγ (100 mcg/m^{2}weekly) on the SS and MRCL tumor immune microenvironment, we piloted a phase 0 trial, aiming at turning "cold" tumor microenvironment "hot" by systemic administration of IFNγ in SS and MRCL patients, and facilitate immunotherapy.

Methods: Eight SS/MRCL patients were treated with subcutaneous systemic IFNγ weekly for 2 or 4 weeks at a dose of 100 mcg/m^2. Pre- and post-treatment biopsies were collected from all but one patient. Flow cytometry and multiplex immunohistochemistry (mIHC) were used to evaluate HLA expression and immune cell infiltration on post-treatment biopsies in comparison to pre-treatment biopsies. Pre- and post-treatment serum samples were collected from all patients, and measured for 79 serum cytokines, chemokines and soluble immune regulatory molecules, as well as antibodies specific for tumor antigens. Tumor antigen-specific T cell functional assay was performed in both PBMCs and expanded tumor-infiltrating lymphocytes (TILs). Additionally, PBMCs and tumor single cell suspension were sorted into specific cellular compartments for gene expression profiling to further elucidate the impact of IFNγ on the tumor and immune cells on a subset of patients.

Results: Patients experienced flu-like symptoms consistent with interferon effects; no serious adverse effects were observed. Flow cytometric analysis of tumor biopsies showed significantly increased class I HLA on the tumor surface ($p<0.05$). In 5/7 patients, TIL frequencies increased (3-10-fold). CXCL-10, a chemokine known to be induced by IFNγ, significantly increased in 6/8 patients ($p<0.05$). Certain cytokines, such as IL-16, changed in the majority of the cohort, but no significant change was seen in soluble immune regulatory molecules including PD-1, PD-L1, and CTLA-4. In all but one evaluable tumors, there was an increase in PD-L1 either on tumor or on infiltrating macrophages, which may have inhibited the activation of antigen-specific T cells.

Conclusion: IFNγ treatment is well tolerated in SS/MRCL patients and can significantly enhance both the expression of HLA on tumor surface, and tumoral T-cell infiltration; paradoxically, increased PD-L1 expression on tumor cells and infiltrating immune cells may help tumors evade T-cell elimination. Data regarding gene expression and antibody responses will also be presented. In collaboration with the Cancer Immunotherapy Trials Network, a multicenter phase 2 trial combining IFNγ and pembrolizumab for SS patients is being developed.

Poster 241 3041695

SARCOMA MOUSE MODEL FOR COMBINED ONCOLYTIC VIRUS AND IMMUNE CHECKPOINT INHIBITOR THERAPY

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Background: Sarcoma is a heterogeneous malignancy with 50 different subtypes. Treatment for high grade sarcomas are so dismal and have severe toxicities especially in older adults so that there is a desperate need for more tolerable and effective therapies. Recent successes of immune checkpoint therapy led to interest in immunotherapy in sarcomas. Combinatorial therapies are now attempted to provide more defined and prolonged responses in solid tumors.
VSV, a negative-strand RNA virus of the family *Rhabdoviridae*, is being investigated as an oncolytic agent for the treatment of prostate, skin, colorectal, pancreatic, brain, and other cancers. VSV is unique in its exquisite sensitivity to the effects of IFN.

Objective: There are few mouse sarcoma immunotherapy models. We will establish syngeneic sarcoma mouse models suitable for analyzing both oncolytic virus and immune checkpoint inhibitor therapies. This will be the first of its kind in evaluating sarcoma biology and immune function. We hypothesize that therapy with immune checkpoint inhibitors can be enhanced by the immune stimulatory effects of therapy with oncolytic viruses. We planned to determine the ability of M51R-VSV and immune checkpoint inhibition to inhibit sarcoma tumor growth in mice.

Methods: In Vitro experiments:
In preliminary experiments five murine sarcoma cell lines (MCTC clone 2472 ,M-MSV-BALB/3T3,Sal/N, Sal and BALB/3T3 were tested for sensitivity or resistance to oncolytic virus VSV. Recombinant virus rGFP-M51R-VSV from Lyles labs was used to infect the sarcoma lines at multiplicities of infection(MOI's) of 0.1,1 and 10.Cell viability was assessed using a MTS assay.(Cell tite 96 aqueous one solution cell proliferation assay; Promega Madison WI) and the extent of virus infection was analyzed by flow cytometry GFP expression. Flow cytometry was also used to quantify PD-L1 expression, From these experiments we found Sal/N was the most sensitive whilst CCL-163 was resistant cell line. In addition all cell lines expressed PDL1 .Based on these results we set up a sarcoma model with Sal/N for analysis of response to the treatment with oncolytic virus and immune check point inhibitors.

In Vivo experiments:
These studies used 20 mice, divided into 4 groups of 5 each and were injected in the flank with the sensitive Sal/N sarcoma cell line. M51R-VSV was then injected in 5 mice that serve as the test group whilst 5 mice in the control group were injected with vehicle, and the animals were observed for tumor growth measured with calipers as described. Tumor size were compared in a similar group of 5 mice injected with PD-L1 antibody. Of these 5 mice injected with M51R-VSV were compared with 5 mice treated with PD-L1 antibody alone. The primary endpoint of immune effects will be analyzed for the effect of oncolytic virus with and without PDL1 antibody.

Results: We evaluated the tumors for immune changes in response to oncolytic virus alone versus PDL1 antibody versus combination of both the oncolytic virus and PDL1 antibody. We used flow cytometry and Immunohistochemistry to show the response of combinatorial regimen compared to controls. We are now analyzing the data for immune markers comparing controls to the combinatorial treatment. The results will be presented at the meeting.

Conclusion: We hope to work on this model in order to effectively analyze combined oncolytic virus and immune checkpoint inhibitor therapies to be able to translate it to human clinical trials in the future.

Poster 242 3042803

EFFICACY OF CHECKPOINT INHIBITORS IN PATIENTS WITH METASTATIC SOFT TISSUE SARCOMAS

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Objective: Though checkpoint inhibitors have been approved in multiple cancers they are still under investigation in soft tissue sarcoma. It is yet not established which subtypes will benefit from them. Herein we conducted a retrospective review to report the prognostic factors to checkpoint inhibitors in soft tissue sarcomas.

Methods: A sequential cohort of patients with soft tissue sarcoma from 2 institutions in the US who were treated with checkpoint inhibitors was assembled. Logistic regression models were applied to determine the effect of patient, prior treatment, and baseline factors on having a best overall response of CR, PR, or SD. Similarly, Cox regression models were used to assess the effect of patient, prior treatment, baseline, and treatment factors on progression-free survival. Time was calculated from date of immunotherapy initiation to progression or death due to any cause; otherwise patients were censored at last follow-up. Estimated effects of predictors are reported as odds ratios (OR) or hazard ratios (HR) along with 95% confidence intervals. All statistical testing was two-sided and assessed for significance at the 5% level using SAS v9.4 (SAS Institute, Cary, NC).

Results: Patient demographics and baseline characteristics are summarized in Table 1. Overall 42 patients with a median age of 53 (range 24 to 80) years received checkpoint inhibitors. Patients received a median 2 prior therapies (range 1 to 6). Checkpoint inhibitor treatment consisted of pembrolizumab in 39, ipilimumab in 1 and combination of anti PD-1 therapy with other immune therapy in 2 patients. The median follow-up was 9.8 months. At the time of analysis, immunotherapy was discontinued in 34 patients for progression (79.4%), toxicity (14.7%) and other reasons (5.9%). 8 patients were still undergoing treatment. The median progression free survival was 5.6 months and median overall survival was 21 months. A complete response in 1 undifferentiated pleomorphic sarcoma (UPS) and partial responses in 4 UPS, 1 leiomyosarcoma (LMS) and 1 radiation induced LMS in setting of giant cell tumor was noticed. Twelve patients had stable disease. Of the 7 patients with a CR/PR, 5 have progressed with median time to progression of 11.1 months. The remaining 2 patients had a PR and had been progression free for 16.7 and 22.6 months after immunotherapy initiation. On univariate analysis gender, prior treatments, ECOG, age and number of prior lines of treatment were not associated with response or progression-free survival.

Conclusion: Our study supports activity of checkpoint inhibitors in UPS. We did see responses in LMS as well. Our results expand the knowledge base currently available from other studies of these agents in advanced soft tissue sarcomas. These findings need to be confirmed in clinical trials.

Poster 243 3042935

TUMOR SLICE CULTURE REPRESENTS A UNIQUE MODEL IN WHICH TO INTERROGATE THE IMMUNE RESPONSE TO HUMAN SOFT TISSUE SARCOMA

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Objective: More effective systemic therapies are imperative for patients with advanced soft tissue sarcoma (STS). Up to 40% of patients with undifferentiated pleomorphic sarcoma (UPS) respond to immune checkpoint inhibition, but efficacy is lower against other histologic subtypes, and durability and predictors of response remain unknown. Preclinical models are needed to better define the immune response to sarcoma and identify relevant immunotherapeutic targets. We investigated the utility of the tumor slice culture model in STS.

Methods: We prospectively analyzed fresh human sarcoma specimens from consenting patients undergoing elective resection. 6 mm punch biopsies were obtained from resected specimens following gross margin assessment by Pathology. A vibratome was used to cut tissue into 250 μm thick slices. Each slice was then maintained in RPMI-based medium atop a collagen membrane insert (0.4 μm pore). Slice architecture and viability were measured by H&E staining and a tetrazolium-based colorimetric assay. Tumor-infiltrating leukocytes (TIL) were visualized by immunohistochemistry.

Results: Tumor slice cultures have been generated from 10 STS patients to date, comprising 3 histologies: 4 dedifferentiated

liposarcomas (DDLS), 3 myxoid/round cell liposarcomas (MRCL), and 3 leiomyosarcomas (LMS). Slices maintained 3-dimensional structure and viability for 1 week *ex vivo*, and histology was reminiscent of the original tumor (**Figure 1**). TIL, including $CD68^+$ and $CD163^+$ macrophages, persisted within slices *ex vivo*. Future studies will investigate whether tumor-specific immune responses can be generated within the sarcoma slice microenvironment, using immune-activating agents such as programmed cell death 1 (PD-1) blockade, IL-10 blockade, colony stimulating factor 1 receptor (CSF1R) inhibition, CD47 blockade, and CD40 agonism.

Conclusion: Sarcoma slice culture represents a novel, 3-dimensional, immunocompetent model that is readily applicable to multiple histologic subtypes, recapitulates the tumor microenvironment, and allows for deeper mechanistic evaluation of immunotherapies in STS.

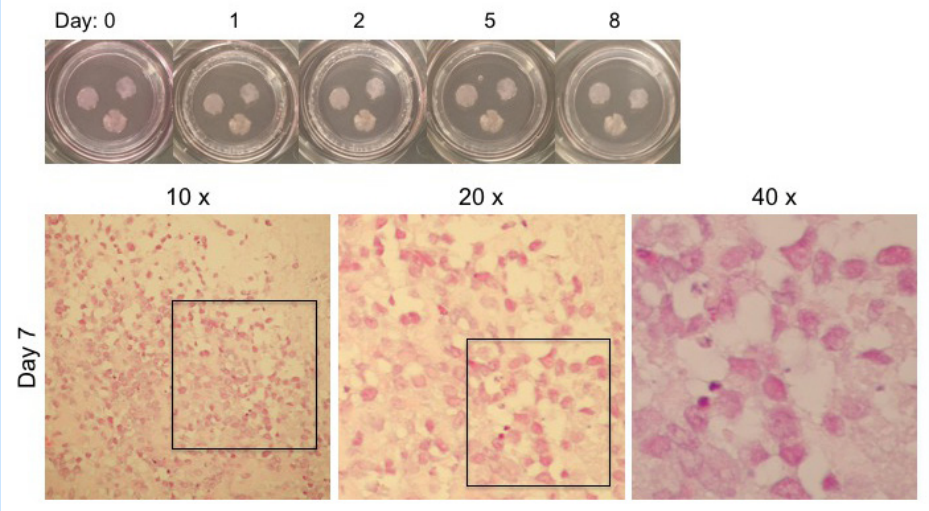

Figure 1. Myxoid round cell liposarcoma (MRCL) maintains tissue architecture in slice culture. Tumor slices maintain 3-dimensional integrity (**top**) and microscopic structure (**bottom**).

Poster 244 3042775

EXPANSION AND CHARACTERIZATION OF TUMOR-INFILTRATING LYMPHOCYTES IN SOFT TISSUE SARCOMA

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Objective: For Soft Tissue Sarcomas (STS), chemotherapy and molecular targeted therapies often provide only short-term disease control, and more effective treatments are urgently needed. Immunotherapy strategies such as checkpoint inhibition or adoptive T-cell therapy (ACT) may be of value in eradicating tumor cells (Figure 1). We hypothesize that some STS contain tumor infiltrating lymphocytes (TILs) in the tumor microenvironment and that these TILs can be isolated and characterized.
Our aims are to investigate the availability and viability of TILs from STS tissue fragments, characterize the TILs, and assess the cytotoxicity of the TILs through functional assays.

Methods: We collected 110 STS tumor specimens from patients undergoing open biopsy or surgical resection without pre-operative adjuvant treatment in order to isolate TILs. We compared the techniques of enzymatic dissociation of tumor tissues as well as plating tumor tissue fragments directly for efficacy in culturing TILs from 12 STS cases. The different immune cell types were characterized by flow cytometric analysis using CD3, CD4, CD14, CD19 and CD56 antibodies.

Results: Following a 4-5-week expansion of STS cases, TILs were harvested from tumor fragments and stored for further experimentation. We found that the tumor fragment method was easier to execute and yielded a cleaner cell culture population. The expansion rate of TILs showed some differences between different cases. We also observed some differences in TIL expansion between different tumor fragments of the same tumor (Figure 2). Preliminary flow cytometry results revealed that TIL cultures exhibited heterogeneous ratios of CD4+ to CD8+ T cells between different cultures from the same tumor and between tumors from different patients (Figure 3).

Conclusion: TILs were successfully harvested from STS tumor fragments and T-cell populations were confirmed through flow cytometry. Preliminary results demonstrated variable cell proportions of CD4+ and CD8+ TILs between different cultures from the same tumor and between different tumors from different patients. These initial studies will enable us to move forward with evaluating the potential of TIL-based ACT in the treatment of patients with STS.

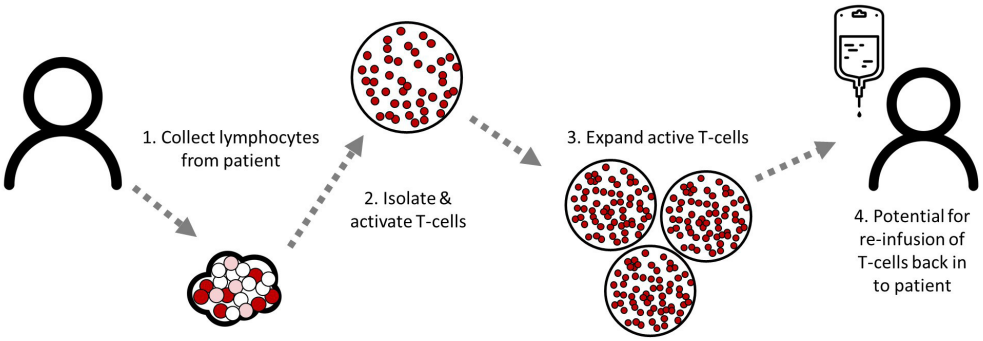

Figure 1. Adoptive T-Cell Therapy

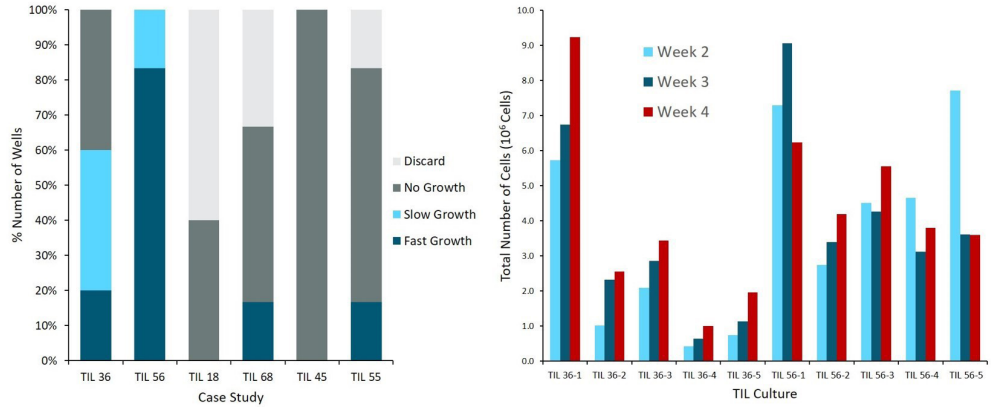

Figure 2 a. Proportion of wells displaying various growth rates b. Cell count of various TIL cultures over 4 weeks

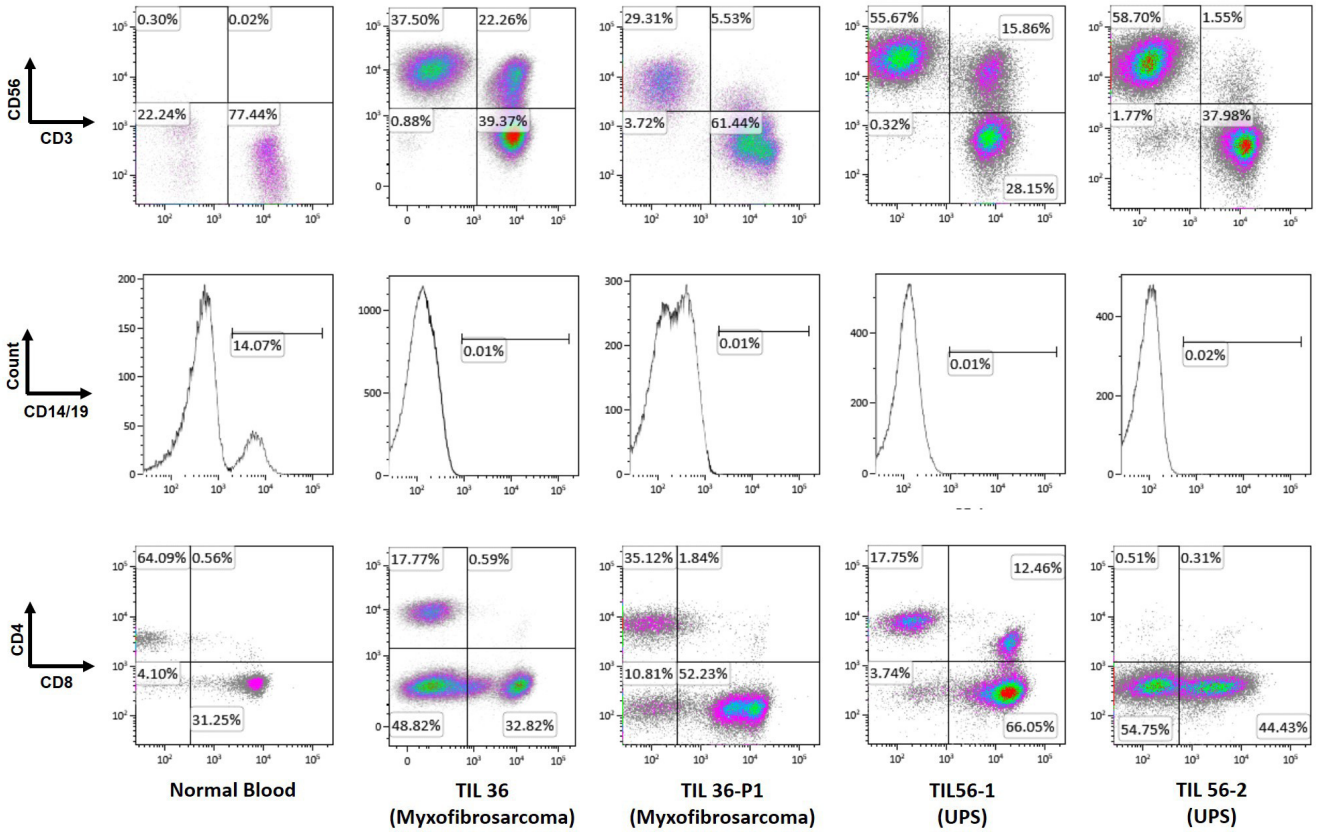

Figure 3. T-Cell composition of TILs in STS

Poster 245 3004039

KAPOSI'S SARCOMA IN THE ERA OF HAART: A SINGLE INSTITUTIONAL RETROSPECTIVE REVIEW

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Objective: Kaposi's Sarcoma (KS) is an angioproliferative tumor with four sub-types described: classic (CKS), endemic, immunosuppression therapy-related, and epidemic (AIDS-KS). HHV-8 is responsible for all varieties of KS. AIDS-KS prevalence has decreased dramatically since the introduction of highly active anti-retroviral therapy (HAART). Even so, KS lesions develop in patients with undetectable viral loads and high CD4 counts. Additionally, KS is variable across its epidemiologic subtypes, disease course, and clinical outcomes. Therefore, treatment must be individualized.

Methods: IRB approval was obtained in order to review pathological and clinical data of KS patients. A retrospective cohort was identified of KS patients evaluated and treated between January 2005 and September 2017 at the Robert H. Lurie Comprehensive Cancer Center at Northwestern University. Patients were identified through the Northwestern Enterprise Data Warehouse (EDW). Patient data was reviewed for demographics, clinical and pathological characteristics, and treatments. Descriptive statistics was used to assess predictors for disease severity and treatment.

Results: 130 patients with a diagnosis of KS were identified, of which 95 (73.1%) had AIDS-KS and 34 (26.2%) had CKS. There were no endemic, and 1 patient with immunosuppression therapy-related KS. Males represented 91.5% of case. The mean age at diagnosis was 66.8 years ± 14.4 among CKS patients and 42.1 years± 9.6 in AIDS-KS patients. 22.1% of AIDS-KS pts had metastatic disease vs. 5.7%in the CKS group. At KS diagnosis, 46.3% of AIDS-KS patients had CD4 count > 200 cells/mm3 and 33.7% had HIV viral load level <=20 copies/mL. Among the 53 patients who received chemotherapy, 45 were AIDS-KS patients (84.9%). 65.2% or patients with metastatic disease (lung or GI involvement) at diagnosis, of which 91.3% had AIDS-KS, received chemotherapy vs 35.5% of patients with skin/mucosa involvement. The most commonly used chemotherapy was doxorubicin hydrochloride liposomal injection (78.4%) with an average of 10 cycles. Other chemotherapy utilized includes paclitaxel and interferon. 16 patients (12.3%) are now deceased, of which only two patients died of disseminated AIDS-KS.

Conclusion: Our retrospective studies confirms that ¾ of patients diagnosed with KS, have AIDS-KS. Despite the introduction of HAART and the well-controlled nature HIV/AIDS, KS continues to develop. AIDS-KS patients are younger, more likely to have metastatic disease and more frequently require chemotherapy. Despite the introduction fof HAART, poorly controlled HIV still portends a worse outcome in AIDS-KS. Further investigations are required to better understand the etiology of AIDS-KS in patients with undetectable HIV viral loads.

Poster 246 3042748

KAPOSI SARCOMA, A SINGLE CENTER EXPERIENCE

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Objective: Kaposi sarcoma (KS) is an angioproliferative disorder, which manifests most commonly through cutaneous and less often with mucosal lesions or visceral attainment. It is classified into four types based on the clinical circumstances in which it develops: classic, endemic, iatrogenic and HIV-associated. Despite the histopathological similarities between the various subgroups, the demographic characteristics, clinical manifestations and course of the disease differ significantly. The objective of this study was to to characterize the population of patients with KS followed at the Centro Hospitalar Lisboa Norte regarding clinical and demographic characteristics as well as behaviour in relation to variables such as treatment and occurrence of relapses.

Methods: Observational retrospective cohort study. Demographic, clinical, pathological, treatment and health outcomes were collected directly from the clinical process of patients with a diagnosis of KS, followed in the hospital until 31-12-2017.

Results: A total of 128 patients were identified. The global population had a predominance of males (97; 75.8%), Caucasian (71; 55.5%) with a median age at diagnosis of 46.5 ([IQR] 37- 63.7) and a higher prevalence of cutaneous lesions (102; 79.7%). Seventy-three (57%) were HIV positive with a median age at the diagnosis of 40 ([IQR] 32,5-46), predominantly males (52; 71.2%) and Caucasians (62; 84.9%). The preferred site for the lesions was the lower limbs (LL) (34; 46.6%), 8 (11%) with disseminated disease and 6 (8.2%) with visceral affectation. The median time between the diagnosis of HIV and KS was 11 months. In the majority of cases (34; 46.6%) the therapeutic approach chosen was the institution of antiretroviral

therapy. Twenty-eight patients (38.4%) did chemotherapy (QT) and 2 (2.7%) radiotherapy (RT). Six patients (8.2%) relapsed and the median time from diagnosis to relapse was 30 months. 21 deaths (37%) were recorded. Regarding the iatrogenic variant 11.7% (15) kidney transplants were included with a median age at the diagnosis of 50 ([IQR] 43-56), predominantly male (8; 53,3%) and negroid (12; 80%). The preferential location for the lesions were the LL (10; 66.7%) and only 1 (6.7%) had visceral attainment. The median time between the diagnosis of kidney transplantation and KS was 11 months. In most cases (6; 40%) the reduction of immunosuppression was the chosen therapeutic approach. Five patients (33.3%) did QT and 3 (20%) RT. Five patients (33.3%) recurred, the median time from diagnosis to relapse was 36 months. 3 deaths (20%) were recorded. Eleven patients (8.59%) presented the endemic subtype with a median age at diagnosis of 58 ([IQR] 50-60), all male. The preferred site for the lesions was the LL (9; 81.8%). The therapeutic approach chosen was QT (7; 63.6%) and 2 (18.2%) did RT. Four recurrences (36.4%) were documented and the median time from diagnosis to relapse was 24 months. Two deaths were recorded (18.2%). In the Classic subtype, 29 patients (22.66%) with a median age at diagnosis of 64 ([IQR] 64-79.5), male predominance (21; 72.4%), were included. The preferred sites for the lesions were the LL (20; 69%) and 2 (6.8%) with mucosal attainment.The therapeutic approach chosen was RT (9; 31%), 4 (13.8%) did QT. 11 recurrences (37.9%) were documented and the median time from diagnosis to relapse was 12 months. Fourteen deaths (48.3%) were recorded. The median duration of follow-up was 74 months with an median overall survival (OS) in the HIV-associated subgroup of 10.6 months. Median OS in the other subgroups was not reached.

Conclusion: KS is a heterogeneous disease with different clinical and prognostic characteristics depending on the subtype of the disease. However, it is very interconnected with states of immunosuppression either by HIV, use of immunosuppressive therapies or even by age as it is possible to prove by older ages in the classic and endemic subgroup. It remains to be noted the limitations of this study as a retrospective and unicentric study

Poster 247 3017154

THE MEF2-CLASS IIA HDAC AXIS IN LEIOMYOSARCOMAS; PROLIFERATIVE OPTIONS AND POSSIBLE THERAPEUTIC TARGETS

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Objective: Members of the MEF2 family of transcription factors (TFs) regulate differentiation and adaptive responses during embryogenesis and in adult life. MEF2 can form complexes with co-activators of transcription or with co-repressors. Class IIa HDACs family members, which include HDAC4, HDAC5, HDAC7 and HDAC9, are important partners of MEF2 and repressors of transcription. Approximately 25% of leiomyosarcomas (LMS) patients are characterized by a significant up-regulation of a class IIa HDAC member and this dysregulation correlates with a worse prognosis, especially in the case of female uterine LMS (Di Giorgio et al. PLoS Genet. 13, e1006752 2017). With this work we were aimed to validate class IIa HDACs as therapeutic targets for the treatment LMS.

Methods: We have recently demonstrated an oncogenic activity of HDAC9 in LMSs, due to its capability to repress MEF2 TFs. In SK-UT-1 cells, an aggressive LMS cell line, HDAC9 is overexpressed. Hence, this cell line is a good model for LMS tumors characterized by high levels of class IIa HDACs. To better understand the class IIa HDACs addiction in these LMS cells we knocked-out, by CRISPR/Cas9 technology, HDAC9 and HDAC4. In order to understand their contribution to proliferation and drug responsiveness, gene expression profile studies and drugstreatments responses analysis were performed.

Results: Gene expression profile studies provided evidences that HDAC4 and HDAC9 regulate common target genes but also, and in higher percentage, specific genes sets. Different regulative pathways are under the influence of these epigenetic regulators. Particularly, HDAC9 compared to HDAC4 regulates a reduced number of genes (approximately 1/4) and among them several are also under MEF2 regulation. KO of HDAC9, but not of HDAC4, makes LMS cells highly susceptible to apoptosis induced by different stimuli. Among apoptotic genes repressed by HDAC9 we have found the death receptor FAS. Blocking FAS apoptotic signaling using the short isoform of FLIPs, abrogates the apoptotic susceptibility of SK-UT-1 HDAC9-/- cells. By testing different possible inhibitors of the MEF2-HDAC axis, we have validated a small molecule that targets the interaction between MEF2 and class IIa HDACs, as an interesting pro-apoptotic drug for LMS treatment. SK-UT-1 cells treated with this compound up-regulate some genes similarly to cells knocked-out for HDAC9.

Conclusion: Our results demonstrate that SK-UT-1, highly aggressive LMS cells, are HDAC9 addicted. Abrogation of HDAC9 renders LMS cells highly responsive in terms of apoptosis to different drugs. HDAC9 is required to repress the transcription of the apoptotic receptor FAS. Importantly, small molecule targeting the interaction between MEF2 and class IIa HDACs can trigger apoptosis in LMS. Overall we provide evidences that targeting class IIa HDACs could provide new therapeutic perspectives for LMS.

Poster 248 3026534

PEDIATRIC LIPOSARCOMA: A REPORT FROM THE TEXAS CHILDREN'S RARE TUMOR REGISTRY

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Objective: Liposarcoma is a rare entity in pediatric age group comprising less than 3% of soft tissue sarcomas in children. Treatment is generally based on adult guidelines. The objective of this study was to describe the treatment and outcomes of children with liposarcoma treated at Texas Children's Hospital.

Methods: After obtaining IRB approval, patients with liposarcoma treated at Texas Children's Cancer Center between 1995 and 2018 were identified through the pathology database. Descriptive statistics, response to treatment and survival analyses were performed.

Results: We identified 13 patients with liposarcoma; 9 female and 4 male. The median age at diagnosis was 16 years (range 4-19 years). The most common histology was myxoid liposarcoma (n=7) followed by well differentiated (n=3), pleomorphic (n=2) and dedifferentiated (n=1). The primary tumor was located in the extremities in majority of patients (77%), with the remainder occurring in the abdomen or trunk. Most (77%) primary tumors were greater than 5 cm in diameter. The three patients with high-grade subtypes (pleomorphic and dedifferentiated histology) had metastatic disease at diagnosis. Upfront complete resection was achieved in 7 patients (in 4 of them after re-resection). Six of seven tumors that were completely resected were in the lower extremity, making complete resection feasible. Eight out of 10 patients with localized disease were treated with surgery alone (including 2 gross total resection), and were alive at last follow-up. One patient with localized disease received adjuvant radiation therapy, and another patient received upfront chemotherapy with partial response followed by complete resection and radiation therapy. Of the four patients who received neoadjuvant chemotherapy (including three metastatic patients), three had partial response. Two patients with metastatic disease are dead after disease recurrence and the third patient is alive with disease. Of the five patients with myxoid liposarcoma who underwent fusion testing, two had FUS-DDIT3 fusion and one had EWS-DDIT3 fusion. MDM2 amplification was detected in the patient with dedifferentiated liposarcoma.

Conclusion: Children with localized liposarcoma, regardless of size, have an excellent prognosis after complete surgical resection. The prognosis for those with metastatic disease is poor despite multimodal therapy. Next generation sequencing of the available tumor tissue is planned to identify molecular signatures unique to pediatric liposarcoma.

Patient	Age at Dx (Yrs)/ Sex	Race/ Ethnicity	Histology	Primary Site	Size of Primary (cm)	Metastases	Treatment	Resection	Time to Progression (Months)	Vital Status
1	17/F	NH White	Well differentiated	Abdomen	60.5	No	Resection	Gross total		Alive
2	19/M	Hispanic	Well differentiated	Lower limb	9.5	No	Resection	Complete		Alive
3	10/F	Hispanic	Well differentiated	Lower limb	10	No	Resection	Complete		Alive
4	17/F	NH Black	Myxoid	Lower limb	5	No	Resection	Complete		Alive
5	14/M	Hispanic	Myxoid	Lower limb	6	No	Resection	Complete		Alive
6	16/F	Hispanic	Myxoid	Lower limb	Unknown	No	Resection	Complete		Alive
7	17/F	NH Black	Myxoid	Trunk	10	No	Resection	Complete		Alive
8	10/F	Hispanic	Myxoid	Upper limb	3.8	No	Resection	Gross total		Alive
9	17/F	Hispanic	Myxoid	Upper limb	7.4	No	AI+ XRT+ Resection	TBD		Alive
10	13/F	NH Black	Myxoid	Lower limb	5.5	No	Resection + XRT	Complete		Alive on therapy
11	4/F	NH White	Pleomorphic	Abdomen	7	Lung, bone, bone marrow	AI + Resection	Palliative partial	1	Deceased
12	13/M	NH White	Pleomorphic	Lower limb	9.2	Lung, brain, liver	AI + Resection	Complete	7.5	Deceased
13	17/M	NH Black	Dedifferentiated	Lower limb	7.9	Lung, brain, lymph nodes	AI + Resection	Complete		Alive on therapy

AI: Doxorubicin, Ifosfamide; XRT: External beam radiation therapy

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INTEGRATED WHOLE EXOME AND RNA SEQUENCING FOR DEDIFFERENTIATED LIPOSARCOMA

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Objective: Previous conventional or comprehensive genomic analyses showed that dedifferentiated liposarcoma (DDLPS) harbored high frequency of somatic copy-number alterations (SCNAs), including 12q13-15 but few somatic mutations. Some studies also displayed that stratification by the featured SCNAs could predict clinical prognosis. However, genomic characteristics of DDLPS associated with clinical parameters remain to be elucidated for further amelioration of treatment strategies for patients with DDLPS.

Methods: Genomic meta-analysis for 119 patients with DDLPS was performed after whole exome and RNA sequence for 66 patients with DDLPS from Japan Sarcoma Genome Consortium and acquisition of FASTQ data of whole exome and RNA sequence for 53 patients with DDLPS from TCGA. In addition, eight pairs of well-differentiated (WD) and de-differentiated (DD) components from DDLPS, were analyzed to compare their genomic alterations.

Results: We identified 2783 somatic mutations, including nonsynonymous single nucleotide variants (SNVs) and short insertions/deletions (Indels), with a mean of 23.4 mutations per sample (0.280 per coding megabase), ranging from 0 to 70 mutations. Copy-number analysis identified 27 gained regions, including 12q15 and 54 lost regions. Fusion analysis revealed that intra-and inter-chromosomal rearrangements at long-arm of Chr. 12 were most frequent and also identified three recurrent inter-chromosomal fusion genes, two of which were novel and verified by capillary sequencing. These inter-chromosomal fusions result in the upregulation of one of the fusion-partner genes, and Gene set enrichment analysis (GSEA) showed significant enrichment of cell-cycle related gene sets in fusion-positive samples, indicating the association of the fusion genes with DDLPS progression. Among the recurrent genomic alterations, gain of 1p32.1 and 12p13.32 were found to be independently associated with poor disease-specific survival. Based on these results, DDLPS was clustered into three groups according to the status of 12q15, 1p32.1 and 12p13.32. This clustering could predict disease-specific survivals, independently of surgical margin and primary tumor site. Subsequent comparative analysis showed DD harbored more somatic mutations than matched WD, but shared few common somatic mutations with WD. In contrast, WD and DD shared more common SCNA regions, while DD harbored more prominent SCNAs as well as additional SCNA regions as compared to WD. GISTIC identified common SCNAs including gain of 1q24.3 and 12q14.3~15 between DD and WD. GSEA showed that gene sets, related to cell cycle progression, were significantly enriched in DD, while those related to adipocyte differentiation or lipid metabolism were enriched in WD. We finally identified 25 genes which showed differential expression, in accordance with the SCNAs, specific for DD.

Conclusion: This study revealed genomic characteristics of DDLPS by integrated genomic analysis, using more than 100 tumor samples, and established novel genomic clustering of DDLPS, which can predict prognosis of the patients with DDLPS. In addition, the current study showed common and differential genomic alterations between DD and WD, which might be associated with tumorigenesis and malignant transformation, respectively. This large-scale analysis reveals the underlying mechanism of DDLPS development and progression, providing novel insights into refining DDLPS therapy.

Poster 251 3008000

SURGICAL AND CLINICAL OUTCOMES OF ATYPICAL LIPOMATOUS TUMOR OF THE TRUNK AND EXTREMITY

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Objective: Previous reports concerning atypical lipomatous tumors (ALTs) demonstrate varied clinical outcomes and lack consensus treatment recommendations. We aimed to assess outcomes of ALTs affecting the extremities and trunk in order to better characterize their clinical behavior and guide treatment.
The purpose of our study was to review the clinical and surgical outcomes of ALTs. We assessed the impact of surgical margins on clinical outcomes such as local recurrence, malignant transformation, and metastatic disease in order to guide specific treatment recommendations for ALTs of the trunk and extremity. Secondarily, we assess the prognostic value of other (demographic and clinical) factors on clinical outcomes for ALTs. To our knowledge, this is the largest series from a single institution evaluating solely ALTs of the extremity and trunk.

Methods: One hundred and three patients treated at a single institution from 1994 to 2016 with pathologically confirmed ALTs of the extremity and trunk were retrospectively reviewed. Demographic and clinical data was recorded including type of surgical excision, recurrence rates, risk of dedifferentiation, and metastasis. We included tumors with pathology results consistent with ALT or WDL arising from the extremity or trunk. All age groups were included. Tumors arising from the retroperitoneum, mediastinum, or para-testcualr region were excluded. Cases that presented primarily as dedifferentiated liposarcoma without prior history of pathology consistent with ALT were excluded.
Demographic patient data was collected including age, sex, tumor size, and anatomic location of the tumor. Clinical outcomes were recorded including margin status, type of surgical excision, local recurrence (and time to recurrence), re-recurrence, malignant transformation, and development of metastatic disease.

Results: One hundred and three patients with an average follow-up of 44 months were included in the final cohort. Local recurrence after primary excision was observed in 24 patients (23%) at an average interval from primary resection of 68 months. Only one lesion recurred with malignant transformation.Of the 24 local recurrences and excluding the single case of malignant transformation, four (17%) experienced re-recurrence. None of the 103 cases developed metastatic disease.
A total of 22 of the 95 cases with marginal excision, two of the six cases with intralesional excision and none of the six cases with wide excision recurred. Compared to marginal excisions (set as the reference), intralesional and wide excisions tended to have higher risk (HR = 1.47, 95% CI 0.29-4.77 and 1.93, 95% CI, 0.01-15.13 respectively), although the confidence intervals for these ratios were wide. Except for the maximum dimension (per 10 cm increment increase in size, p = 0.03), other prognostic factors did not have a statistically significant association with the risk of local recurrence (Table 2). Men (HR = 0.72, 95% CI 0.32-1.64) and younger patients (HR = 0.93, 95% CI 0.68-1.29) tended to have smaller risk. Compared to tumors located in the lower extremity, tumors located in the trunk and upper extremity tended to have higher risk (HR = 1.76, 95% CI 0.35-5.74 and 2.28, 95% CI, 0.58-6.88 respectively).

Conclusion: In summary, we present the largest series from a signal institution evaluating ALTs from the extremity and trunk. We concur with the nomenclature of ALTs representing WDLs of the trunk and extremity and should be conceptualized as benign tumors. Further, marginal excision of extremity based atypical lipomatous tumors can be expected to yield approximately a 23% risk of local recurrence, with an exceedingly low incidence of malignant transformation or metastasis.

Table 1. Patient Demographics and Surgery Characteristics.

	N	Mean±SD (range) or N (%)
Sex	103	
Female		49 (47.6%)
Male		54 (52.4%)
Age at Surgery	103	55.7±13.6 (17.6-84.7)
Anatomic Location	103	
Lower extremity		76 (73.8%)
Trunk		7 (6.8%)
Upper extremity		20 (19.4%)
Depth	103	
Superficial		5 (4.9%)
Deep		98 (95.1%)
Maximum Dimension (cm)	103	16.6±7.2 (1.3-42.0)
Excision Type	103	
Marginal		95 (92.2%)
Wide		2 (1.9%)
Intralesional		6 (5.8%)

Mean/median follow-up duration = 44/20 months

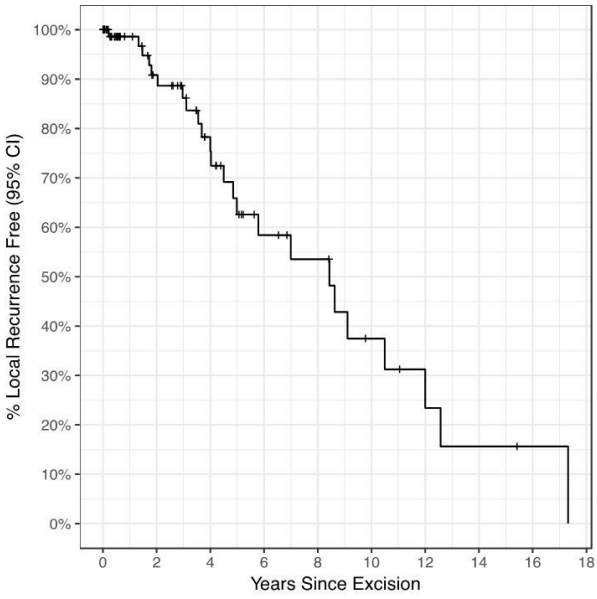

Figure 1. Local recurrence free survival **for all patients**. Kaplan-Meier estimates.

Previously Reported Local Recurrence Rates of Extremity Based ALTs/WDLs				
Author	**Local Recurrences**	**N**	**Rate of Local Recurrence**	**Comments**
Rozental	16	31	51.61%	
Mavrogenis	5	47	10.64%	5 cases treated with radiation
Mussi	16	151	10.6%	Derived from 2 different institutions with varying surgical treatments
Evans	1	12	8.33%	
Sommerville	5	61	8.2%	Marginal excision only
Billings	4	38	10.53%	
Bassett	14	51	27.45%	
Serpel	3	11	27.27%	
Weiss	20	46	42.49%	
Lucas	15	32	46.88%	
Kubo	1	12	8.33%	
Kito	7	41	17.07%	Included wide (0/11 recurred) and marginal excision (7/30 recurred)
Total	**107**	**533**	**20.08%**	

Table 3. Historical local recurrence rates for ALTs

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CLINICOPATHOLOGIC CHARACTERISTICS AND CLINICAL OUTCOMES OF LIPOSARCOMA: A RETROSPECTIVE ANALYSIS OF SINGLE CENTER EXPERIENCE FOR 25 YEARS

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Objective: Liposarcoma (LPS) is a mesenchymal-origin cancer arising from precursors of adipocyte and accounts for 15-20% of all adult malignant soft-tissue sarcoma. It is a heterogenous group of cancers histologically classified into 4 subtypes; well-differentiated, dedifferentiated, myxoid/round and pleomorphic. Due to its rarity and heterogeneity, clinical characteristics, oncologic outcomes, and proper treatment strategies have not been well-established. Hence, we aimed to determine the clinical course and treatment outcome of LPS in the real-world setting.

Methods: We retrospectively reviewed all consecutive patients who were treated for liposarcoma in Asan Medical Center between July 1989 and January 2017, using a clinical database system (Asan BiomedicaL research Environment, ABLE).

Results: Out of 482 patients identified from the database, 346 patients who had been treated for pathologically-confirmed LPS and had sufficient medical records were finally included in this retrospective analysis. The median age was 56 years (range, 19—87) with males comprising 62% (n=213). The most common subtype was well-differentiated LPS (n=126, 36%), followed by dedifferentiated (n=106, 31%), myxoid/round (n=98, 28%), pleomorphic (n=13, 4%) and unspecified (n=1, 0.3%). By primary site, abdomen-pelvis (n=165, 48%) was most frequently involved; extremity (n=142, 41%), thorax (n=23, 7%) and head-neck (n=16, 5%) came next. Most patients (n=334, 97%) were presented with localized disease at the time of diagnosis and the rest twelve (3%) showed distant metastases in the first place; lung (n=3), liver (n=4), peritoneal seeding (n=2), soft tissue (n=4), bone (n=3), and others (n=2). Median overall survival (OS) of the whole cohort was 129.7 months with median follow-up of 60.7 months. By primary site, LPS occurring in abdomen-pelvis showed the shortest OS (median 99.0 vs. thorax, 129.7; head-neck, 198.4; extremity, 209.2 months). According to histologic subtypes, well-differentiated type tended to have the most favorable OS (median, 192.0 months) compared to myxoid/round (116.0 months), pleomorphic (95.1 months), or dedifferentiated (89.2 months) type. Every patients with localized disease except two with high-perioperative risk (n=332, 99%) underwent curative-intent surgical resection. R0 resection rate was 53% (n=177/332) and post-operative treatment was applied to about a half (n=157/332, 47%) of the patients; radiotherapy (RT) (n=111), chemotherapy (n=17), or both (n=29). Recurrence was observed in 135 patients (41%) after surgery, and 87% (n=117/135) of them were loco-regional recurrence. Margin status was significantly related with recurrence-free survival (RFS); median RFS after R0 and R1 resection were 130.9 and 46.7 months, respectively (P<0.001). Dedifferentiated type was associated with the poorest RFS (median 23.4 months) compared to other histologic subtypes (P<0.001). Depending on primary sites, abdomen-pelvis origin showed the shortest RFS (median 30.4 months) while extremity-origin was the least

likely to recur after surgery with 10-year disease control rate of 86% (median RFS, not reached; P<0.001). Furthermore, adjuvant RT brought longer RFS (vs. no adjuvant RT; 149.6 vs. 37.7 months; P<0.001). Meanwhile, adjuvant chemotherapy was not significantly improved RFS (vs. no adjuvant chemotherapy; 115.7 vs. 82.9 months; P=0.54). Initially metastatic disease was substantially associated with dismal prognosis with median OS of 19.1 months.

Conclusion: Our result showed that clinical course of LPS is heterogeneous according to its histologic type and anatomic location. Abdomen-pelvis origin and dedifferentiated type were related to poor clinical outcomes, whereas extremity origin and well-differentiated type showed favorable prognosis. Even following the curative resection, majority of recurrences occured at loco-regional sites. Complete resection is important to lower recurrence rate. Adjuvant RT may have additional benefit to surgical resection in patients with localized LPS.

Poster 253 3041958

WATCHFUL WAITING IN PATIENTS WITH WELL-DIFFERENTIATED LIPOSARCOMA IN THE EXTREMITY

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Objective: Patients with well-differentiated liposarcomas (WDLPS) of the extremity are mostly treated with surgery, possibly inducing severe morbidities. Despite the limited metastatic potential and excellent prognosis, watchful waiting (WW) is barely applied in these patients. This retrospective cohort study aimed to get a more detailed insight into the outcome of patients with extremity WDLPS, to estimate whether WW is applied and if so, how often, and to determine the outcomes of these patients.

Methods: A large retrospective database of patients treated for extremity WDLPS from two soft tissue sarcoma expertise centers was assessed to evaluate treatment, dedifferentiation and disease-specific survival. The Dutch Pathology Registry (PALGA) was consulted to identify patients treated with WW from 1991-2017 in the Dutch population. Lastly, our experience with patients undergoing WW was explored.

Results: Distant metastases (5/192 patients) were seen mainly after a dedifferentiated local recurrence. Death of disease occurred in 4/192 patients. Two patients were likely to have died from metastatic disease, although in both cases the metastases were not pathologically confirmed. The other two died of treatment-related complications. In the PALGA-database 72 patients treated with WW were identified, with an increasing trend over time. Currently in our center, 18 patients with localized tumors considered as potentially resectable with severe morbidity and without symptoms are treated with WW. Time of WW varies from 0.2-8.9 years. Four patients underwent surgery after a period of WW (range 14-52 months) because of symptoms and/or tumor growth. No areas of dedifferentiation were found in these resection specimens.

Conclusion: WW in selected patients with extremity WDLPS might be an option, since active surgical treatment might lead to morbidity and even mortality. Prospective studies on WW in patients with extremity WDLPS are worthwhile to consider.

Poster 254 3025636

TRANSIENT INTERFERON SUPPRESSION RENDERS NERVE SHEATH SARCOMAS SUSCEPTIBLE TO VIRO-IMMUNOTHERAPY

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Objective: Malignant Peripheral Nerve Sheath tumors (MPNSTs) are aggressive soft tissue sarcomas resistant to most cancer treatments. Surgical resection remains the primary treatment; however this is often incomplete, ultimately resulting in high mortality and morbidity rates. There has been a resurgence of interest in oncolytic virotherapy because of encouraging preclinical and clinical trial results. Oncolytic Herpes simplex virus (oHSV) selectively replicates in cancer cells, lysing the cell and inducing antitumor immunity. We previously showed that basal interferon (IFN) signaling increases interferon stimulated gene (ISG) expression, restricting viral replication in almost 50% of MPNSTs. The FDA approved drug Ruxolitinib (RUX) temporarily resets this constitutively active STAT signaling and renders the sarcoma cells susceptible to oHSV infection in cell culture. In these studies we sought to assess the effect of the oHSV and Ruxolitinib combination therapy in resistant synegeic MPNST murine tumor model.

Methods: To test how JAK/STAT inhibition influences oHSV therapy, we chose one of the more resistant MPNST lines (67C-4) which constitutively activates STAT1 pathway signaling and restricts viral replication. Tumor cells were pretreated with Ruxolitinib for 2 days and the expression of the ISGs and virus spread was evaluated. For the in vivo studies, animals were pre-treated with 3 consecutive doses of Ruxlitinib followed by intratumoral adminstration of oHSV. Tumors were measured in one set os tudies. In a second set of studies, tumors tissue and spleens were harveted for immuno-phenotyping.

Results: Murine MPNSTs exhibit a similar IFN- and ISG-mediated oHSV mechanism and virotherapy alone provides no antitumor benefit *in vivo*. However, when mice are pretreated with Ruxolitinib, this reduces ISG expression making the tumors susceptible to oHSV infection. Ruxolitinib pretreatment improves viral replication and alters the oHSV-induced immune-mediated response. Ruxolitinib pretreatment not only enhances virus infection and replication but also boosts the immune-mediated antitumor immune response, improving survival and 412 reducing tumor growth. Our results show that this combination therapy increases CD8 T cell activation in the tumor microenvironment and that this population is indispensable for RUX+oHSV antitumor benefit. Of note, animals treated with the combination therapy have developed a systemic memory response against tumor antigens.

Conclusion: JAK/STAT inhibition prior to oncolytic virus treatment augments both oHSV replication and the immunotherapeutic efficacy of oncolytic herpes virotherapy.

Poster 255 3036063

STING ACTIVITY PREDICTS RESISTANCE TO ONCOLYTIC VIROTHERAPY IN MALIGNANT PERIPHERAL NERVE SHEATH TUMORS

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Objective: Malignant peripheral nerve sheath tumors (MPNSTs) are a highly aggressive soft-tissue sarcoma amenable only to surgical resection. Conditionally replicating oncolytic herpes simplex viruses type-1 (oHSVs) are a promising alternative treatment. We previously showed that basal IFN and NF-kB signaling upregulates interferon stimulated gene (ISG) expression and that this restricts efficient virus infection and cell-to-cell spread in ~50% of tested MPNSTs. Stimulator of Interferon Genes (STING) integrates DNA sensor activity and is important in triggering interferon signaling in infected cells. We sought to identify STING's potential role in oHSV resistance and its contribution to basal ISG upregulation in MPNSTs.

Methods: oHSV-sensitive and resistant cell lines were assayed for level of STING activity, and STING-knockdown cell lines were generated.to evaluate the impact upon the cell-to-cell spread and viral replication of first and second-generation oHSVs. In addition, the impact of STING knockdown upon basal ISG expression was evaluated.

Results: We show that the level of STING activity in human MPNST cell lines is predictive of oHSV sensitivity, and that resistant cell lines have intact mechanisms for the detection of cytosolic dsDNA. Furthermore, we show that STING downregulation renders oHSV-resistant MPNSTs sensitive to oHSV infection and cell-to-cell spread. Our data show that STING knockdown makes previously resistant cells susceptible to next-generation chimeric oHSV infection; however, these knockdown cells maintain their restriction to older first-generation oHSVs. Finally, while STING is important for oHSV recognition and a rapid anti-viral response in resistant tumor cells, it is not integral to basal ISG upregulation—indicating that other pathways contribute to basal IFN signaling and ISG upregulation in MPNSTs.

Conclusion: These data broaden our understanding of the intrinsic pathways in MPNSTs, their role in oHSV resistance, and offer potential targets to potentiate oncolytic virus activity.

Poster 256 3042150

S-100 EXPRESSION AS A POSSIBLE PROGNOSTIC FACTOR FOR MALIGNANT PERIPHERAL NERVE SHEATH TUMOR

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Objective: Malignant peripheral nerve sheath tumors (MPNST) is a rare sarcoma thought to have neural origin from the perineural cells, frequently associated to type 1 neurofibromatosis (NF1). They are a particularly challenging group of sarcomas to treat. As they originate from the neural tissue, malignant cells have a direct access to neural infiltration and dissemination.

In combination with the high-grade nature of MPNST, when these sarcomas recur or metastasize, prognosis is poor. S-100 expression has been mentioned as prognostic marker. We sought to analyze the impact of this marker in our population of patients.

Methods: We've performed a retrospective analysis of patients treated consecutively at our center with the diagnosis of MPSNT between 2008 and 2017. Demographic, pathologic and treatment data were determined, and prognostic factors were analyzed using de Kaplan-Mayer method. S-100 expression was determined as equivocal, absent, focal, multifocal and diffuse.

Results: Thirty-three patients were identified. There was an equal distribution of gender (17 women) with a median age of 44 years. Ten patients had NF1. Most lesions were in the lower limb (24 cases) and the second most commonly involved area was the head and neck (8 patients). At presentation, only 27 patients had potentially resectable locoregional disease with a median size of 9 cm. Neoadjuvant therapy was used in 6 cases. Ten patients were referred after surgery. Formal nerve resection during surgery was described in 11 patients. Only 21 patients had negative margins after the first surgery. In most cases, MPSNT was classified as high grade.
Recurrence occurred in 18 patients, most commonly as metastasis. Locoregional recurrence occurred in 6 patients while lung metastases occurred in 13 cases. Overall survival (OS), disease specific survival (DSS) and disease-free survival (DFS) at 5 years were respectively 48%, 56% and 38%.
Nerve resection during surgery did not influenced DSS and DFS. Survival according to grade was different albeit not statistically. Margin positivity influenced recurrence ($p<0.001$), tumor size and recurrence adversely affected DSS ($p=0.030$ and $p=0.013$ respectively). In our cohort, NF1 patients did not had worst outcome. S-100 expression correlated with DSS ($p<0.001$). Tumors with equivocal or negative expression had worse outcomes and patients with multifocal expression had more favorable outcomes.

Conclusion: These results overlap previous described experiences. Although small, this group is representative of larger cohorts regarding patients' characteristics namely the percentage of patients with NF1 (30%). Recurrence occurs mostly as metastases and disease survival is adversely affected. These findings suggest MPSNT is, very early on, a systemic disease requiring innovative therapies. Level of S-100 grade of expression correlates with prognosis. Nevertheless, the number of patients is to small for definitive conclusions. Due to the rarity of this entity, collaborative efforts should be at the center of research in MPSNT and new therapies are a crucial.

Poster 257 3005918

STAGING AND SURVEILLANCE OF MYXOIDLIPOSARCOMA: IS CT SCAN ENOUGH?

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Objective: Myxoidliposarcoma, unlike other sarcoma subtypes, has a propensity for extra-pleural metastases. While the ideal imaging modality and schedule for detection of metastatic disease has yet to be established, CT scan of the chest/abdomen/pelvis (CT c/a/p) has become an accepted practice. This is in contrast to chest imaging alone, which is the standard for staging and surveillance of other soft tissue sarcomas. However, recent literature suggests that even this may be inadequate, particularly in the setting of bone and soft tissue extremity metastases. **I**n this study we review patients with metastatic myxoidliposarcoma from our institution, describe the patterns of metastasis, and assess the imaging modalities used for diagnosis. Our goal was to assess the ability of CT c/a/p to adequately assess metastatic disease in this population.

Methods: Using our institute's prospective registry, we identified 169 patients diagnosed with myxoidliposarcoma between 2000-2016, of which 32 had metastatic disease. We then performed a detailed retrospective review of the 31 patients whose records were available, including clinical visits and imaging reports related to the diagnosis of each patient's metastases. We recorded timing and location of metastatic lesions, reasons leading to diagnosis of metastasis, and imaging modalities used in diagnosis. Anatomic locations of metastases were classified into: pulmonary, soft tissue, bone, retroperitoneal, intra-peritoneal, solid organ, and lymph node.

Results: Of the 31 patients available for chart review, the average follow up was 73 months from sarcoma diagnosis (range 2-182mo). Initial diagnosis of M1 status was made at presentation on staging CT in 3/31 (10%), on surveillance CT in 15/31 (48%), or on imaging obtained in response to patient-reported symptoms in 13/31 (42%). Average disease free survival was 48 months (range 0-143 mo), with 15/31 (48%) of patients having metastases in multiple anatomic locations upon initial M1 diagnosis.
The proportion of patients developing metastases in each anatomic location are presented in Table 1. Average number of anatomic sites of disease per patient was 3.5 (range 1-7), with only 5/31 (16%) of patients having only 1 anatomic site of

metastasis (2 pulmonary, 3 soft tissue). The most common location diagnosed from self-reported symptoms was soft tissue (67%), and the most common location diagnosed incidentally was bone (92%). Fourteen patients had bone metastases; however, only two with a blastic presentation were identified on CT. Of the remaining 12 diagnosed on MRI, 11 had a CT scan and 7 had a bone scan within 1 month of diagnosis, all of which reported no evidence of bone metastasis. Four patients with spinal metastasis required urgent decompression upon identification (2 symptomatic, 2 incidental) due to cord compression from epidural extension. Additionally, many lesions reported as soft tissue masses on CT, were subsequently reported as bone lesions with associated soft tissue masses on MRI (Figure1).

Conclusion: With 58% of patients having metastatic disease identified outside of surveillance imaging, the diversity of metastatic locations, and the significant failure of CT and bone scan to identify bone metastases, this study quesitons the adequacy of CT scan for evaluation of metastatic disease. Furthermore, given the heterogeneity and paucity of extremity imaging in our cohort, the rate of soft tissue and bone metastases are likely underestimated. In addition to identifying metastatic disease, knowing the extent of disease is important when considering metastatectomy in the setting of presumed solitary metastasis, or preventing catastrophic complications such as those seen with spinal metastases. Further investigation is needed to determine the ideal imaging modality and schedule for staging and surveillance of myxoidliposarcoma, with consideration of whole body MRI for screening of bone and extremity soft tissue metastases.

Anatomic Location of Metastasis	Number of Patients (n=31)	Description
Soft Tissue	26 (84%)	Abdominal/Chest Wall=15 Pelvis=11 Lower Extremity/Groin=8 Back/Paraspinal=6 Mediastinal=6 Upper Extremity/Axillary=2
Pulmonary	21 (68%)	
Intra-Abdominal	15 (48%)	
Solid Organ	15 (48%)	Liver=6 Heart=4 Pancreas=4 Brain=1 Adrenal=1 Colon=1
Bone	14 (45%)	Spine=13 Pelvis/Sacrum=10 Long Bone=7 Other=3
Lymph Node	10 (32%)	
Retroperitoneal	9 (29%)	

Table 1. Classification of metastatic locations in myxoidliposarcoma, displayed as number of patients with metastatic deposit in given anatomic location.

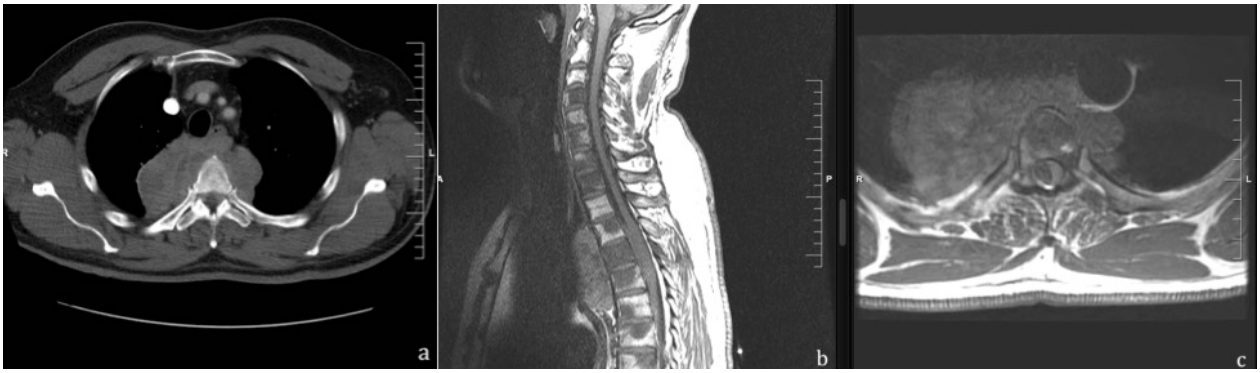

Figure 1. Paravertebral thoracic soft tissue metastatsis noted on surveillance CT scan (a) 58mo after initial diagnosis of myxoidliposarcoma of the thigh. Follow up MRI scan (b-c) done the same day revealed this to be a thoracic vertebral metastatsis with paravertebral soft tissue and epidural extension. CT scan and subsequent bone scan 4 days later both reported no evidence of bony metastasis despite extensive spinal metastasis seen on MRI.

Poster 258 3032305

DEVELOPMENT OF A MODEL TO PREDICT OVERALL SURVIVAL OF MYXOID LIPOSARCOMA PATIENTS

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Objective: Predicting patient outcomes in clinical oncology is significant for decision making from both a patient and clinician perspective. While some predictors such as clinical stage (i.e. stage 1-4) have been developed to aid in patient prognostication based on limited patient specific clinical features, improved outcomes predictions are likely possibly if more detailed patient or treatment specific factors are taken into account. Because it is difficult for clinicians to utilize predictive models which use multiple patient variables, simple ones like clinical stage are often more widespread. Nomograms seeking to incorperate numerous predictive variables have been created for outcomes prediction, but can be cumbersome to use. Recent advances in machine learning methods (or artificial intellifence) has made it feasable to create highly predictive and usable models. Our goal is to develop an accurate and user-friendly interactive model based on general machine learning practices which is predictive of patient overall survival at 5-years using a publicly available database comprising factors easily assessed by clinicians.

Methods: Cases of patients diagnosed with myxoid or round cell liposarcoma were collected from both the SEER (Surveillance, Epidemiology, and End Results Program) database and an institutional case repository. All patients in our analysis had tumors originating from the lower extremities, and information available related to patient clinical status, treatment received, and survival outcomes at 5-years. Patient information was evaluated to determine it's importance for predicting survival status at 5-years, and only important features were utilized. Various machine learning models including neural networks, support vector machines, and decision trees were evaluated in addition to a traditional logistic regression model for their ability to predict 5-year overall survival. All models were trained on a subset of patients in the SEER dataset, and validation of how well the models predicted 5-year overall survival was performed on both the SEER and institutional cohorts. An optimal prediction model was chosen and it's user friendly interface was created using free open-source software.

Results: Important features for determining overall survival included patient age at diagnosis, tumor size, tumor histology, tumor grade, presence of metastasis at diagnosis, type of surgery undergone, and if the patient received radiation and/or chemotherapy. Presence of positive lymph nodes at diagnosis was not important. Multiple predictive models were evaluated, with a Bayesian linear model determined to be the best at predicting overall survival at 5 years. The model was validated using patients in the SEER dataset and its accuracy was 80.6%, positive predictive value (PPV) 85.5%, negative predictive value (NPV) 76.7%, and area under the curve (AUC) 71.0%. When validated using institutionally collected data, the model had an accuracy of 87.1%, PPV of 87.7%, NPV of 80.0%, and AUC of 65.8%. A publicly available user-interface for the model was created allowing clinicians to access it on any web browser.

Conclusion: Using a large publicly available database we were able evaluate multiple machine learning models to develop an optimal predictive model for overall survival. The model accounts for patient clinical and treatment variables and predicts overall survival at 5 years. Using a similar approach, other survival outcomes could feasibly be predicted for oncologic patients and made available in a user-friendly manner. This can serve as a useful clinical and research tool for personalizing patient prognosis beyond traditional population level tools such as clinical stage.

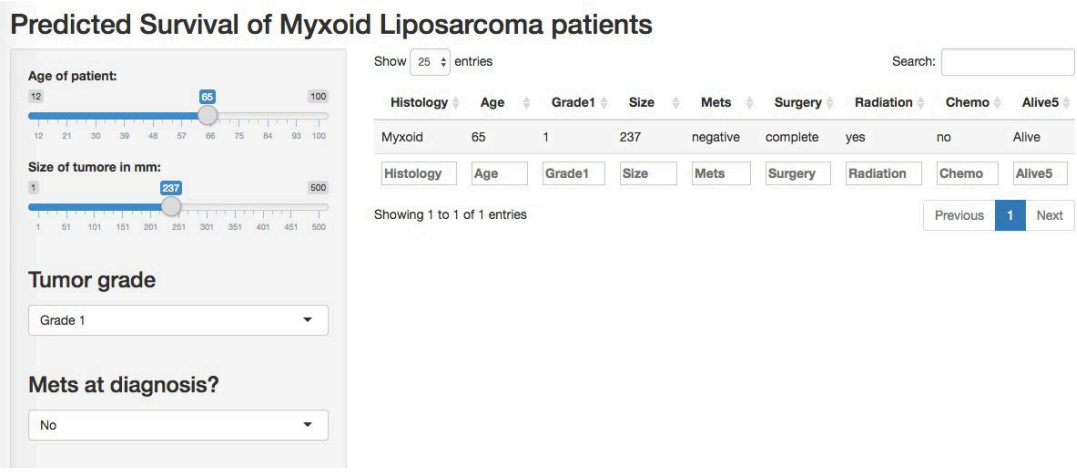

Image 1: Sample screenshot of user friendly, publicly available outcomes prediction tool. Patient specific clinical and treatment related variables are inputed for prediction of 5-year overall survival.

Patient Characteristics

	SEER	MGH
	Number (%)	Number (%)
Age: Median Range	49 12-91	40.5 19-80
Histology: Myxoid Round Cell	507 (91.4) 48 (8.6)	60 (85.7) 10 (14.3)
Grade: 1 2 3	197 (35.4) 256 (46.1) 102 (18.5)	6 (8.6) 56 (80.0) 8 (11.4)
Size (cm): Median Range	11 0.5-50	9 1.5-25
Positive Metastasis	35 (6.3)	4 (5.7)
Surgery: None Partial Complete	30 (5.4) 202 (36.4) 323 (58.2)	1 (1.4) 3 (4.3) 66 (94.3)
Received Radiation	269 (48.5)	61 (87.1)
Received Chemotherapy	72 (13.0)	33 (47.1)
Survival at 5 Years: Alive Deceased	393 (70.8) 162 (29.2)	58 (82.9) 12 (13.1)

Table 2: Predicted vs Actual outcomes for SEER validation set

	Actual Alive	Actual Deceased
Predicted Alive	110	25
Predicted Deceased	7	23

Poster 259 3042699

TIME TRENDS AND PROGNOSTIC FACTORS FOR OVERALL SURVIVAL IN MYXOID LIPOSARCOMA: 901 CASES WITH A MEDIAN FOLLOW-UP OF 8 YEARS

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Objective: The purpose of this study was to characterize the clinical course of myxoid liposarcoma (MLS) and further substantiate known and possible new prognostic factors.

Methods: A nationwide population-based study was performed to analyze data obtained by the Netherlands Cancer Registry of patients with localized (n=851) and metastatic (n=50) disease treated between 1989 and 2016. Overall Survival (OS) was used as primary endpoint and was estimated by Kaplan–Meier survival curves. Prognostic factors were identified by Multivariable Cox-proportional hazards modelling.

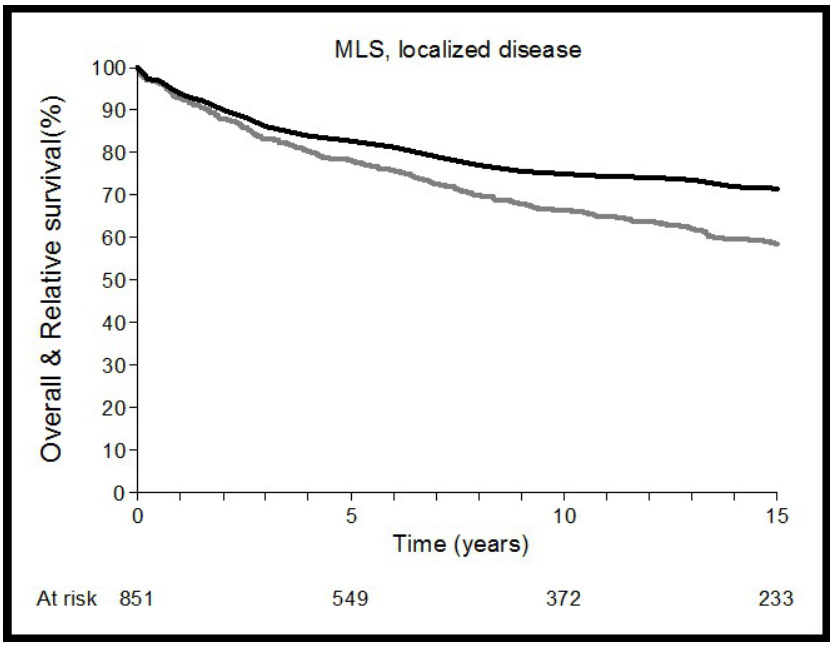
Results: There was a slight predilection for men (56%), a median age of 49 years and approximately two-thirds originating in the lower extremity. With respect to localized disease, OS rates of 93%, 83%, 78% and 66% after 1, 3, 5 and 10 years, respectively were observed. Relative Survival rates at the same time points were 94%, 86%, 83% and 75%. The prescription rate of RT doubled within the timeframe of this study. Preoperative RT gradually replaced postoperative RT. The higher the age, the higher was the chance of tumors with a round cell component >5% and subsequent decreased OS. A previously unreported correlation between tumor localization and OS in MLS was found; as compared to localizations in the lower extremity, the upper extremity shows superior outcome, while the trunk and “other” localizations are associated with inferior OS. Age and tumor size >5cm were confirmed as independent prognostic factors for OS. Significant improvement of OS has been observed in both localized and metastatic disease.

Conclusion: Older patients are at extra high risk because they have higher probability to have RC tumors in addition to their decreased age-related prognosis. Age, tumor size and tumor localization are independent prognostic factors for OS in MLS patients with localized disease.

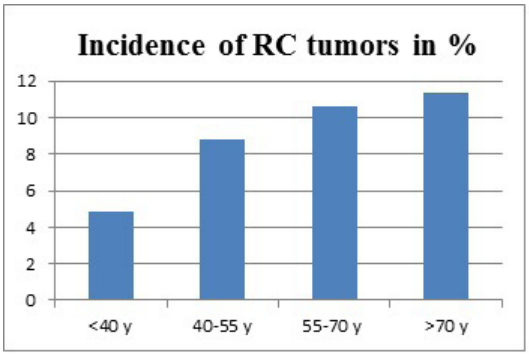
Localized myxoid liposarcoma: prognostic factors for overall survival

		Univariate analysis			Multivariate analysis		
Factor	n=	HR	95% CI	P	HR	95% CI	P
Age (continuous)	851	1.053	1.045-1.061	0.000	1.050	1.041-1.060	0.000
Tumor size >5cm	773	2.416	1.732-3.370	0.000	2.176	1.536-3.083	0.000
Round cell component >5%	851	1.664	1.199-2.308	0.002	1.425	0.996-2.039	0.053
Male gender	851	1.252	1.004-1.562	0.046	1.228	0.960-1.570	0.103
Positive resection margin	440	0.924	0.567-1.506	0.751			
Localization*	851			0.000			0.000
Trunk	185	1.739	1.336-2.263	0.000	1.277	0.953-1.712	0.102
Upper Extremity	53	0.790	0.466-1.341	0.383	0.794	0.433-1.455	0.455
Other	86	3.779	2.824-5.058	0.000	2.755	1.896-4.003	0.000
Radiotherapy	851	0.725	0.582-0.904	0.004	0.936	0.723-1.210	0.612

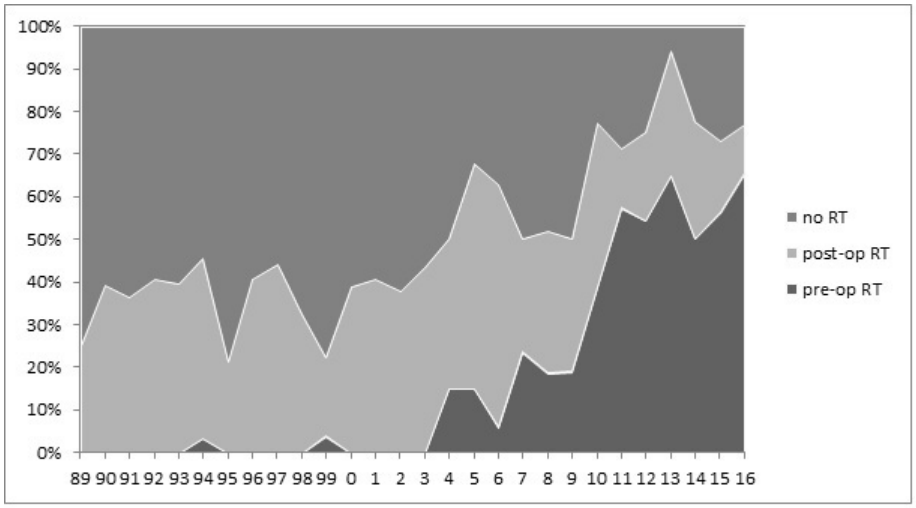
*Lower Extremity (n=551) was used as reference localization. Abbreviations: HR= Hazard Ratio, CI= Confidence Interval



Overall survival (grey) and relative survival (black) of myxoid liposarcoma patients with localized disease



The incidence of tumors with a round cell component >5% per age group in localized disease



The use and the timing of radiotherapy during the study period per year in localized disease

Poster 260 3042648

SHORT TAU INVERSION RECOVERY MAGNETIC RESONANCE IMAGING FOR STAGING AND SCREENING IN MYXOID LIPOSARCOMA

*Alexander Chien[2]; Craig Zuppan[3]; Li Lei[3]; **Troy G. Shields**[1]; Joseph Elsissy[1]; Peter Pham[2]; Lee M. Zuckerman[1]*
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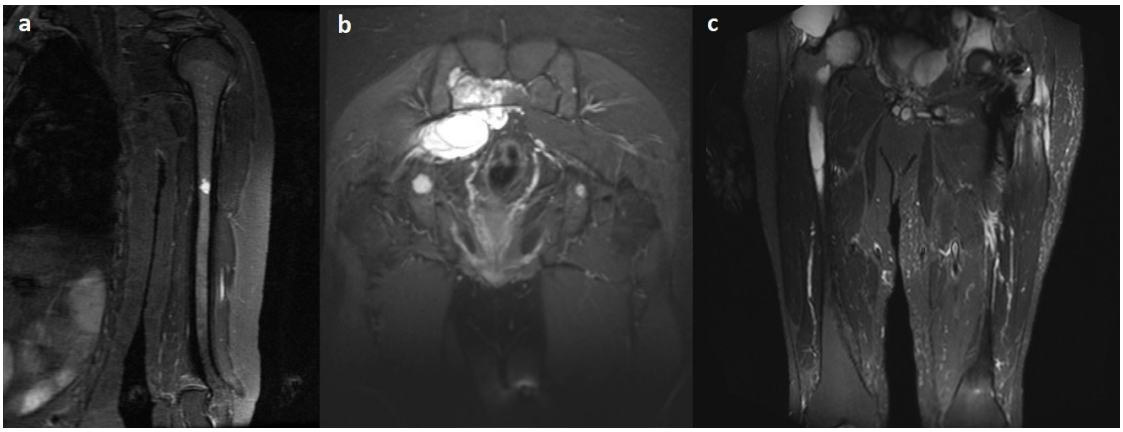
Objective: Myxoid liposarcoma has a propensity to metastasize to osseous sites. Reports in the literature suggest that FDG-PET, CT, and bone scan are insensitive and that MRI is the preferred modality for detecting metastatic disease. Whole body MRI is relatively time consuming to perform when multiple sequences are used with standard equipment. We present our initial experience utilizing whole body MRI to evaluate for metastatic myxoid liposarcoma and propose whole body STIR sequences as a methodology for screening for metastatic disease.

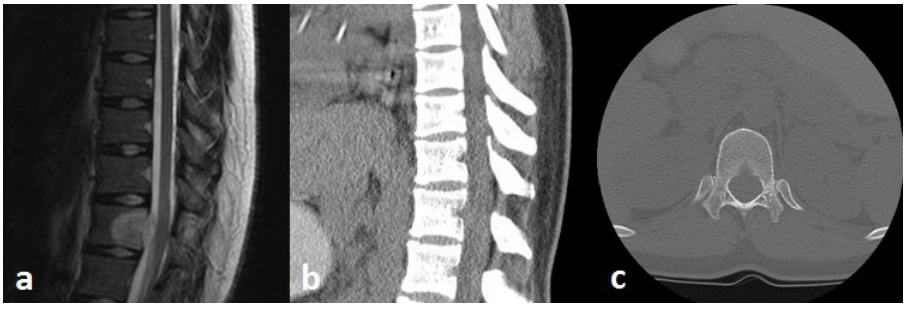
Methods: A retrospective review all patients with myxoid liposarcoma who underwent whole body MRI examinations was performed between 2012 and 2018. All patients underwent additional imaging with a CT chest, abdomen, and pelvis, whole body PET-CT and whole body bone scan. The number and locations of the sites found by imaging as well as round cell component of the sites sampled were evaluated.

Results: We found a total of 48 osseous only lesions, including 8 osseous lesions extending into the surrounding soft tissues by MRI. None of the osseous only lesions were detected by FDG-PET or CT. FDG-PET and CT were able to identify only some of the osseous lesions that extended outside of the bone. No pulmonary metastases were found. STIR and T1 fat suppressed contrast enhanced images provided the best contrast of the metastases compared to the normal bone marrow. Multiple metastatic lesions were noted to have <5% round cell component on pathologic evaluation. Whole body MRI utilizing STIR only sequences decreased imaging time by 83.6%.

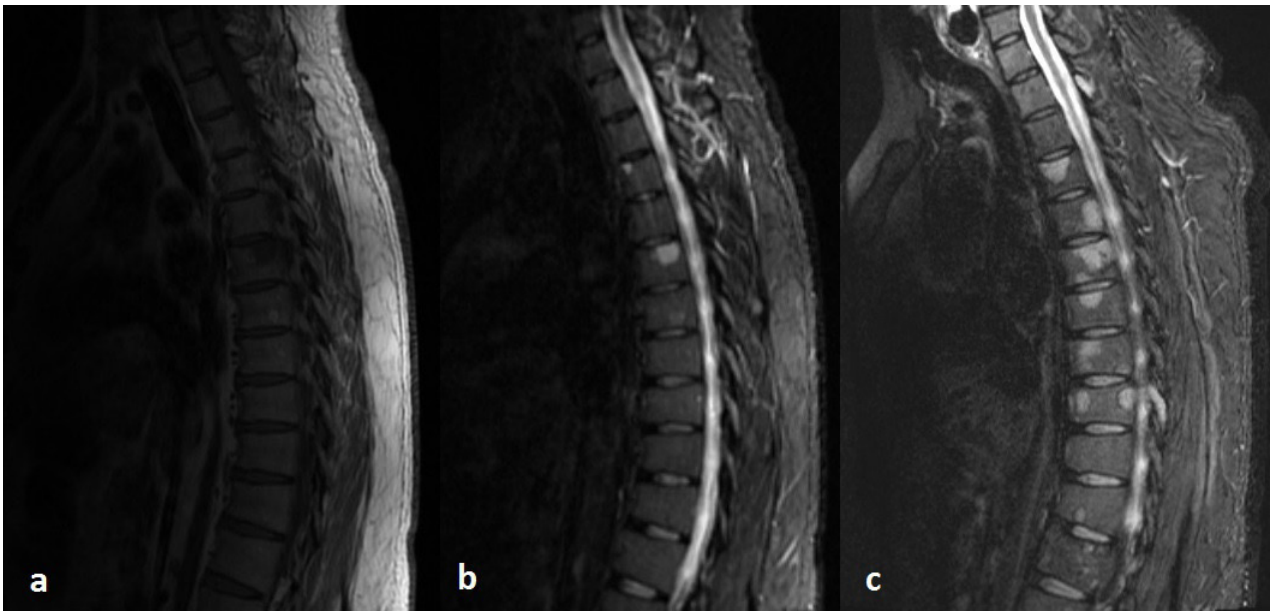
Conclusion: The MRI appearance of metastatic myxoid liposarcoma closely mimicked the primary tumor. We support the literature's suggestion that MRI is the preferred modality to screen for metastatic myxoid liposarcoma, and that it should be used regardless of round cell component. STIR sequences demonstrated the lesions the best and can be exclusively used during staging and screening.



Images depicting the wide view coronal images obtained with the STIR only protocol. (a) Images of the left humerus that include the chest with ribs and scapula. A metastatic lesion is noted in the humeral shaft. (b) Images of the pelvis demonstrating a sacral tumor with soft tissue extension and well as bilateral pubic rami tumors. (c) Images of both femurs after the patient's disease had progressed with diffuse osseous disease of the pelvis and femurs in addition to soft tissue metastases.



Metastatic bone disease in the spine with cortical breakthrough not noted on CT. (a) Sagittal STIR MRI of T12 demonstrating a spinal metastasis extending into spinal canal. (b) Corresponding sagittal soft tissue window CT and axial bone window CT images of T12. The osseous portion and soft tissue portions were not seen on CT.



Images depicting better visualization of metastases on STIR sequences when compared to T1 sequences. (a) T1 images of the thoracic spine with lesions at T2 and T4 that are not well visualized. (b) Corresponding STIR images with better visualization of the tumors. (c) Significant progression of disease with an increase in the size of the T2 and T4 lesions, in addition to multiple new tumors throughout the spine.

Poster 261 3042848

MANAGEMENT OF MYXOID LIPOSARCOMA: A SURVEY OF THE MEMBERS OF THE CONNECTIVE TISSUE ONCOLOGY SOCIETY

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Objective: Myxoid liposarcoma can occur throughout the body and is most commonly treated in the extremities and retroperitoneum. Metastatic myxoid liposarcoma has a propensity to invade the bone marrow. Multiple studies have shown that whole body magnetic resonance imaging (MRI) is the only reliable modality to detect bone marrow metastases. Round cell componenet has been felt to affect overall prognosis and may impact treatment options. This study aims to evaluate the perspectives of the members of the Connective Tissue Oncology Society on how to stage and treat myxoid liposarcoma, and to determine any discrepancies in care.

Methods: A link to a 16-question survey through SurveyMonkey was sent to the members of the Connective Tissue Oncology Society. A list of questions is noted in Table 1. Surveys were obtained from Hematology/Oncology, Surgical Oncology and Orthopaedic Oncology.

Results: A total of 89 members responded to the survey. There was no significant difference in the number of specialists that replied to the survey. The majority of respondents worked in a University setting that was associated with a cancer center. 64% were located in Northern America. Most practitioners staged and monitored the patient with an MRI of the primary tumor site and with a CT of the chest, abdomen and pelvis. Only 18% of respondents staged the patient with a whole body MRI when the round cell component was <5% and 23% when the round cell component was >5%. If the round cell component was >5%, 54% would recommend chemotherapy versus 10% if the round cell component was <5%. Most respondents would recommend repeat surgery and radiation to the area if there were positive margins, with a 20% increase in recommending chemotherapy if the round cell component was >5%. 75% would monitor the patient for at least 10 years.

Conclusion: This study demonstrates that members of the Connective Tissue Oncology Society are more likely to be more aggressive with treatment and monitoring the patient if the round cell component is >5%. This study also highlights that only a small minority of practitioners are using whole body MRI to monitor the patient for bone marrow disease despite literature that supports this. This finding demonstrates that further education is necessary regarding the utility of MRI. Further studies could evaluate potential road blocks to implementing a whole body MRI protocol.

Survey questions

What is your speciality?
What best described your practice setting?
Where is your practice located?
Are you affiliated with a cancer center?
How many years have you been in practice?
On average, how many myxoid liposarcomas do you treat per year?
What part of the body do you typically treat these tumors?
What staging studies do you routinely order if the round cell component is
What staging studies do you routinely order if the round cell component is >5%, and how frequently do you order these tests during the first two years?
Who typically performs the biopsy of the primary tumor?
What is your preferred method of biopsy?
What treatment do you routinely recommend for non-metastatic disease if the round cell component is <5%?
What treatment do you routinely recommend for non-metastatic disease if the round cell component is >5%?
How many years do you monitor the patient for recurrence and/or metastatic spread?
If a tumor with
If a tumor with >5% round cell component is resected with positive margins, what further treatment do you recommend?

Poster 262 3036403

ONCOLOGICAL OUTOMES OF MYXOID LIPOSARCOMA IN EXTREMITIES AND TRUNK AFTER WIDE EXCISION AND ADJUVANT TREATMENT

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Objective: This study aimed to investigate oncologic outcomes of myxoid liposarcoma treated with wide excision and adjuvant therapies with a special emphasis on local control rate and initial metastasis pattern.

Methods: We retrospectively reviewed medical records of 41 myxoid liposarcoma patients (26 males and 15 females) without metastasis at diagnosis who were treated and followed up over 24 months in our institution. Mean age of the population was 46.7 years (range, 19.5-77.9) and mean follow-up duration was 66.8 months (range, 24.7-130.4). All patients underwent wide excision and had R0 resection margin. Thirty-four patients underwent adjuvant treatment (19 chemotherapy, 34 postoperative radiation therapy, and 17 both).

Results: Three patients (7.3%) died during follow-up period due to metastatic diseases. The overall survival rate at 5 and 10 years was 92.9% and 87.1%, respectively. Local recurrence developed in 1 patient (2.4%) who already had developed several local recurrences prior to referral to our institution. Six patients (14.6%) developed distant metastases, and the median interval between initial diagnosis and distant metastases was 26.3 months (range, 22.6-32.2 month). All distant metastases were extrapulmonary and half of them were bone metastasis. Univariate analysis showed distant metastasis (P<0.001) and round cell component more than 5% (P=0.025) as statistically significant variables predictive of disease-specific survival.

Conclusion: The results of our study suggest that primary site of myxoid liposarcoma can be satisfactorily controlled after wide excision and proper adjuvant treatments. As noted, all initial metastases in our study were extrapulmonary metastases, and half of them were in the bone. Clinicians should pay special attention to proper imaging modality for surveillance of myxoid liposarcoma considering those unique initial metastasis locations.

Poster 263 3042698

OVERCOMING TRABECTEDIN RESISTANCE OF MYXOID LIPOSARCOMA BY COMBINING IT WITH PPARγ AGONISTS

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Objective: Myxoid liposarcoma (MLS) is a specific histological subtype of liposarcoma. It accounts for about 10% of all adult soft tissue sarcomas. Its pathogenesis is associated in more than 90% of cases with a specific chromosomal translocation t(12;16)(q13;p11), which produces the FUS-CHOP chimeric protein. MLS has been proven to be particularly sensitive to trabectedin (ET-743, Yondelis), a marine alkaloid isolated from the tunicate Ecteinascidia turbinata, approved in Europe and US for the 2nd line therapy of soft tissue sarcomas. A peculiar mechanism of action was proposed to explain the peculiar efficacy of trabectedin in MLS. In a set of patient derived xenograft of MLS, trabectedin was able to remove FUS-CHOP from its own target genes causing adipocytic maturation and tumor regression. (Di Giandomenico et al, Oncogene, 2014 Oct 30; 33(44): 5201-10). The absence of cumulative toxicity allows to prolong patient's treatment with trabectedin up to tumor progression (Saponara et al Exp rev of anticancer therapy 2016). At this point no effective agents are available on progression. PPARγ agonists have demonstrated pro-differentiation effects in MLS patients (Demetri G. et al Proc.Natl. Acad.Sci 1999, Pishvaian M. et al Cancer 2012), and a previous study in a transgenic mouse models of MLS suggested a possible synergy between trabectedin PPARγ agonists (Charytonowicz E. et al JCI 2012). In this study we aimed to test the combination of trabectedin with the PPARγ agonist pioglitazone in MLS xenograft resistant to trabectedin.

Methods: ML006 xenograft (with innate resistance to trabectedin), and ML017/ET xenograft (with acquired resistance to trabectedin) were treated with trabectedin 0.15 mg/kg iv every seven days for three times, pioglitazone 150 mg/kg po daily for 28 days or with their combination. For antitumor activity evaluation, tumor growth was measured with a caliper and the tumor weights (1 mm^3 = 1 mg) were calculated with the formula: length × $(width)^2/2$. Fifteen days after the last dose of trabectedin and 4 h after the last dose of pioglitazone tumors were collected from a separate group of mice to perform histological and molecular analyses.

Results: In ML006, trabectedin and pioglitazone as single agents had a comparable antitumor activity, with no tumor regressions observed. In the combination group, a late but impressive tumor regression followed by a long lasting tumor stability was observed. Combined treatment induced a stabilization followed by late tumor shrinkage. Tumor regrowth occurred in only one out of nine tumors. In ML017/ET model pioglitazone was completely inactive but when administered in combination with trabectedin a significant delay in tumor growth was observed. The histological analyses showed adipocytic maturation in tumors treated with pioglitazone alone or in combination but not in samples from mice treated with only trabectedin. In particular, in ML006 tumors that regressed after the combination treatment a diffuse mostly monovacuolated lipoblastic growth in myxoid matrix was observed (figure 1). The expression of adiponectin in PCR and Western Blot confirmed the histological observations. Pathways analysis showed that pioglitazone but not trabectedin was able to activate the adipogenic pathway in the two resistant xenografts.

Conclusion: The combination of trabectedin with pioglitazone was able to restore tumor response and adipocytic maturation in MLS xenografts that were or had become resistant to trabectedin alone. Gene expression profile, RT-PCR and Western Blot analysis confirm the reactivation of the adipogenic process at molecular levels. These preclinical observations prompted us to design a clinical study on the combination of trabectedin and pioglitazone in patients with MLS or dedifferentiated liposarcomas with stable or progressive disease after two cycles of treatments with trabectedin alone.

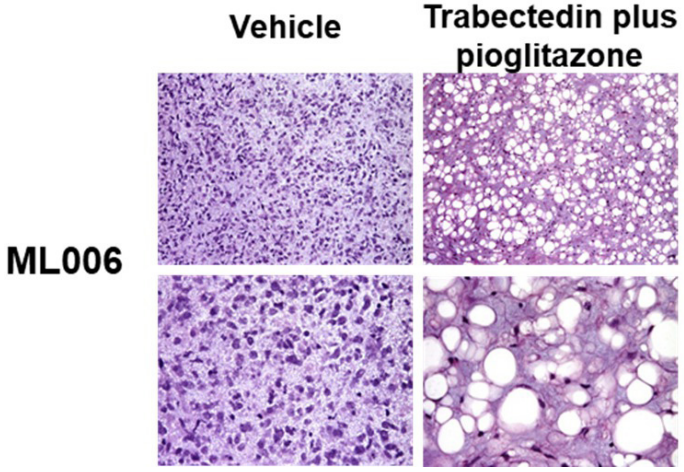

Figure 1 H&E sections of ML006 xenograft regressed after treatment with trabectedin and pioglitazone compared to those of a vehicle treated mouse

Poster 264 3042591

A COMPARISON OF ONCOLOGICAL AND SURGICAL OUTCOMES IN ENDOPROSTHETIC RECONSTRUCTION VERSUS ROTATIONPLASTY FOR PEDIATRIC LOWER EXTREMITY BONE SARCOMAS

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Objective: Pediatric bone sarcomas most commonly occur around the knee. Lesions that affect the distal femur or proximal tibia are amenable to either endoprosthetic reconstruction or rotationplasty following wide excision. Outcome studies have demonstrated similar patient function between these two approaches but the impact on oncological and surgical outcomes has not been compared.

Methods: Following ethics approval, patients treated for a bone sarcoma at our institution between June 2004 and December 2014 were identified via hospital database query. Inclusion criteria included appendicular location and a minimum 6 months of follow-up. Detailed chart review was carried out for patients that met our inclusion criteria with follow-up data collected until December 2016.

Results: We identified 115 patients with 116 primary sarcomas that met our inclusion criteria. In this cohort, 36.2% of lesions were located in the distal femur (n=42) and 13.8% in the proximal tibia (n=16). High grade osteosarcoma was the most common tumour pathology (n=51). All patients received adjuvant chemotherapy as per our institution's protocol. Of these patients, 38 were appropriate for limb-salvage surgery and underwent wide resection and either endoprosthetic reconstruction or rotationplasty. Patients were grouped by treatment and their outcomes compared. As shown in Table 1, patients in the endoprosthesis and rotationplasty groups were comparable at baseline. We found that selection of endoprosthetic reconstruction versus rotationplasty did not impact overall survival (see Figure 1). In the endoprosthesis group, 9 patients died with 2- and 5-year survival rates of 86.7% and 36.8% respectively. In comparison, 6 patients died in the rotationplasty group representing 2- and 5-year survival rates of 85.6% and 68.1% (X^2=0.339, p=0.561). Similarly, when considering both development of metastatic disease and local recurrence, surgical approach did not have a statistically significant impact (see Figure 2). 2- and 5-year event-free survival in the endoprosthesis group was 66.0% and 52.8% while values were 66.7% and 58.3% in the rotationplasty patients (X^2=0.001, p=0.975). We did, however, find a difference in local recurrence rates. While margins in all patients were negative, there were no local recurrences in the rotationplasty group and three local recurrences in the endoprosthesis group. While our numbers are small, these results suggest that endoprosthetic reconstruction may correlate with increased local recurrence rates, a negative prognostic factor. With regards to surgical outcomes, we report a higher complication rate in patients that received an endoprosthesis compared with a rotationplasty. Including all reasons for re-operation, 78.9% (n=15) of endoprosthesis patients required a minimum of one additional surgery compared with only 26.3% (n=5) of rotationplasty patients. The most common reasons for re-operation in endoprosthesis patients were wound breakdown/infection (n=6), limb length discrepancy (n=6) and periprosthetic fracture (n=2). Excluding limb length equalization procedures, average time to re-operation was 5.6 months (1 week to 23 months). Similarly, the most common reason for repeat procedure in rotationplasty patients was wound breakdown/infection though only two patients experienced this complication. Average time to re-operation in this group was 23.8 months (5 to 49 months).

Conclusion: Endoprosthetic reconstruction and rotationplasty are both viable limb-salvage options following wide resection of bony sarcomas located around the knee in children. It is accepted that both options provide good functional outcomes. While an endoprosthesis may offer a superior cosmetic result, this procedure is associated with a higher complication rate and may negatively impact local recurrence. Study of a larger number of patients is needed to determine whether sarcoma surgery including an endoprosthesis affects survival.

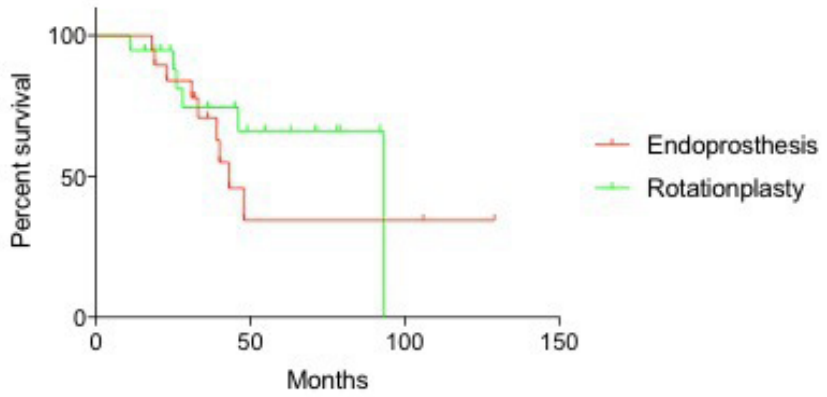

Figure 1: Overall survival using Kaplan-Meier analysis. No significant difference between the groups was identified (Log-Rank Test, Chi square 0.339, p=0.561).

Table 1: Patient demographics and oncological parameters at presentation

Surgical Group		Endoprosthesis (n=19)	Rotationplasty (n=19)
Tumour Pathology	Osteosarcoma	17	19
	Ewing Sarcoma	2	0
Gender	Male	9	9
	Female	10	10
Age at Diagnosis		12.1 years (Range 4-17)	11.7 years (Range 6-16)
Location of Primary Lesion	Distal Femur	16	15
	Proximal Tibia	3	4
Pre-operative Pathologic Fracture	Yes	0	4
	No	19	
Metastatic Disease at Presentation	No	14	15
	Lung only	2	2
	Skip metastasis only	2	1
	>1 site	1	1
Identified Genetic Syndrome	Yes	0	2
	No	19	17
Biochemical Markers	ALP (U/L)	336.5± 152.2	317.4 ±178.0
	LDH (U/L)	746.7±275.1	716.8±142.0
Tumour Volume at Presentation (cm^3)		419.2±441.8	597.7±418.0
% Tumour Necrosis	<90%	10	10
	>90%	9	8

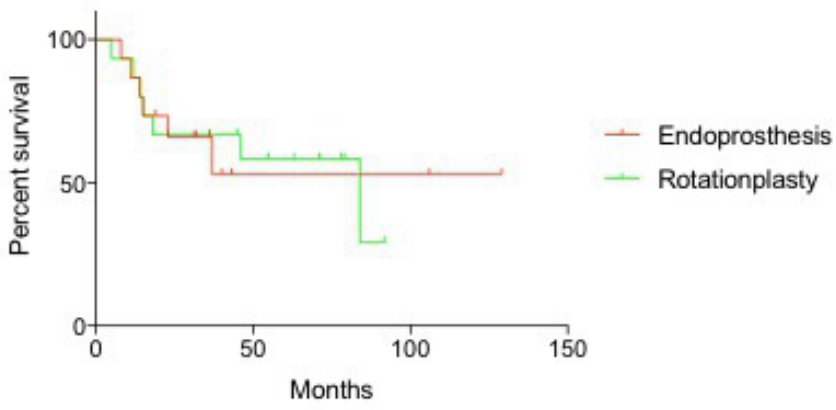

Figure 2: Event-free survival using Kaplan-Meier analysis. An event is considered development of local recurrence or a new distant metastatic deposit. Excludes patients that presented with metastatic disease. There is no significant difference between the groups (Log-Rank Test, Chi square 0.001, p=0.975)

Poster 265 3042779

PRESS FIT VS. CEMENTED FEMORAL STEMS IN ARTHROPLASTY FOR ONCOLOGIC INDICATIONS

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Objective: Limb salvage has largely replaced amputation in the treatment of primary bone tumors and encompasses multiple reconstructive modalities. Studies have shown varied success in arthroplasty with both cemented and press fit stems. Currently there is no consensus regarding which method is superior. The cemented stem provides immediate, stable

fixation that is not affected by adjuvant chemotherapy or radiation but carries a known risk of aseptic loosening. Press fit stems allow for ingrowth of native bone, hypothetically creating a durable reconstruction, which is particularly appealing in younger, more active patients. However, inadequate osteointegration and stress shielding may lead to need for revision. There remains a need for analysis of which components, surgical techniques, or patient factors contribute to failure, and how this should influence choice of reconstruction modality in a given patient. We aim to determine whether the rate of failure differs between cemented and press fit femoral stems and the predictors of failure in each stem.

Methods: We retrospectively identified all patients treated between 1990-2015 with resection of primary bone tumor and subsequent arthroplasty with either a cemented or press fit femoral stem. Patients were excluded if they had previous reconstruction at the site, the implant was placed in allograft rather than native bone, or if inadequate imaging was available for analysis. Demographics, treatment, and follow up data were collected. Eighty-one patients (31 male, 50 female) were included; the median age at date of surgery was 54 years. For image analysis, post-operative AP radiographs were measured using the PACS system. In press fit stems, the width of the canal, stem, and diaphysis were measured at the base, middle, and distal end of the stem. In cemented stems, the stem, diaphysis, and width of the cement mantle were measured at the base, middle, and distal end of the stem. To determine the stem to canal ratio, stem to diaphyseal ratio, and cement mantle width, measurements at the base, mid, and distal sites were averaged. Failure was defined as any event that led to revision of the implant (fracture, hardware failure, loosening, dislocation, mechanical failure, infection). The Mann-Whitney test was used for continuous variables and Fisher's exact test for categorical variables. Factors that reached significance, defined as $p<0.05$, were then analyzed via logistic regression to determine an odds ratio.

Results: There was no significant difference in overall failure rates between patients with a press fit stem versus cemented stem ($p=0.783$). The median stem to canal ratio in press fit implants was 0.91 (IQR 0.88-0.94) and 0.72 (0.63-0.76) in cemented, and median cement mantle width was 2.75 mm (IQR 2.0-3.5). Neither stem to canal ratio, stem to diaphyseal ratio, nor cement mantle width were associated with a higher rate of implant failure in press fit or cemented stems, respectively. BMI was associated with an increased risk of failure in press fit stems (OR 1.25, 95% CI 1.05 -1.50), and age was inversely related to increased risk of failure in cemented stems (OR 0.92, 95% CI 0.87-0.97).

Conclusion: The all-cause failure rate was not significantly different in arthroplasty with press fit versus cemented femoral stems, suggesting that both are appropriate methods of post-resection reconstruction and can be selected according to relevant patient factors. Age was inversely associated with failure in cemented stem, indicating that press fit is the more appropriate option for younger, active patients. However, the stability of a cemented stem may improve durability and survival in patients with higher BMI.
There were several limitations to this study, including its retrospective nature and limited sample size. Additionally, surgical procedures were performed by multiple surgeons within our institution using several implant systems. Despite the limitations, these preliminary results provide direction for further investigation.

Table 1. Baseline Characteristics

Variable	Press Fit	Cemented
	Median (IQR)	*Median (IQR)*
Age (years)	51 (37-57)	60 (48-72)
BMI (kg/m²)	26.5 (23.3-29.3)	29.9 (24.3-32.6)
Stem:canal	0.91 (0.88-0.94)	0.72 (0.63-0.76)
Stem:diaphysis	0.51 (0.46-0.53)	0.43 (0.39-0.46)
Cement Mantle (mm)	---	2.75 (2-3.5)
	n (%)	*n (%)*
Gender		
Female	23 (68)	27 (57)
Male	11 (32)	20 (43)
Smoker	10 (29)	7 (15)
Diabetes Mellitus	3 (9)	7 (15)
Site		
Proximal femur	15 (44)	28 (60)
Distal femur	19 (56)	19 (40)
Chemotherapy	11 (32)	21 (45)
Radiation	13 (38)	16 (34)
Infection	4 (12)	8 (17)
All cause failure	8 (24)	9 (19)

Table 2. Bivariate analysis of predictors of failure

Variable	Press Fit	Cemented
	p-value	*p-value*
Age	0.16	**<0.001**
BMI	**0.02**	0.94
Site	1	0.13
Smoker	0.67	0.32
Diabetes	1	0.611
Chemotherapy	1	0.48
Radiation	1	0.70
Stem:canal	0.61	0.30
Stem:diaphysis	0.79	0.21
Cement mantle	----	0.49
	OR (95%CI)	*OR (95%CI)*
Age	----	0.92 (0.87-0.97)
BMI	1.25 (1.05-1.50)	---

Poster 266 2986857

THE IMPACT OF FACILITY VOLUME ON SURVIVAL IN PATIENTS WITH PRIMARY BONE TUMORS OF THE VERTEBRAL COLUMN

Alexander L. Lazarides[1]*; Brian L. Dial*[1]*; David Kerr*[1]*; John Steele*[1]*; Whitney Lane*[1]*; Dan Blazer III*[2]*; William Eward*[1]*; Brian Brigman*[1]*; Melissa Erickson*[1]*; Sergio Mendoza*[1]

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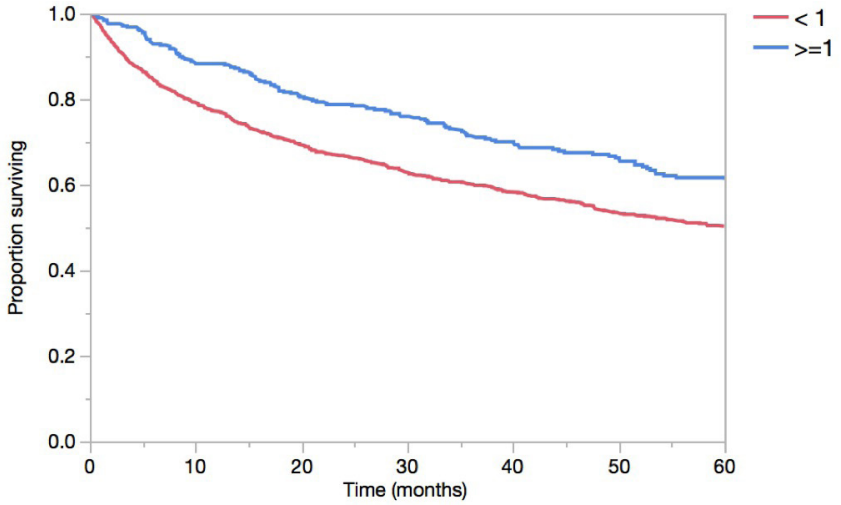
Objective: Primary bone tumors of the vertebral column (BTVC) are rare and represent a challenge when considering management options. It stands to reason that these complicated tumors would be best treated at high volume centers. However, this has not been well established. We investigated the largest registry of primary bone tumors, the national cancer database (NCDB); our goal was to investigate whether facility patient volume is associated with overall survival in patients with primary BTVCs. Specifically, our goal was to (1) investigate the differences in demographics and tumor characteristics in patients receiving treatment at high- and low-volume facilities (2) estimate the 5-year survival by facility volume; (3) examine differences in the treatment characteristics of high- and low-volume facilities; and (4) examine the independent impact of facility volume on survival.

Methods: We retrospectively analyzed 941 patients in the NCDB from 2004 through 2015. Patients were stratified based on per year facility volume for primary BTVCs. Then, long-term survival between groups was evaluated using the Kaplan-Meier (KM) method with statistical comparisons based on the log-rank test. Multiple variables were analyzed between the two groups.

Results: We identified 941 patients presenting with primary BTVCs; histological diagnosis was chondrosarcoma (n=243), chordoma (n=407), Ewing's sarcoma (n=164) and osteosarcoma (n=127). 199 patients were treated at HVCs (>1 case annually) and 742 were treated at low-volume centers (LVC). Patients treated at high-volume centers were, on average, younger (48 vs 52 years, p=0.0076), more likely to be insured (p<0.0001), and more likely to travel farther to the treating facility (mean 278 vs 47 miles, p<0.0001). There were no significant differences between high- and low-volume facilities regarding tumor characteristics. In a KM survival analysis, patients treated at high-volume facilities had better survival, with five-year survival rate of 67.7% vs. 58.7% (p=0.0262). Patients treated at HVCs were also more likely to receive surgical treatment (87% vs. 79%, p=0.0191), and, if surgery was performed, they were more likely to receive a radical resection (52.5% vs. 32.7%, p<0.0001) and a trend towards fewer positive margins (29% vs 38%, p=0.084). In a multivariate analysis, facility volume was not independently associated with improved survival overall.



Conclusion: This is the largest patient cohort to date examining the impact of facility volume on outcomes in patients with primary BTVCs. Primary BTVCs are rare, even for HVCs; despite this, patient survival was significantly improved when treatment was performed at HVCs. Patients receiving treatment at HVC were more likely to receive a radical resection. There was a trend towards fewer margin positive resections.

Poster 267 3005698

POSTIVE MARGIN STATUS IS PROGNOSTIC OF POORER SURVIVAL IN PRIMARY BONE TUMORS OF THE SPINE: A NATIONAL CANCER DATABASE STUDY

Brian L. Dial[1]*; David Kerr*[1]*; Alexander L. Lazarides*[1]*; Anthony Catanzano*[1]*; Whitney Lane*[2]*; Dan Blazer III*[2]*; Melissa Erickson*[1]*; Sergio Mendoza*[1]

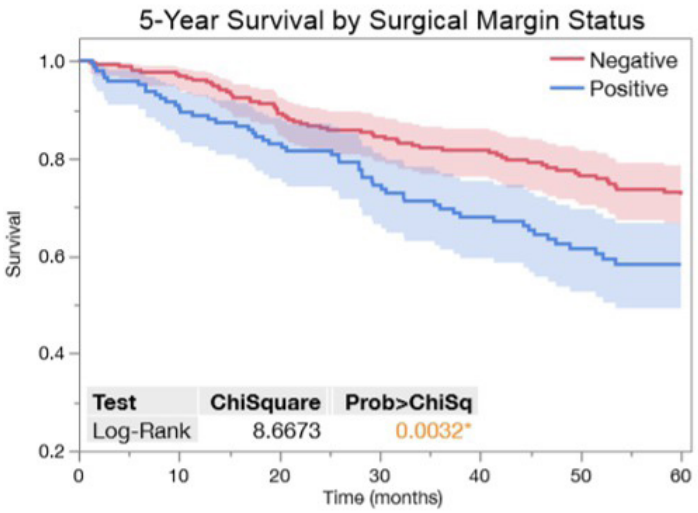
[1]*Orthopaedic Surgery, Duke University Medical Center, Durham, NC, USA;* [2]*General Surgery, Duke University Medical Center, Durham, NC, USA*

Objective: Surgical resection is the primary mode of treatment for primary osseous neoplasms of the spine. While resection type and margin status have been well demonstrated in primary bone tumors of the extremity, the low prevalence of

these tumors in the spine makes it difficult to determine the prognostic significance of these factors for spinal tumors. We investigated the largest registry of primary bone tumors, the national cancer database (NCDB). Our hypothesis was negative margin status and radical resection would correlate with increased length of survival (LOS).

Methods: We retrospectively analyzed patients in the NCDB from 2004-2015 with a histologic diagnosis of primary spinal chordoma, osteosarcoma, chondrosarcoma, and Ewing's sarcoma. Only patients who underwent surgical resection were included. Patients were stratified by margin of resection (negative margin vs. positive margin) and type of surgical resection (radical resection vs. local excision). The Kaplan-Meier (KM) method with statistical comparisons based on the log-rank test was used to identify univariate factors associated with LOS. Multivariate analysis was subsequently utilized to confirm positive survival prognosticators from the univariate analysis.

Results: A total of 759 patients with primary spinal tumors undergoing surgical resection were identified with diagnoses of chordoma (n=332), chondrosarcoma (n=217), Ewing's sarcoma (n=112), and osteosarcoma (n=98). Following resection, 36% had a negative margin (n=274), 20% had a positive margin (n=153), and 44% were unspecified (n=332). Improved 5-year survival was seen with a negative resection margin (73% vs 58%, p=0.003). Patients undergoing radical resection were more likely to have negative margins (80%) than those undergoing local or partial excisions (52%) (p<0.001). No significant difference in 5-year survival was observed in patients undergoing radical excision compared to local and/or partial excision (p=0.131). For all spinal tumors, surgery improved 5-year survival as compared to no surgery; chordoma (73% vs 60%, p=0.015), chondrosarcoma (71% vs 39%, p<0.001), Ewing's sarcoma (51% vs 34%, p=0.003), and osteosarcoma (37% vs 22%, p=0.002). In a multivariate proportional hazards survival analysis, positive margins were associated with increased mortality, hazard ratio [HR] 1.59 (1.12-2.27), p=0.010.



Conclusion: Surgical resection is the primary mode of treatment for primary osseous neoplasms of the spine, and this study confirms improved 5-year survival rates with surgical resection. Achieving a negative margin following resection improves survival. The type of resection (radical vs local or partial excision) was not associated with length of survival; however, a radical tumor excision was more likely to achieve a negative margin. This study confirms the role of tumor excision in bony neoplasms of the spine and provides evidence towards the importance of achieving a negative margin.

Poster 268 3005744

EPIDEMIOLOGIC AND SURVIVAL TRENDS IN PRIMARY MALIGNANT OSSEOUS TUMORS OF THE SPINE: A NATIONAL CANCER DATABASE STUDY

David Kerr[1]*; Brian L. Dial*[1]*; Alexander L. Lazarides*[1]*; Anthony Catanzano*[1]*; Whitney Lane*[2]*; Dan Blazer III*[2]*; Melissa Erickson*[1]*; Sergio Mendoza*[1]

[1]*Orthopaedic Surgery, Duke University Medical Center, Durham, NC, USA;* [2]*General Surgery, Duke University Medical Center, Durham, NC, USA*

Objective: Primary malignant osseous spinal tumors (PMOTS) are rare and difficult to manage tumors with poor outcomes despite multimodal treatment regiments. The rarity of these neoplasms makes it difficult to perform large studies comparing epidemiologic, survival, and treatment trends. We investigated the largest registry of primary bone tumors, the national cancer database (NCDB), to compare epidemiologic and survival trends between these tumors. The purpose of our study was to (1) compare 5-year survival rates between primary bone tumors of the spine, (2) compare treatment trends between primary bone tumors of the spine, and (3) determine profnostic factors for extended length of survival.

Methods: We retrospectively reviewed 941 adult patients in the NCDB from 2004 through 2015 with histologically confirmed primary osteosarcoma, chondrosarcoma, Ewing's sarcoma, or chordoma of the spine. Demographic, clinical, and outcomes data were compiled and compared using Chi Squared tests and ANOVA. Long term survival was compared using the Kaplan-Meier (KM) method with statistical comparisons based on the log-rank test. Multivariate analysis was performed to determine survival determinants. Study variables included age, sex, ethnicity, insurance status, comorbidity score, year of diagnosis, grade of tumor, size of tumor, stage of tumor, surgical resection, chemotherapy, and radiation therapy.

Results: The cohort included 941 patients; histological diagnosis was chordoma (n=407), chondrosarcoma (n=243), Ewing's sarcoma (n=164), and osteosarcoma (n=127). The average age at diagnosis was younger in Ewing's sarcoma (p<0.0001), and there was no difference in gender, race, or comorbidity score between tumor types. Surgical resection was the primary mode of treatment for chondrosarcoma (89.3%), chordoma (81.6%), osteosarcoma (77.2%), and Ewing's sarcoma (68.3%). Ewing's sarcoma patients were more likely to be managed with radiation and chemotherapy (p<0.0001). 5-year survival rates varied significantly between tumor types with chordomas having the greatest survival (70.5%) and osteosarcomas having the worse survival (32.9%) (p<0.0001). Multivariate analysis demonstrated significantly decreased 5-year survival rates with age >60, non-private health insurance, comorbidity score >1, high grade tumor, and metastasis at time of surgery. The multivariate analysis demonstrated improved survival following surgical resection; however, radiotherapy and chemotherapy did not impact survival.

Conclusion: This study provides the most comprehensive comparison of epidemiologic, survival, and management trends in PMOTS. Surgical resection is the most common form of treatment for all PMOTS. Ewing's sarcoma was treated with adjuvant chemotherapy and radiation therapy more frequently than other tumor types. Osteosarcoma has the worst 5-year survival prognosis of 32.9%, which did not improve from 2004-2015. Radiotherapy and chemotherapy did not provide survival benefits when looking at all PMOTS.

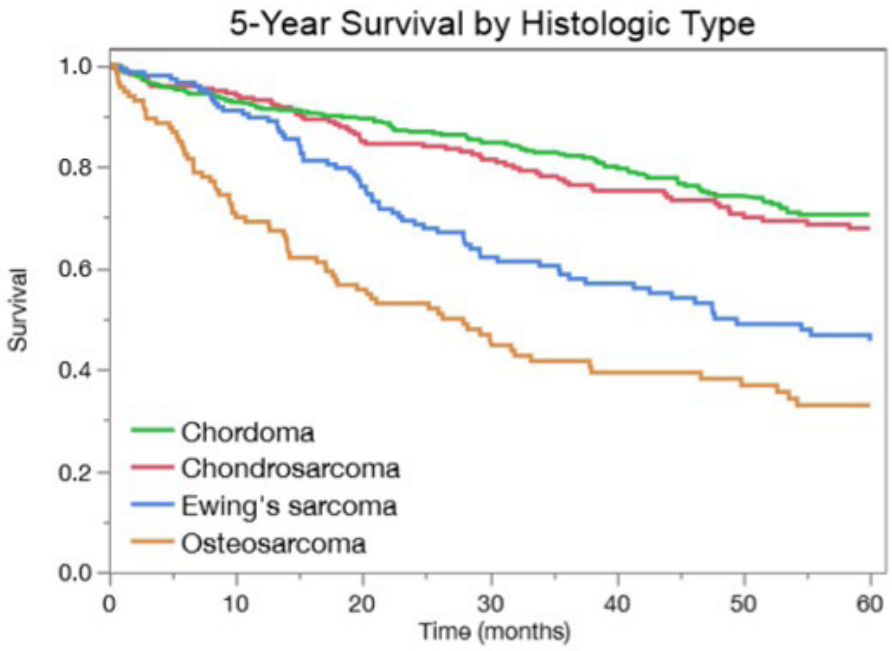
Table 1: Independant Predictors of Survival

Table 1: Independent Predictors of Mortality in Multivariate Hazards Analysis

Variable	HR	Lower 95%	Upper 95%	P value
Patient variables				
Age (years) (Ref=0-40)	Ref			
40-60	1.36	0.99	1.87	0.056
>60	1.72	1.14	2.58	0.010*
Male sex (Ref=Female)	1.27	1.00	1.62	0.046*
Hispanic (Ref=Non-Hispanic)	1.27	0.80	2.00	0.306
Race (Ref=Caucasian)				
African-American	1.00	0.61	1.64	0.992
Asian	1.10	0.48	2.54	0.821
Comorbidity Score >1 (Ref=0-1)	2.15	1.38	3.36	<0.001*
Insurance (Ref=Private Insurance)				
Medicare	1.82	1.26	2.64	0.001*
Medicaid	1.75	1.16	2.64	0.008*
No insurance	2.57	1.56	4.24	<0.001*
Income below median ($48,000)	1.10	0.85	1.43	0.476
Tumor and treatment variables				
Grade (Ref=Low grade)				
Intermediate grade	1.87	1.05	3.33	0.034*
High grade	2.88	1.58	5.23	0.001*
Metastases at diagnosis	2.66	1.86	3.78	<0.001*
Surgery (Ref=No surgery)				
All types	0.63	0.47	0.85	0.002*
Local resection	0.64	0.47	0.87	0.005*
Radical resection	0.62	0.43	0.89	0.010*
Surgical margins positive	1.59	1.12	2.27	0.010*
Radiation use	0.92	0.72	1.18	0.515
Chemotherapy use	0.88	0.62	1.26	0.492

HR = hazard ratio; * indicates statistical significance

Figure 1: Survival of Primary Bone Tumors of the Spine



Poster 269 3026668

PIN OR REPLACE: AN ALGORITHM FOR THE MANAGEMENT OF NON-PATHOLOGIC FEMORAL NECK FRACTURES IN CANCER PATIENTS

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Objective: Advances in cancer treatment has increased overall survival for patients living with osseous metastases. As a result, the incidence of hip fractures in patients presenting with a history of cancer is expected to increase, whether the fracture is directly related to their cancer or not. The primary purpose is to evaluate the durability of closed reduction and percutaneous pinning (CRPP) versus short-stem cemented hip hemiarthroplasty (HHA) for the management of non-pathologic femoral neck fractures in patients with metastatic cancer. Secondary aims are to determine the appropriate imaging to accurately identify non-pathologic fractures and to create an algorithm to guide the management of non-pathologic femoral neck fractures in metastatic cancer patients.

Methods: A retrospective review of patients presenting with femoral neck fractures that underwent CRPP or HHA at a single oncologic referral center was performed, excluding patients treated with femoral stems greater than 155mm. 127 total patients were identified, 109 underwent HHA and 18 underwent CRPP. For the HHA patients, analysis of the imaging accuracy was performed by determining the sensitivity and specificity of x-rays and advanced imaging modalities. Based on these results an algorithm was created to help aid in diagnostic evaluation and surgical indication. The algorithm was retrospectively validated for patients radiographically diagnosed with non-pathologic fractures that underwent CRPP or HHA. Primary end-point was revision surgery or death.

Results: Analysis of radiographic imaging for all 109 patients undergoing HHA demonstrated that radiographs alone were accurate 74% of the time with sensitivity of 0.76 and specificity of 0.70 in predicting an underlying pathological cause of the fracture. Adding any advanced imaging improved the results to 90%, 0.97, and 0.74, respectively.The algorithm created is presented in Figure 1. Revision surgery was required for 1 patient that developed an intertrochanteric fracture within one month of CRPP. One patient in the CRPP series is alive and 17 patients died without requiring revision surgery at average follow-up of 11.3 months. HHA was utilized for 36 patients with non-pathologic fractures. No revision surgeries were required. Nine patients are alive and 27 patients died without requiring revision surgery at average follow-up of 34.7 months. CRPP patients had a different primary cancer distribution and were more likely to be non-displaced fractures than HHA patients. Otherwise there were no statistical differences in age, extent of disease, mobility status, advanced imaging obtained, ASA classification, and post-operative complications. Of interest, a greater percentage of patients had better or the same mobility after CRPP versus HHA but this difference did not reach statistical significance.

Conclusion: CRPP and HHA both offer durable reconstructive options for patients with cancer presenting with non-pathologic fractures. The difficulty in these patients is ruling out pathologic fractures. Radiographs without advanced imaging for comparison are incorrect 26% of the time. To improve this accuracy advanced imaging is recommended. Based on the treating institutes available facilities either CT scan, MRI, bone scan, or PET scan can be obtained. Depending on the underlying histology and results of previous studies these studies may not be equivalent in guiding decision making. However, CT scan allows for improved accuracy, sensitivity, and specificity and is easily obtained at initial presentation. Figure 1 presents an algorithm for evaluating cancer patients presenting with femoral neck fractures that will allow practitioners to identify which patients may require a referral to an orthopedic oncologist for management of a pathologic fracture and which patients can treated using standard orthopedic practices.

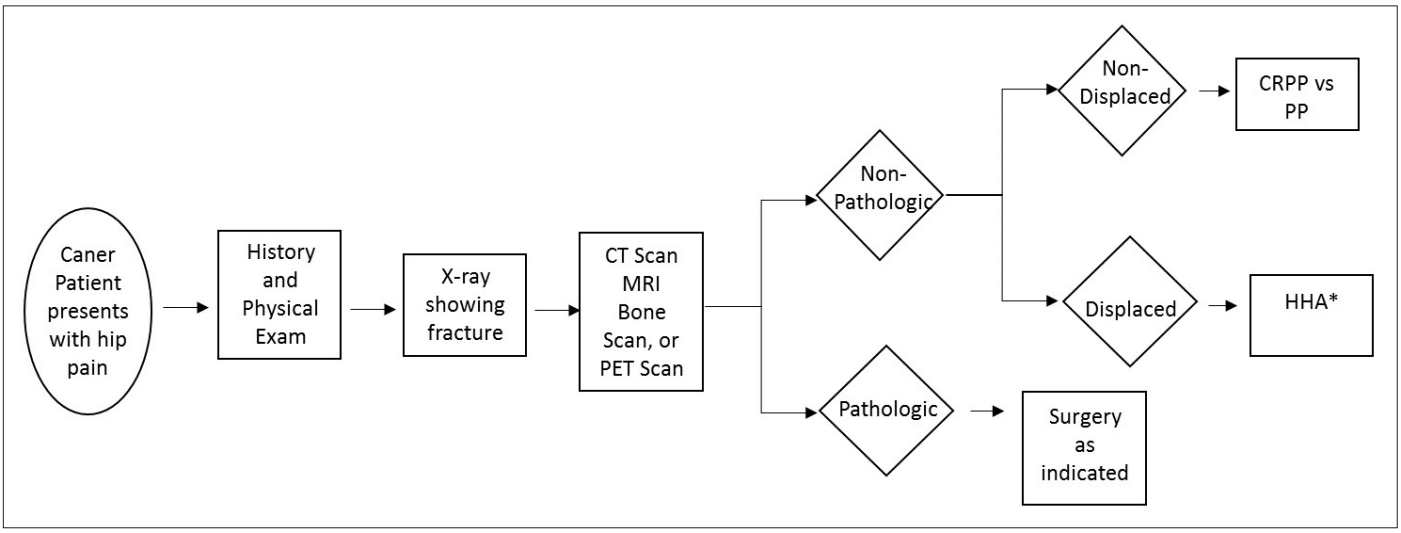

Figure 1. Algorithm for management of cancer patients with femoral neck fractures. Once history, physical exam and radiographic imaging are consistent with femoral neck fracture. Advanced imaging is recommended. Based on the treating institutes available facilities either CT Scan, MRI, Bone Scan, or PET Scan can be obtained. Non-pathologic non-displaced fractures can be closed reduced (CRPP) if needed, and then percutaneously pinned (PP). Non-pathologic displaced fractures can be replaced *unless an excellent reduction can be performed, then CRPP can be considered.

Poster 270 3041708

SOFT TISSUE SARCOMAS OF THE ANKLE AND FOOT: CLINICAL OUTCOME AND PROGNOSTIC FACTORS

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Objective: Soft tissue sarcomas (STSs) rarely arise in the ankle and foot, and are often excised inappropriately before the referral to a tertiary musculoskeletal oncology hospital. Such unplanned excision may make the further treatment more complicated. In addition, it is reported that the frequency of clear cell sarcoma and synovial sarcoma is relatively high compared with other sites, and the high frequency of these types of tumor also may affect the clinical outcome. We studied prognostic variables that may affect the outcome of patients with STS of the foot and ankle.

Methods: Forty-six patients who were treated for STS of the ankle and foot between 1994 and 2018 (for the last 25 years) at three institutions were identified from the institutional database and were retrospectively reviewed. There were 26 males and 20 females, with an age range from 0 to 81 years (median 48 years). Follow-up of patients ranged from 2 to 210 (mean 61.1) months. Survival rates were estimated by Kaplan-Meier's method, and prognostic variables were tested for statistical significance.

Results: The histopathological diagnoses were clear cell sarcoma (10 patients), synovial sarcoma (4), dermatofibrosarcoma protuberance (4), epithelioidsarcoma (3), myxoid liposarcoma (3), myxoinflammatory fibroblastic sarcoma (3), myxofibrosarcoma (3), leiomyosarcoma (3), and others. Thirty-one (67.4%) tumors were interpreted as high grade. Of 46 patients, 21 (45.6%) had undergone excision at the previous hospital. The 5-year over-all survival of all patients was estimated as 73.1%. Six patients with distant metastases at diagnosis had significantly worse prognosis. Excluding these

six, overall survival of patients with tumor larger than 5 cm was significantly worse, and that of patients with high-grade tumor was also worse but not significant. Event-free survival of patients with deeply located (beneath the fascia) tumor and that of patients with positive surgical margin was significantly worse. Previous unplanned excision did not make the prognosis worse.

Conclusion: Clinical outcome of patients with STS of the ankle and foot was improved in this series compared with our previous study. Clear cell sarcoma relatively prefers this site. Large-sized (>5cm), high-grade, and deep-located tumor, and positive surgical margin seemed to negatively affect the prognosis of patients with STS of the ankle and foot but unplanned excision did not.

Poster 271 3042687

EFFECT OF BODY MASS INDEX (BMI) ON OUTCOMES OF PATIENTS WITH BONE TUMORS WHO UNDERGO ENDOPROSTHETIC JOINT RECONSTRUCTION

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Objective: The detrimental effects of high body mass index (BMI) on the outcomes of primary hip and knee arthroplasty have been well described. Studies have shown increased rates of readmission, reoperations, wound complications, DVT, and other various medical complications in patients with BMI ranging from 30-40+. The effects of BMI have yet to be studied in patients undergoing joint reconstruction after resection of bone tumors. We seek to understand if BMI effects post operative outcomes in this patient population.

Methods: Patient data from a single surgeon's practice was pulled from an electronic hospital database from 2010-2018. The patients were identified based on codes for tumor resection and endoprosthetic reconstructions. Appropriate IRB approval was obtained prior to chart investigation. All patients who underwent resection of primary or metastatic bone tumors with associated endoprosthetic reconstruction were included with a minimum of 1 year follow-up. Patients were then divided into groups over and under a BMI of 30. Patients were then matched based on ASA score, age, tumor type (primary versus metastatic), operative site and type of replacement. The two groups were then compared based on reoperation, 30 day and 90 day readmission as well as 30 day, 90 day, and 1 year complications. Implant related issues were evaluated over the entire follow-up. Statistical analysis was performed with a Chi Squared Test.

Results: After matching was complete, a total of 42 patients were identified with 21 in each group. Complete patient demographics including matching data as well as tumor type and operative sites are listed in detail in Tables 1&2. There were no statistical differences in reoperation, readmissions at 30 and 90 days, or complications at 30 and 90 days, and at 1 year. Overall mortality at 30 and 90 days and at 1 year was also similar. At final follow-up, 12 patients in the BMI > 30 group had passed away compared to 10 in the BMI < 30 group. Implant related issues that required revision occurred in 3 patients in each group.

Conclusion: The role of BMI in patients undergoing endoprosthetic joint reconstruction after bone tumor resection has not been investigated. In this retrospective evaluation there was no statistically significant effect of BMI on outcomes in this patient population.

Demographics

BMI	**<30**	**>30**
Average BMI	23.1	36.4
Average age	59.7	56.8
Average ASA	2.9	3.1
Upper Extremity Reconstruction	**8**	**8**
Proximal humerus replacement	5	7
Total humerus replacement	1	0
Total elbow replacement	2	1
Lower Extremity Reconstruction	**13**	**13**
Distal femoral replacement	1	1
Proximal femoral replacement	4	4
Long stem hip hemiarthroplasty	7	7
Proximal tibial replacement	1	1

Type of tumor

BMI	<30	>30
Primary Bone Tumor	**8**	**9**
Osteosarcoma	3	4
Chondrosarcoma	2	1
Plasmacytoma	0	1
Multiple myeloma	1	1
Giant cell tumor	1	0
Undifferentiated pleomorphic sarcoma	1	0
Clear cell sarcoma	0	1
Angiosarcoma	0	1
Metastatic Bone Tumor	**13**	**12**
Lung cancer	3	5
Breast cancer	3	3
Renal cancer	2	3
Prostate cancer	1	0
Cervical cancer	0	1
Uterine cancer	1	0
Melanoma	2	0
Carcinoma with unknown primary	1	0

Poster 272 3042938

COMPUTER-ASSISTED NAVIGATION FOR SURGERY OF ILIOSACRAL BONE SARCOMAS: WHAT IS THE EVIDENCE?

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Objective: Surgical management of iliosacral sarcomas (Enneking zone I-IV) has been in particular associated with high risk of positive margins and local recurrence, making computer-assisted navigation surgery an appealing option. However, literature still lacks evidence-based data documenting superior clinical results of computer-assisted navigation surgery in the management of iliosacral bone malignancies.

Study questions:
1- What is the risk of positive margin and local recurrence when using computer-assisted navigated surgery to assist excision of iliosacral sarcomas compared to standard (non-navigated) surgery?
2- Is the use of computer-assisted navigated surgery associated with narrower negative margins and possibly increased risk of local recurrence?
3- Is computer-assisted navigated surgery associated with superior clinical outcome, in terms of function, root/nerve preservation, postoperative pain and incidence of complications?

Methods: A retrospective case-control study of prospectively collected data was designed using propensity score matching to compare computer-assisted navigation and standard surgery. There were 11 patients in the navigation group and 20 patients in the non-navigation group.
Design: Retrospective case-control study of prospectively collected data using propensity score matching.
Population: 31 patients with bone sarcomas originating in the ilium and involving the sacro-iliac region, from 1994 to 2014.
Treatment: iliosacral resection, with or without computer-assisted navigation
Functional outcome assessment method: MSTS score.
Pain assessment method: New York State Department of Health and Mental Hygiene Morphine Milligram Equivalent (MME).
Statistical analysis used ANOVA for quantitative outcomes and Chi-square for proportions comparison.

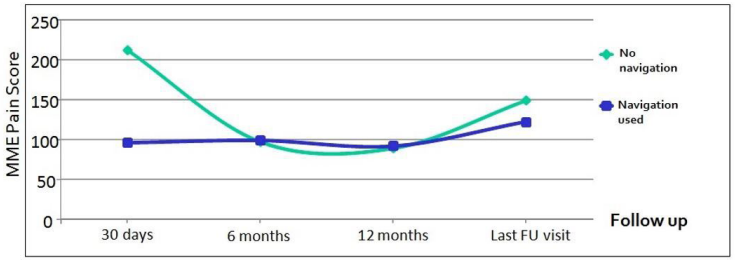
Results: A positive margin was obtained in a total of 8 patients (26%), 6 patients (30%) in the non-navigation group and 2 patients (18%) in the navigation group; although risk of positive margin was higher in the non-navigated patients, the difference was not statistically significant (p=0.47). Six patients (19%) developed local recurrence (LR), 3 in each group. LR was observed in 4 of 23 patients with a negative margin and 2 of 8 patients with a positive margin (17% vs 25%; p=0.6). Minimum negative margin width (closest margin) was 7 mm in both navigated and non-navigated groups. Mean closest

margin to the tumor was 6 mm in patients who didn't develop LR and 9 mm in patients who developed LR (*p*=0.5). Mean MSTS score was 20 in non-navigation group and 23 in the navigation group (*p*=0.23). The use of computer-assisted navigation surgery did not decrease the rate of nerve and/or roots sacrifice when compared to non-navigated surgery (p-value=0.52). Computer-assisted navigated surgery was associated with less postoperative consumption of narcotics per day at one month (96 vs 212 MME) although difference was not significant (*p*=0.1).

Conclusion: In this study, the use of computer-assisted navigated surgery for management of iliosacral bone sarcomas was associated with a lower incidence of positive margin, although the difference did not reach statistical significance. Navigation was not associated with narrower closest margin than conventional surgery and the width of the closest margin was not obviously correlated with LR. Although computer-assisted navigated surgery was associated with less postoperative consumption of narcotics, there was no significant difference in the clinical outcome between patients managed by computer-assisted navigated surgery and non-navigated surgery.

Limitations of the study are the retrospective design, although the propensity score matching statistical method adds rigor to the control group, the relatively small number of patients and shorter follow-up for the navigated group, similar to numerous other studies focusing on pelvic surgery for bone sarcomas. Further research is warranted to validate the use of computer-assisted navigated surgery and understand the risk of local recurrence.

Results



- Computer-assisted navigated surgery was associated with lower daily narcotics consumption at 1 month post-surgery (96 vs 212 MME) although the difference was not statistically significant (p=0.1).

Poster 273 3012715

FUNCTION AFTER DISTRACTION OSTEOGENESIS FONR BONE RECONSTRUCTION OF OSSEOUS TUMORS IN THE UPPER AND LOWER EXTREMITY

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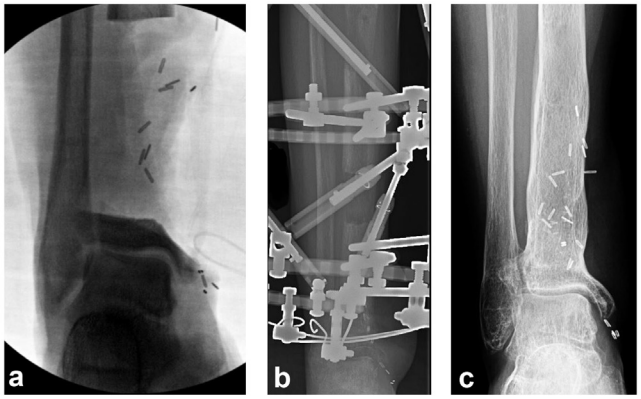
Objective: Surgical resection with wide margins is a critical step in achieving local control for the majority of bone sarcomas. Limb salvage surgery has been shown to be comparable to amputation to achieve oncological goals as long as negative margins can be attained. Various techniques of distraction osteogenesis (DO) are currently used to manage large and massive bone defects in trauma, infection and congenital deformities, and less commonly used for oncological osseous defects. The inhibitory effect of chemotherapy, especially in multi-agent protocols, has not been sufficiently studied previously. The main questions of our study are: Is distraction osteogenesis safe and effective for the reconstruction of bone defects in the upper and lower extremity during concomitant delivery of chemotherapy? What are the midterm functional outcomes in oncology patients treated with DO? What is the rate of complications with this technique in this subset of patients?

Methods: We evaluated 44 patients who underwent DO reconstruction of the upper and lower extremity between 08/2014 and 06/2018. Indications were primary and revision reconstructions for osseous malignant neoplasms, including nonunion, fracture, infection, loosening, length discrepancy or deformity. The method of DO included single and double level bone transport via internal or external fixation. The majority of patients (n=31, 70%) completed treatment with DO using an external fixator with 12 patients (30%) used an internal device. Adjuvant and neoadjuvant chemotherapy, radiation dose and timing, total defect size, and complications were reviewed for all eligible patients. Functional and emotional outcomes were assessed using the MSTS score. Three groups of patients undergoing DO reconstruction were identified: patients undergoing concomitant chemotherapy, patients who had previously received chemotherapy, and those without chemotherapy.

Results: In 40 (91%) cases, the defect was in the lower extremity (femur= 25 cases, tibia= 15 cases). In 4 (9%) cases, the upper extremity was affected (humerus= 2 cases, forearm/hand= 2 cases). All surgical margins were free of tumor. 41 (93%) patients underwent reconstruction for primary neoplasms involving bone, with osteogenic sarcoma being the most common diagnosis (50%). 3 (7%) patients needed surgery because of bone metastases. The median closest margin was 7 mm (range 1-40mm) The median total defect size in tumor patients was 14 cm (range 9-25 cm), the median total length of regenerate bone was 14.5 cm (range 6-26 cm). 17 (39%) patients received chemotherapy prior to DO, 15 (34%) patients

during the reconstruction surgery; 4 (9%) patients received radiation therapy before surgery. The rate of complications was 43%. Median follow-up time was 18 months (range 0.5-39.75). Median MSTS score at the last follow-up visit was 21 (range 6-30). In patients with external and internal devices, MSTS scores nadir 3 months after lengthening surgery (8 and 13, respectively). After that, the values increase consistently. 15 (36%) patients needed unplanned revision surgery. Patients with an external fixator had more infections and bone healing issues during concomitant chemotherapy than patients with an internal device (p 0.024). However, there is no significant relationship between functional outcome and size of bone defect (p 1.0), presence or absence of chemotherapy (p 0.074), postoperative complications (p 0.4), revision surgery (p 0.3), and internal or external device (p 0.9).

Conclusion: We postulate that the use of DO is safe for the primary and secondary reconstruction of malignant bone neoplasms. It is also an effective technique to regenerate bone during systemic chemotherapy. Despite high complication rate, DO is an effective method for reconstructing even large bony defects and yields good, sustainable functional results.



a+b: Patient A ; intra- and postoperative imaging: The patient had synovial sarcoma involving the right medial ankle with osseous involvement of the right tibia. She underwent radial resection of the right distal tibia and application of a multiplanar external fixator to the ankle and foot for bone transport.
c: Patient A ; 3 years after surgery : The patient had removal of hardware 6 months after initial surgery. 3 years after surgery, the patient can participate in multiple activities such as ice skating or skiing, and has no limitations on her activity level. Recent imaging showed no evidence of local recurrence or distant metastases.

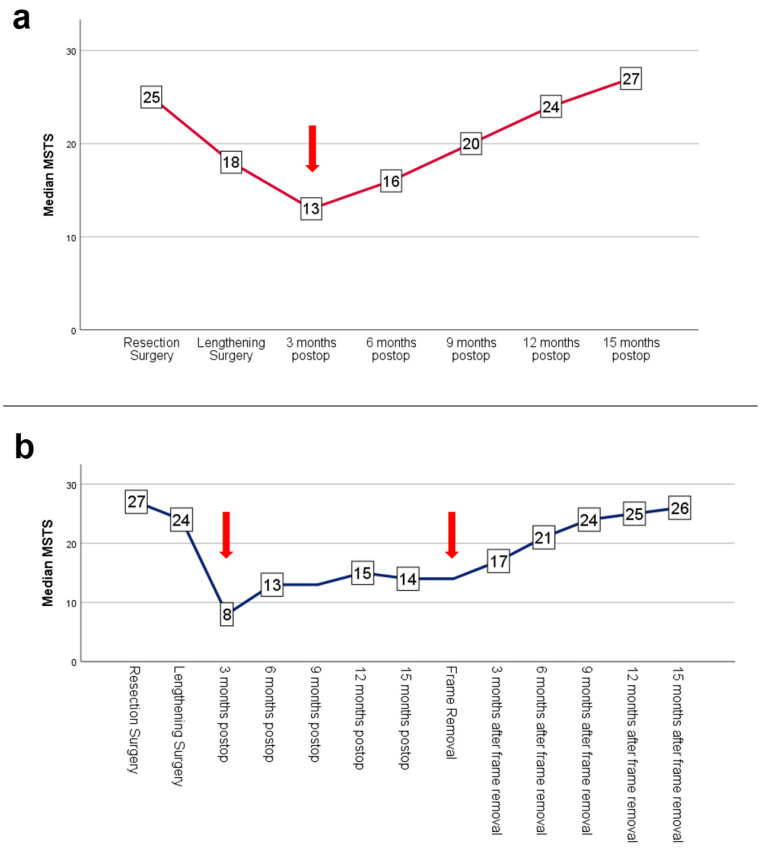


Figure a: Median MSTS scores over time for patients with an internal device. MSTS scores sink to their lowest value 3 months after lengthening surgery. After that, the values increase constantly.
Figure b: Median MSTS scores over time for patients with an internal device. MSTS scores sink to their lowest value 3 months after lengthening surgery. After frame removal, the values increase constantly.

Poster 274 3017401

USE OF MAGNETIC GROWING INTRAMEDULLARY NAILS IN COMPRESSION DURING INTERCALARY ALLOGRAFT RECONSTRUCTION

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Objective: Intercalary allograft reconstruction after tumor resection traditionally has a high rate of complications, particularly non-union. Both plate and intramedullary nail fixation have been used alone and in combination to improve union rates. This study sought to evaluate a new technique that uses a magnetic growing intramedullary nail to compress the osteotomy sites in order to aid in healing. The current study questions: (1) What is the union rate and the time to union when using magnetic growing intramedullary nails? (2) What are the complications that occur with this technique?

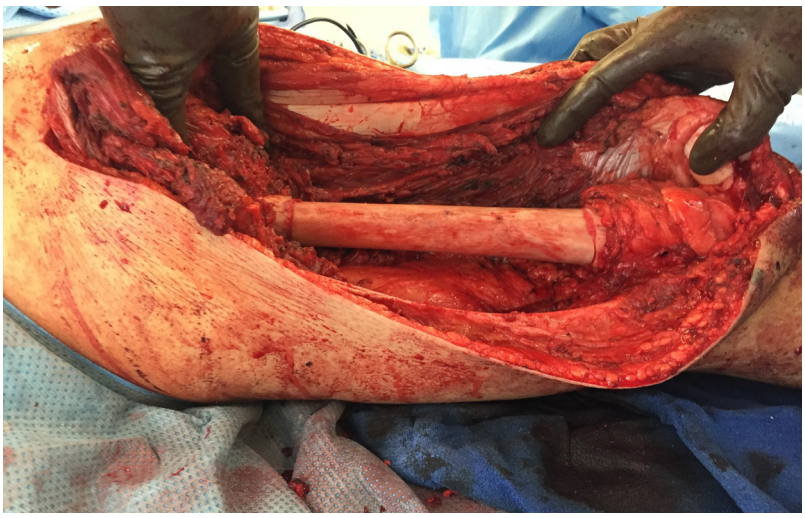
Methods: A retrospective review of 8 patients with 15 osteotomy sites were evaluated with a minimum follow-up of 12 months to evaluate healing and complications.

Results: Twelve of 15 osteotomy sites had healed by an average of nine months after surgery. Non-unions occurred in two patients with an associated failure of the hardware. Of the patients that healed both their sites, one sustained a fracture through the allograft, one had backing out of a distal locking screw that required removal, and one required a manipulation of their knee under anesthesia. Two patients underwent a successful limb-lengthening due to an expected limb-length discrepancy after healing occurred.

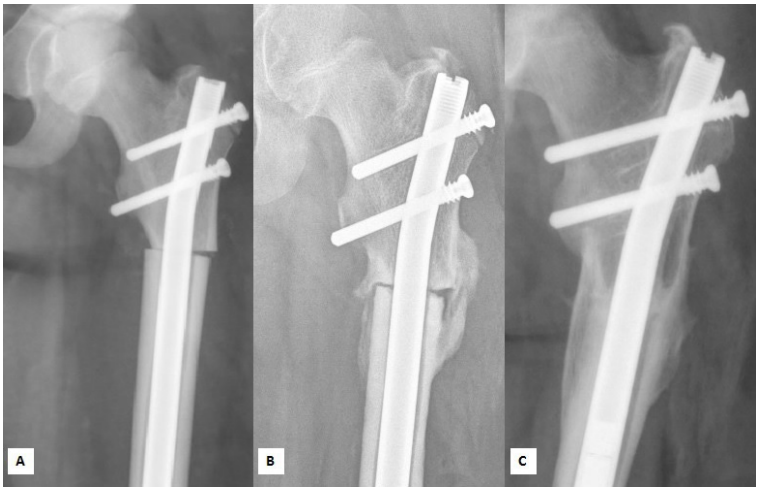
Conclusion: Using growing intramedullary nails in compression mode provided an 80% union rate with acceptable complications. This technique provides a good alternative to standard nail and plate fixation when intercalary allografts are used.

Demographics of Patients Undergoing Intercalary Allograft Reconstruction with a Magnetic Lengthening Nail

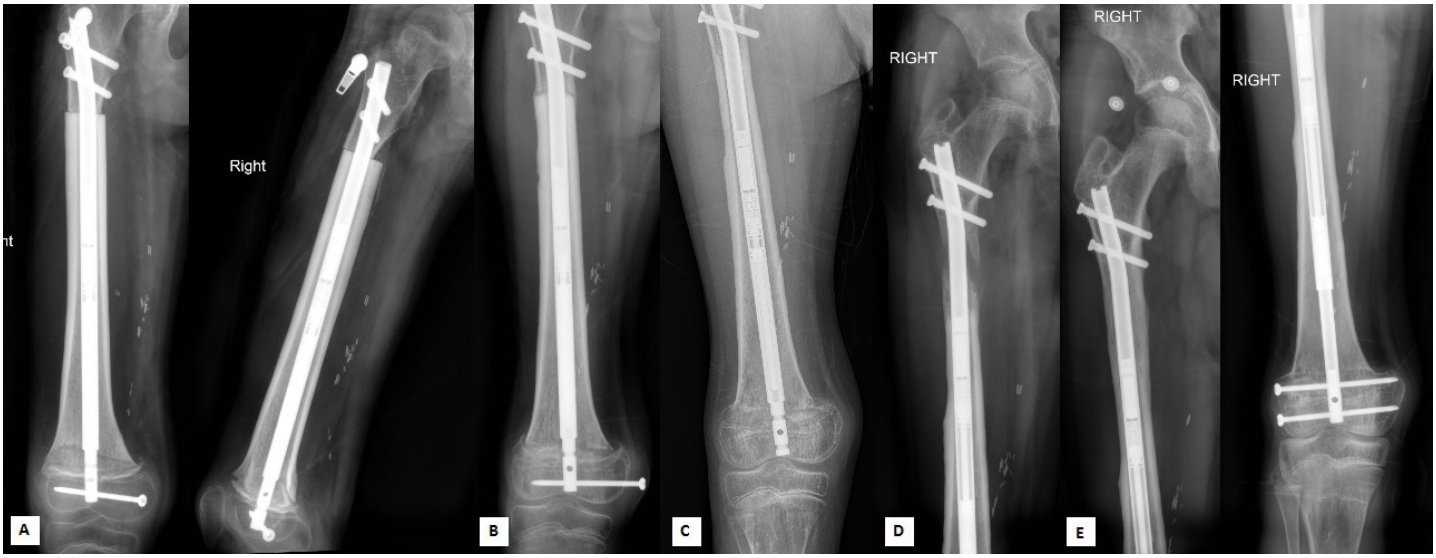
Patient No.	Age	Sex	Site	Cancer type	Allograft length (cm)	Follow-up (months)
1	9	M	Femur	Pleomorphic sarcoma	23	38
2	11	F	Femur	Osteosarcoma	29	38
3	66	M	Humerus	Renal cell carcinoma	6.5	14
4	37	M	Femur	Pleomorphic sarcoma	18	23
5	71	F	Humerus	Endometrial stromal sarcoma	13.5	18
6	14	M	Femur	Osteosarcoma	14	19
7	21	F	Femur	Osteosarcoma	20.5	14
8	50	F	Humerus	Renal cell carcinoma	12	12



Intraoperative photograph of a femur after compression of the allograft. The graft was noted to be rotationally stable with no gapping of the osteotomy sites.



Demonstration of the bone reabsorption and remodeling that occurred at one diaphyseal site in all primary reconstructions. The AP radiograph of the proximal femur immediately after surgery demonstrates a mismatch of the host-allograft site that was filled with additional allograft bone (A). At 3.6 months after surgery, AP radiographs demonstrate reabsorption and remodeling at both the medial and lateral aspects of the host and allograft bone (B). An AP radiograph at 12 months after surgery demonstrates uneventful healing and consolidation of the allograft (C).



Immediate postoperative AP and lateral radiographs of a femur after resection of a pleomorphic sarcoma and reconstruction with a 23 cm allograft (A). At 5.5 months after surgery, an AP radiograph of the femur shows progressive healing of the allograft with backing out of the distal locking screw (B). An AP radiograph of the femur 13 months after surgery demonstrating complete healing of the allograft with subsequent removal of the distal locking screw (C). An AP radiograph of the proximal femur during the limb-lengthening process that started 15.5 months after the initial surgery (D). The femur was lengthened a total of 6 cm. Complete healing is noted on AP radiographs of the femur at 3 years after the initial surgery (E).

Poster 275 3033167

LONG TERM (>15 YEARS) OUTCOME OF CUSTOM CROSS-PIN FIXATION OF TUMOR ENDOPROSTHESES STEMS

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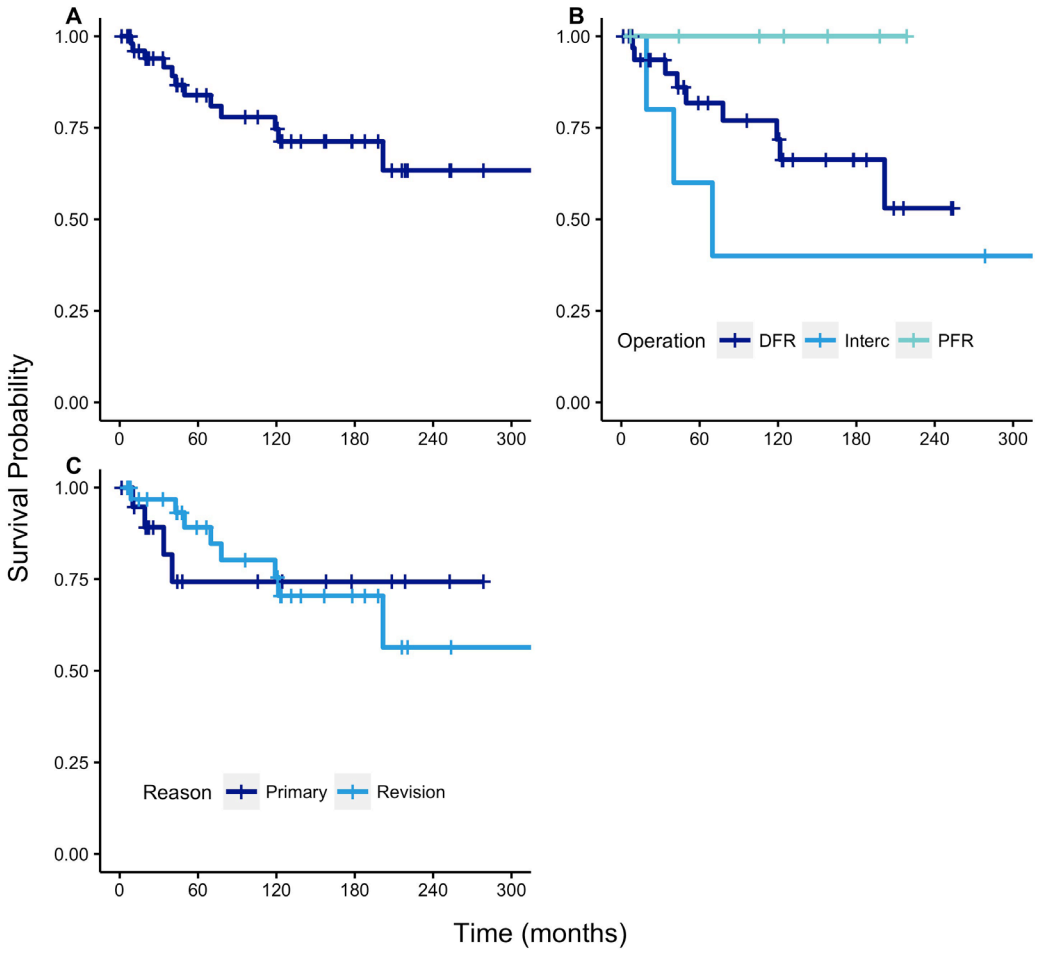
Objective: Aseptic loosening due to rotational stress is a major cause of failure in cemented endoprosthetic reconstructions, particularly in large resections or revisions with short residual segments of bone requiring short intramedullary stems. Reconstructive techniques developed specifically for short segment fixation have been proposed, including extra-cortical plates and compressive osseointegration. Existing series demonstrate 8-14% mechanical failure rate at short-to-intermediate term follow-up using these techniques. We have previously reported on a custom cross-pin fixation technique that creates a bone-cement-prosthesis composite to resist rotatory stress with no cases of aseptic loosening in 24 endoprosthesis at mean 57 month follow up. Here we present the long-term outcomes and mechanical survivorship of this construct. We aim to examine the long-term survivorship, outcomes, and modes of failure of a custom cross-pin fixation technique for endoprosthetic reconstruction for primary bone tumors.

Methods: This is a retrospective review of our endoprosthesis database consisting of 512 consecutive cemented

endoprosthetic reconstructions performed for oncologic diagnoses at a single-center between 1980 and 2016. We identified 51 patients with 56 endoprosthetic implants with cross-pin fixation between August 1985 and November 2009. 21 endoprosthesis were implanted following primary resection of tumor (9 osteosarcoma, 6 Ewing's sarcoma, 5 chondrosarcoma, 1 spindle-cell sarcoma), with the remaining 35 implanted as revision prostheses (21 for aseptic loosening, 6 structural failure, 6 infection, 2 soft tissue failure). Prosthesis locations included distal femoral (36), proximal femoral (7), intercalary (6; 5 femoral, 1 tibial), proximal humeral (3), proximal tibial (3), and distal humeral (1). Bushing changes, cross-pin changes, and planned expansions of growing implants were excluded. Outcomes evaluated were implant survival, revision surgery categorized according to the Henderson Failure Mode Classification, complications, and functional outcomes. Prosthesis survival is analyzed at 5-year, 10-year and 15-years using Kaplan-Meier analysis.

Results: Median follow-up period was 132 months (25th-75th percentile, 44 to 189 months). A total of 22 stems required revision: 8 for infection, 7 for structural failure, 5 for aseptic loosening and 2 for tumor progression. Of those stems requiring revision for aseptic loosening, two were in the same patient with a primary femoral intercalary endoprosthesis with proximal loosening. Mechanical survivorship at 5, 10, and 15 years was 84%, 75% and 71% respectively (Figure 1A). All cause survivorship at 5, 10, and 15 years was 72%, 64% and 51%, respectively. Mechanical failure varied by location, with no mechanical failures detected of PFR constructs. Distal femoral survivorship was 82%, 72%, and 66% at 5, 10 and 15 years, while femoral intercalary survivorship was 60%, 40% and 40% respectively (Figure 1B). There was not a substantial difference in survival between primary and revision reconstructions with survival at 5, 10, and 15 years of 74% for primary and 89%, 76% and 71% for revisions (Figure 1C).

Conclusion: The rate of mechanical survivorship (84% at 5 years) in our series is similar to those reported for other methods of reconstruction for short diaphyseal segments such as compressive osseointegration and extra-cortical plating. The mechanical failure rate differed by location with no failures of proximal femoral constructs and 40% survival of femoral intercalary constructs at 10 years. There were no differences in mechanical failure between primary and revision constructs. However, when primary constructs failed, they did so in the first five years with no failures after that time in contrast to revisions. Overall, custom cross-pin fixation remains a viable option for challenging endoprosthetic reconstruction of short metaphyseal segments with an acceptable rate of mechanical failure at long term follow up.



Kaplan-Meier survival curves for mechanical failure of endoprosthetic stems with cross pins. (A) Mechanical failure for all endoprosthesis, (B) by type of reconstruction for three most common operations, (C) by indication, either primary resection or revision.

Poster 276 3042772

OPTIMIZING THE USE OF INDOCYANINE GREEN FOR OSTEOSARCOMA TUMOR DETECTION USING A XENOGRAFT MURINE MODEL

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Objective: Local control for osteosarcoma (OS) commonly involves limb-salvage techniques, underscoring an evolution in surgical management. Currently, the only method for assessing adequacy of a surgical resection is either waiting until final pathology results in the weeks following surgery or by sampling the surgical bed intra-operatively. There remains an unmet need for a surgical tool that provides real-time accurate and specific guidance, to allow for the identification and removal of residual disease. Recently, indocyanine green (ICG) has been utilized to augment tumor visibility within the context of a preclinical model. IGF2R is a transmembrane surface receptor, consistently over expressed in OS. We present a novel technique, combining non-specific ICG use with that of an ICG-labeled IGF2R monoclonal antibody (mAb), in an effort to optimize the sensitivity and specificity of the technique.

1) Can ICG-labeled IGF2R mAb be used to bind and detect osteosarcoma cells *in vitro*?
2) Can ICG-labeled IGF2R mAb be used to bind and detect osteosarcoma tumor *in vivo*?
3) Will the combination of both targeted and non-targeted ICG administration improve the technique?

Methods: *In Vitro* Experiment
Indocyanine green was conjugated to an IGF2R mAb using a commercially available labeling kit. The binding efficiency for the ICG-labeled IGF2R mAb was calculated using a dye-to-protein ratio. The IGF2R-ICG mAb construct was then incubated at varying concentrations with 143b OS cells in a slide chamber. After incubation overnight at 4°C, near-infrared fluorescence was detected using an automated, digital, inverted multi-channel fluorescent imaging system (EVOS FL Auto microscope) equipped with a custom filter that detects near-infrared wavelengths. DAPI counterstaining was performed and used as an overlay for ICG signal confirmation.

In Vivo Experiment
Sixteen, three to five-week-old NOD-scid IL2rγ^{null} (NSG) mice underwent orthotopic implantation of approximately 10^6 143b OS cells into the proximal tibia. Once tumors reached palpable size, each animal was administered either: ICG alone, IGF2R-ICG mAb alone, or a combination of the two. This was accomplished via tail vein injection and at varying concentrations and time-points. ICG was administered at either 1mg/kg or 5mg/kg at either 0, 24 or 48 hours prior to imaging. ICG-labeled IGF2R mAb was administered at 10ug, 20ug, or 50ug at either 0, 24, or 48 hours prior to imaging. After euthanasia, the animals and their tumors were imaged using a commercially available near-infrared fluorescent imaging system (SPY Elite).

Results: Adequate conjugation of ICG-labeled IGF2R mAb was demonstrated with a dye-to-protein ratio of 3.57:1. 143b OS cells were successfully incubated with ICG-labeled IGF2R mAb and demonstrated a readily detectable near-infrared fluorescent signal. Fluorescence primarily localized to the cell membrane. Overlay imagery using DAPI and ICG were concordant.
Mice injected with ICG alone, demonstrated improved near-infrared fluorescence at 5 mg/kg at 24 hours. Mice injected with ICG-labeled IGF2R mAb alone, demonstrated improved near-infrared fluorescence at 50ug at 48 hours. Optimal fluorescent signal was detected following dual administration of ICG at 5mg/kg and ICG-labeled IGF2R mAb at 50ug at 48 hours prior to imaging.

Conclusion: ICG has been previously utilized for surgical imagery and visual augmentation and has a well regarded safety profile. There is increasing interest in the use of ICG for the purpose of OS tumor detection. We sought to further optimize this approach. Our findings demonstrate that OS can be successfully imaged via an ICG-labeled IGF2R mAb both *in vitro* and *in vivo* within the described preclinical model. Furthermore, combining targeted and unbound ICG appears to confer an optimized signal. Future goals include validating imaging with histologic outcomes, quantitatively characterizing near-infrared signal and expanding the investigation to include a panel of OS tumors.

Poster 277 3042640

TARGETED MUSCLE REINNERVATION: A STRATEGY TO PREVENT NEUROMAS AND PHANTOM LIMB PAIN IN ONCOLOGIC AMPUTEES

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Objective: Residual limb pain affects an amputee's ability to tolerate and utilize a prosthesis thus impacting their function and overall quality of life. Neuromas and phantom limb pain (NPLP) are common causes of residual limb pain in amputees. Oncology patients in particular experience high rates of phantom limb pain and poor prosthetic tolerance.
Current treatment strategies for NPLP yield inconsistent and incomplete relief. Targeted muscle reinnervation (TMR) is a novel strategy to prevent NPLP in amputees. TMR involves the transfer of transected peripheral nerves to redundant target muscle motor units. TMR is thought to prevent symptomatic neuromas and phantom limb pain and allow for enhanced bioprosthetic function by re-establishing a neural pathway to provide a functional circuit for the transected nerve.
Our objective was to determine the effect of TMR on the prevention of symptomatic neuromas and phantom limb pain in an oncologic amputee population. Secondary outcomes were assessed including prosthetic use, oncologic outcome, complications and post-operative narcotic and neuromodulator use.

Methods: Patients undergoing amputation with concurrent TMR for a neoplastic diagnoses at The Ohio State University and Nationwide Children's Hospital between April 2015 and May 2017 were included. One patient was lost to follow-up after 5 months and excluded. Patient medical records were reviewed for demographics including age, sex, oncologic diagnosis and utilization of adjuvant therapies. The presence of post-operative neuromas and phantom limb pain as well as prosthetic use were assessed and noted in the chart by providers within the Plastic and Orthopaedic Surgery departments at 1 month, 1-3 month, 3-6 month, 12 month, 24 month and 36 month follow-up. The Ohio Automated Rx Reporting System was utilized to assess patient pre- and post-operative narcotic and neuromodulator (gabapentin or pregabalin) use at the following time points: pre-operatively, 2 weeks, 4 weeks, 6 weeks, 3 months, 6 months, 9 months, 12 months, 24 months and 36 months post-operatively. Reporting of gabapentin and pregabalin was initiated on December 1, 2016 thus patients undergoing surgery prior to this data were excluded from analysis.

Results: Nineteen patients with neoplastic diagnoses and at least 12-month follow-up have undergone amputation with concomitant TMR. Ten amputations were index resections. Nine patients underwent secondary amputation for local recurrence (N = 9) or failed reconstruction (N = 1). Average patient age was 49 years (range of 9-83). Average follow-up duration was 20 months (range of 13-37). Phantom limb pain was reported in 78.9% at 1 month, 42.1% between 1-3 months, 36.8% at both 3-6 months and 12 month follow-up. In patients completing 24-month follow-up (N = 5), 40% of patients reported having phantom limb pain. Three patients developed symptomatic neuromas. Two neuromas developed in non-transferred sensory nerves. 79% of patients use a prosthesis and began prosthetic wear at an average of 3.5 months. 79% of patients are without evidence of disease, 21% developed a local recurrence and 16% developed metastatic disease of whom one patient died 13 months after amputation. Wound complications requiring a operative intervention occurred in 21% of patients. At 12-month follow-up only 27% of patients required narcotic medication and of the eleven patients available for analysis only 37% of patients continued to use neuromodulators.

Conclusion: Oncology patients undergoing amputation with targeted muscle re-innervation at our institution developed neuromas at comparatively lower rate and have improved control of phantom limb pain related symptoms. Neuromas were noted to develop in large sensory peripheral nerves that were not included in initial transfer algorithms and has prompted change our practice. In addition, we observed high rates of prosthetic use early in the post-operative period, low rates of chronic narcotic and neuromodulator use and acceptable oncologic outcomes.

	Level of Amputation	Age (yrs)	Sex	Oncologic Diagnosis	Adjuvant Therapy			
					Pre-Operative		Post-Operative	
					Chemotherapy	XRT	Chemotherapy	XRT
1	AKA	9	F	Osteosarcoma	Yes	-	Yes	-
2	Trans-radial	49	M	Synovial Sarcoma	-	-	Yes	-
3	BKA	42	M	Leiomyosarcoma	Yes	-	-	-
4	Forequarter	58	M	Recurrent Chondroblastic Osteosarcoma	Yes	-	Yes	-
6	BKA	18	M	Ewing Sarcoma	Yes	-	Yes	-
7	AKA	51	M	Recurrent Malignant Peripheral Nerve Sheath Tumor	-	-	Yes	Yes
8	AKA	62	M	B-Cell Lymphoma	Yes	Yes	Yes	-
9	AKA	51	F	Recurrent PVNS	-	-	Yes	-
10	Forequarter	62	M	Recurrent Metastatic Colonic Adenocarcinoma	Yes	Yes	Yes	Yes
11	AKA	45	M	Pseudomyogenic Hemangioendothelioma	-	-	Yes	-
12	BKA	69	F	Synovial Cell Sarcoma	-	-	-	-
13	AKA	44	F	Recurrent Squamous Cell Carcinoma	-	-	Yes	-
14	BKA	51	M	Clear Cell Sarcoma	-	-	-	-
15	AKA	83	F	Recurrent High-grade Myxofibrosarcoma	-	-	Yes	-
16	Forequarter	54	M	Osteosarcoma	Yes	-	Yes	Yes
17	Forequarter	66	F	Recurrent Undiffentiated Pleomorphic Sarcoma	-	Yes	-	-
18	AKA	17	M	Osteosarcoma	-	-	Yes	-
19	AKA	47	M	High-grade Myxofibrosarcoma	Yes	Yes	Yes	-
20	Trans-humeral	60	F	Recurrent Epithelioid Sarcoma	-	-	Yes	Yes

Patient demographics including level of amputation, age, sex, oncologic diagnosis and the use of adjuvant therapies.

	Level of Amputation	Duration of Follow-up	Symptomatic Neuroma Follow-Up Interval (mos)						Phantom Limb Pain Follow-Up Interval (mos)						Time to Prosthetic (mos)	Oncologic Outcome
			1	1-3	3-6	12	24	36	1	1-3	3-6	12	24	36		
1	AKA	37	No	No	No	No	No	No	Yes	No	No	No	No	No	2	No evidence of disease
2	Trans-radial	35	No	No	No	No	No	*N/A*	Yes	No	No	Yes	Yes	*N/A*	6	Local recurrence/metastatic disease
3	BKA	30	No	No	No	No	No	*N/A*	Yes	No	No	No	No	*N/A*	2	No evidence of disease
4	Forequarter	29	No	No	No	No	No	*N/A*	No	No	Yes	No	Yes	*N/A*	-	No evidence of disease
5	BKA	24	No	No	No	No	No	*N/A*	Yes	No	No	No	No	*N/A*	3	No evidence of disease
6	AKA	20	No	No	No	No	*N/A*		Yes	No	No	Yes	*N/A*		3	No evidence of disease
7	AKA	12	No	No	No	No	*N/A*		Yes	Yes	Yes	No	*N/A*		3	No evidence of disease
8	AKA	19	No	No	No	Yes	*N/A*		Yes	Yes	Yes	Yes	*N/A*		4	No evidence of disease
9	Forequarter	19	No	No	No	No	*N/A*		No	No	No	No	*N/A*		7	No evidence of disease
10	AKA	19	No	No	No	No	*N/A*		Yes	Yes	Yes	Yes	*N/A*		2	No evidence of disease
11	BKA	15	No	No	No	No	*N/A*		Yes	Yes	No	No	*N/A*		4	No evidence of disease
12	AKA	18	No	No	No	No	*N/A*		No	No	No	No	*N/A*		5	No evidence of disease
13	BKA	15	No	No	No	No	*N/A*		Yes	Yes	No	No	*N/A*		2	No evidence of disease
14	AKA	16	No	No	No	No	*N/A*		No	No	No	No	*N/A*		3	Local recurrence/metastatic disease
15	Forequarter	13	No	No	No	No	*N/A*		Yes	No	Yes	Yes	*N/A*		-	Deceased
16	Forequarter	14	No	No	No	No	*N/A*		Yes	Yes	Yes	Yes	*N/A*		-	Local recurrence
17	AKA	13	No	No	Yes	No	*N/A*		Yes	Yes	No	No	*N/A*		2	No evidence of disease
18	AKA	14	No	No	No	No	*N/A*		Yes	No	No	No	*N/A*		4	No evidence of disease
19	Trans-humeral	13	No	No	Yes	No	*N/A*		Yes	Yes	Yes	Yes	*N/A*		-	No evidence of disease

Post-amputation with targeted muscle re-innervation outcomes with regards to level of amputation, duration of follow-up, incidence of symptomatic neuroma and phantom limb pain, time to prosthetic use and oncologic outcome.

Poster 278 3042850

USE OF FLAP RECONSTRUCTION AFTER RADICAL SURGERY FOR TRUNCAL AND EXTREMITY SARCOMAS

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Objective: To evaluate the characteristics and results of flap reconstruction in patients with truncal and extremities sarcomas.

Methods: Patients with sarcomas treated between 2008 and 2018 who required the use of flap reconstruction after complete surgical resection were retrospectively evaluated. Population and tumor data were evaluated. Location of the tumor and the defect. Type of flap used. Morbidity and mortality of the surgical procedure.

Results: Forty-three flaps were utilised in 42 patients with sarcomas to reconstruct the defect after resection. Twenty-seven patients had extremities sarcomas and 6 truncal sarcomas. Twenty-six patients were male. Free flaps were used in 20 patients (11 anterolateral thigh flap, 3 latissimus dorsi flap, 1 radial forearm flap, 2 gracilis flap and 1 lateral arm flap, 2 fillet flap). Pedicled flaps were used in 17 patients (3 gastrocnemius flap, 3 vertical rectus abdominis flap, 3 latissimus dorsi flap, 3 tensor fasciae latae flap, 5 other flap) and fasciocutaneous flap were used in 6 patients. The donor site could be closed with graft or primary closure in 41 patients. Local recurrence was observed in 25% of trunk sarcomas (2/8) and in 20% of extremity sarcomas (7/34). We observed 2 flap necrosis (one free flap and one pedicled flap) corresponding to 4.6% of failure, in 2 patients partial dehiscences occurred that did not require surgical resolution, one patient had to be amputated due to infection of the femoral prosthesis. No perioperative mortality was observed.

Conclusion: In our series, the use of flaps in surgical reconstruction after radical resection of sarcomas proved to be a useful tool with 95% of success and being more used in extremities sarcomas. In almost half of the cases the use of free flaps was required. This small series of patients evidences the variety of reconstructive options that should be taken into account when treating patients with sarcomas, especially in extremities, emphasizing the importance of the multidisciplinary management of these patients.

Poster 279 3005268

MIDTERM FOLLOW-UP OF A CUSTOM NON-FLUTED DIAPHYSEAL PRESS-FIT TUMOR PROSTHESIS SYSTEM

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Objective: Historically, endoprosthetic reconstruction in limb salvage surgery has predominantly involved cemented prostheses; however, the potential for biologic fixation with bone ingrowth of modern implants has resulted in an increased use of uncemented reconstructions. Due to theoretical concerns for early rotational instability with mega-prosthetic tumor reconstruction, early uncemented stem designs included de-rotational components (side plate in the Kotz MFTR, and fluted stems in the Stryker GMRS systems). However, these additions are not without their own complications, and mechanical data suggests that these stabilizers are an unnecessary component of a well-designed diaphyseal fitting stem. The goal of this study is to evaluate the midterm results of a custom non-fluted diaphyseal press-fit stem, used with the GMRS tumor prosthesis system.

Methods: Data was collected from our institute's prospective registry. A total of 53 patients (54 implants) underwent limb reconstruction using one of two non-fluted diaphyseal press-fit stem designs between 2005-2012. Initially we used a Stryker Restoration stem with a custom GMRS adapter (Cohort 1), however beginning in 2009 we used a custom GMRS press-fit stem (Cohort 2). Both stems were fully porous coated, straight, diaphyseal press-fit stems without de-rotational flutes. Patients were included in this study if they had at least 3years of follow-up. A total of 37 stems in 36 patients were included for this analysis. All complications and need for revision surgery were reviewed. Additionally, we specifically reviewed stem specific complications and radiographic evaluation of stems at most recent follow-up was performed by three independent observers. Three patients who underwent early stem removal due to local recurrence or infection with less than 2 years of stem follow-up were censored from the stem specific analyses and radiographic review.

Results: A total of 24 femoral (16 Restoration, 8 custom) and 13 tibial (7 Restoration, 6 custom) press-fit stems were reviewed. Average follow up was 7.1 years (range 3.1 to 11.7 years). Repeat surgery for implant-related complications occurred in 8/37 (22%) patients. All of these patients were from the Restoration stem group, and included three patients with failure of the stem-adapter junction (requiring revision of the adapter only), four patients requiring revision for polyethylene wear, and one patient with an unrecognized intraoperative fracture that required subsequent ORIF (although the stem was stable and remained in-situ). No patients with the non-fluted custom GMRS stems had any implant-related complications.

Of the 34 stems included in the stem specific analyses, none required revision by the time of final follow up. On radiographic review, all stems were well ingrown, without evidence of loosening, although 7/34 (21%) stems exhibited mild stress shielding. Overall, we saw no difference in complications or radiographic outcomes of stems placed in the femur or tibia.

Conclusion: A custom non-fluted diaphyseal press-fit stem, used with the GMRS tumor prosthesis system provides a stable bone-prosthesis interface without evidence of loosening or other fixation failures at mid-term follow up. While some complications occurred as a result of the custom adapter required to use the Stryker Restoration stem with the GMRS prosthesis, all stems achieved excellent biologic ingrowth. Additionally, this mode of failure has been resolved with the creation and use of the custom non-fluted Stryker GMRS stem, and we have seen no stem related failures in this group to date.

Poster 280 3007952

DUAL MOBILITY COMPONENTS CEMENTED INTO AN ACETABULAR RECONSTRUCTIVE CAGE FOR LARGE OSSEOUS DEFECTS IN THE SETTING OF PERIACETABULAR METASTATIC DISEASE

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Objective: Large osseous acetabular defects secondary to periacetabular metastatic disease frequently require advanced methods of acetabular reinforcement and reconstruction. Various techniques of acetabular reconstruction along with numerous constructs to increase stability have been described, but no consensus for the optimal management of these osseous defects has been reached so far. We present our technique and patient outcomes for acetabular reconstruction by cementing a dual mobility bearing into an acetabular cage construct.

Methods: We reviewed 152 total hip arthroplasties (THA) and identified eighteen patients with periacetabular metastatic disease and large osseous defects who required complex acetabular reconstruction utilizing a modular dual mobility cup cemented into an acetabular reconstructive cage. The following outcomes were evaluated: pain relief, functional improvement, and postoperative complications.

Results: Mean follow-up was three years (range, 2-5.5 years), with eleven (61%) of the eighteen patients identified being alive for two-year postoperative follow-up. Patients reported a significant improvement in both pain and functional outcomes. There were no dislocations reported or signs of loosening detected on radiographs. Two patient developed postoperative infections requiring irrigation and debridement with retention of components. One patient went on to require a hemipelvectomy sixteen months following acetabular cage reconstruction due to recurrence of metastatic renal cell carcinoma.

Conclusion: Cementing a dual mobility bearing into an acetabular cage construct provides a highly stable and durable reconstruction option for patients with periacetabular metastatic disease and large osseous defects. Patients are able to return to immediate full weight bearing with significant improvement in both function and pain.

Poster 281 3033191

LONG TERM OUTCOMES OF TOTAL HUMERAL REPLACEMENT FOR PRIMARY BONE TUMORS IN 18 PATIENTS

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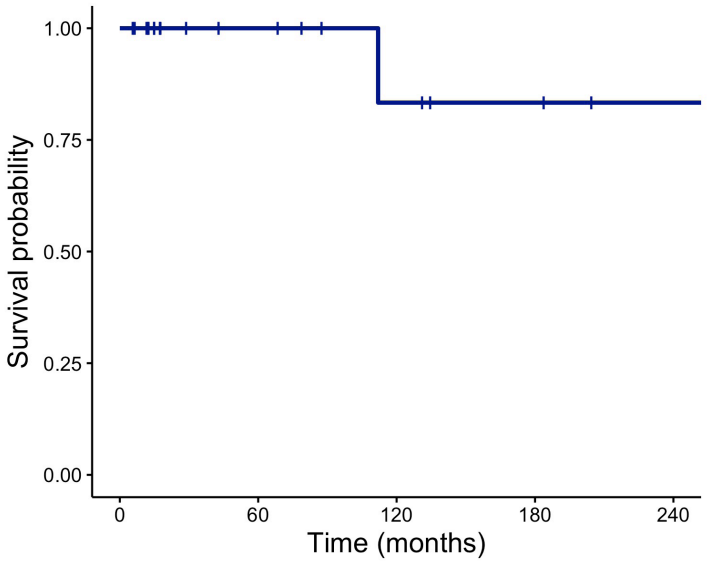
Objective: The proximal humerus is amongst the most common locations of primary bone sarcoma, but tumors requiring total humeral replacement (THR) are rare, representing < 2% of endoprosthetic reconsuctions. As with proximal humeral resection, THR is complicated by instability of the poly-axial glenohumeral joint, whereas the common complication of aseptic loosening that is inherent in endoprosthetic reconstruction is not a significant concern. Data describing the outcomes, survivorship, and complication of THR are limited. Soft-tissue failure at the shoulder and mechanical failure of the ulnar stem are the most frequently documented mechanical complications. Nerve palsy has also been documented as a common complication. There is a paucity of data on long-term survivorship and outcomes for THR with only two series reporting 10-year survival. We aim to examine the long-term survivorship, outcomes, and modes of failure of total humeral endoprosthetic replacement.

Methods: This is a retrospective review of a prospectively collected database consisting of 512 consecutive endoprosthetic reconstructions performed for oncologic diagnoses at a single-center between 1980 and 2018. We identified 17 patients with

20 THR implants. 16 endoprosthesis were implanted following primary resection of tumor (8 osteosarcoma, 1 metastatic osteosarcoma, 3 Ewing's sarcoma, 2 chondrosarcoma, 1 malignant fibrous histiocytoma, 1 multiple myeloma). The remaining 5 were implanted as revision prostheses. 12 patients were alive at recent follow-up; 15 patients had a minimum of 1 year follow up. 13 patients had MSTS scores available, 12 of which had a minimum of 1 year follow up. 11 patients had sufficient data for complete analysis of radial nerve palsy and shoulder instability. Outcomes evaluated were implant survival, revision surgery categorized according to the Henderson Classification, complications, and functional outcomes. Bushing changes expansion related revisions were not considered failures. Prosthesis survival is analyzed at 5, 10 and 15 years using Kaplan-Meier analysis.

Results: The median follow-up for surviving patients was 123 months (25^{th}-75^{th} percentile, 15 to 204 months) and 43 months (25th-75th percentile, 15 to 131 months) for all patients analyzed. A total of 2 prostheses required revision for mechanical failure, both for soft-tissue failure resulting in symptomatic shoulder dislocation. Both mechanical failure and all-cause survival at 5, 10, and 15 years were 100%, 83% and 83%, respectively (Figure 1). Mean MSTS score for the upper extremity was 70% (range 34-100%). There were no cases of ulnar component failure, and 3 of 11 analyzed patients (27%) experienced symptomatic shoulder instability, 2 of which required revision. There were no cases of nerve palsy. 1 patient underwent revision of expandable prostheses due to lack of further expansion, and one underwent a procedure for augmentation of collapsed expansion mechanism. 1 patient underwent radial heal excision for symptomatic elbow instability. There was 1 wound dehiscence that was taken for debridement at 1 month in an irradiated patient. There were no infections.

Conclusion: Total humerus endoprosthetic replacement is a reasonable reconstruction option for patients who require complete excision of the humerus for malignant bone tumors. THR offers limited but satisfactory functional outcomes with low failure and complication rates. In our study, survivorship is comparable to previous series. Soft tissue failure at the shoulder necessitating revision was the only mode of failure in this series. Previous series have cited periprosthetic infection as the most common cause of all cause failure, but no infections were documented in this series. There were no nerve palsies or failures of the ulnar component as have been documented previously. Despite expected range of motion and strength limitations, total humeral reconstruction offers preservation of upper extremity function with a low rate of complications and failure.



Kaplan-Meier survival curves for failure of total humerus endoprostheses.

Poster 282 3036524

CHARACTERIZATION OF A BONE BIOREPOSITORY: COMPARISON OF SARCOMAS AND BONE METASTASES FROM BREAST, PROSTATE, RENAL, LUNG CANCERS, AND MYELOMA

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Objective: While bone is one of the most common sites of metastasis for many cancer types, there is a lack of access to the necessary quantity and quality of human specimens. Collection of sarcomas and metastatic cancer tissue will advance the understanding of the bone microenvironment. Our multidisciplinary team has developed a method of intraoperative rapid retrieval of human bone tissue and blood as well as acquisition of matching primary tissue and clinical data.

Methods: The Bone Biorepository Bank (BBB) is notified when patients (pts) with primary or metastatic cancer to the bone with standard of care surgeries are identified and consented. Biospecimens are processed within minutes and stored as

FFPE blocks, preserved in RNA*later*, and snap frozen. Plasma and buffy coat are extracted from whole blood within four hours. H&E sections are reviewed by Pathology for tumor burden (TB), presence of tumor necrosis (TN), osteoblastic and osteoclastic activity level (OBC), and fibrous stromal proliferation level (SP). Primary tumor slides are obtained, and clinical information is extracted from medical records.

Results: From December 2016 to March 2018 the BBB enrolled 80 pts with 99 bone, 56 blood, and 35 primary samples. The bank includes 16 cancer types with the largest sample amounts in breast (N=35), sarcoma (31), prostate (17), myeloma (17), renal (16), and lung (13) out of 173 FFPE blocks. 66.4% of samples had systemic treatment (tx) before surgery. Preliminary analysis of H&Es in the 6 largest cancer types revealed no differences in TB or OBC. There was significant difference in TN (p=0.026); in pairwise comparisons more samples of lung cancer contained necrosis compared to samples of myeloma (0.0121) despite having similar tx statuses. SP also had statistical significance (<0.001); pairwise comparisons showed that SP was significantly higher in breast compared to SP in myeloma (0.0002), prostate (0.041), renal (0.0015), and sarcoma (0.014). Analysis of pts who were tx naïve versus pts who received tx did not show histological difference. However, tx between cancers was significantly different (0.01); pairwise comparisons showed the significance to be between breast and lung with more breast cancer patients receiving systemic treatment before the surgeries than lung cancer patients.

Conclusion: Specimen analysis showed more similarities than differences in histological patterns between cancer types regardless of tx status. In cases of differences, breast was often a point of significance in the comparisons. Continued growth of the BBB will be an invaluable resource to better understand the metastatic bone microenvironment. Additional molecular and genetic tests are ongoing.

Poster 283 3042485

AN INVESTIGATION OF BONE REGENERATION BY USING BONE SUBSTITUTE MATERIALS AFTER BONE TUMOR CURETTAGE

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Objective: The bone substitute materials are often used after bone tumor curettage. In recent years, we have been able to use the porous hydroxyapatite collagen composite (HA/Col) in Japan. The purpose of this study was to investigate the efficacy of HA/Col for bone regeneration after bone tumor curettage comparing with β-tricalcium phosphate (β-TCP) which has been used conventionally.

Methods: Bone tumors of patients which were performed tumor curettage in Tohoku University Hospital between January 2011 – December 2017 were included in this study. Cox proportional hazards analysis was conducted to calculate the hazard ratio (HR) and 95% confidence interval (CI) for the appearance of new bone at 6 weeks after surgery according to type of bone substitute materials and potential risk factors as follows: age, sex, pathological fracture, tumor length, tumor volume, area of fenestration, internal fixation, intraoperative anhydrous ethanol therapy, histological grade.

Results: The final study population was comprised of 38 cases (aged 6 to 70 years old, male 55.2%). The follow up period was 1 to 71 months. Among them, 50% (n = 19) of patients were in the HA/Col group and 50% (n = 19) of patients were in the β-TCP group. Appearance of new bone at 6 weeks after surgery was occurred in 47.3% (n = 18) cases. In HA/Col group, the new bone appearance rate was higher than β-TCP group significantly (Sex, age-adjusted HR [95% CI]: 36.01 [4.239-305.894], p=0.001). In young cases, new bone appearance rate was higher than old cases significantly (Sex, age-adjusted HR [95 CI]: 1.032 [1.004-1.060], p = 0.023).

Conclusion: HA/Col can induce new bone appearance earlier than β-TCP after bone tumor curettage.

Poster 284 3033250

FUNCTIONAL OUTCOME AND COMPLICATIONS OF EXTERNAL HEMIPELVECTOMY IN THE SEVEN PATIENTS UNDERWENT FOR MALIGNANT BONE AND SOFT TISSUE TUMORS

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Objective: Indication of external hemipelvectomy is rare, when the major neurovascular are involved by malignant tumors. Only few studies have done as for functional analysis or complications after the surgery. We investigated postoperative

complications and functional outcome of seven patients who have undergone external hemipelvectomy as a surgery for malignant bone and soft tissue tumors.

Methods: There were six male and one female patients undergoing external hemipelvectomy from 2010 to 2016 at our institution. The median age was 72.6 years (range, 65-83) at the time of diagnosis. The mean follow-up period was 22.6 months (range, 6-42). Five patients had bone tumor and two patients, soft tissue sarcoma. The pathological diagnoses were as follows: undifferentiated pleomorphic sarcoma (n=3), dedifferentiated liposarcoma (n=2), osteosarcoma (n=1) and chondrosarcoma (n=1). Mean operative time was 375 minutes (range, 295-431) and a median blood loss was 2,108 ml (range, 541-7,613)(Table 1). The clinical information including postoperative complications, local recurrence, distant metastasis, oncological outcome, activity of daily living in preoperative period and final period among survivors, Musculoskeletal Tumour Society (MSTS) score, and prosthesis fitting were obtained from medical records.

Results: Postoperative complications were as follow: lymphocele formation (n=5), deep vein thrombosis (DVT) (n=3), asymptomatic pulmonary embolism (PE) (n=1), wound infection (n=1), urinary tract infection (n=1), pleural effusion / atelectasis (n=1) and pneumonia (n=1). No local recurrence was observed in all cases. Distant metastases developed in three cases, and the site of metastases were lung in 3, and brain in 1. Oncological outcomes were three CDF, one AWD, two DOD and one DOC. All 7 patients were able to walk before the operation. At the final follow-up, mean MSTS score of all four survivors was 25.8%, one patient used only walker and three patients were wheelchair-bound; one of them only used it and another two used crutches for short. There was no patient with successful use of prosthesis at the final follow-up (Table 2).

Conclusion: Previous study reported that DVT or PE incidences of 14.7% after hemipelvectomy. In this study, 42.9% and 14.3% of cases developed DVT and PE, respectively. Our study showed that we should be concerned about development of DVT and PE after external hemipelvectomy. More than half patients were wheelchair-bound after external hemipelvectomy. On the other hand, 75% of all survivors were able to walk using crutches or walker without limb prosthesis.

Table 1. Patient characteristics

Case	Age/sex	Site (ST/B)*	Pathological diagnosis	Stage (AJCC 7th)	Size (cm)	Chemotherapy	Radiotherapy	Operation time (min)	Bleeding volume (ml)	Margin
1	78/F	proximal thigh (ST)	Undifferentated pleomorphic sarcoma	III	20	-	-	367	688	R0
2	69/F	proximal thigh (ST)	Dedifferentiated liposarcoma	III	7	-	-	295	541	R0
3	68/M	proximal femur (B)	Osteosarcoma	IIB	24	-	-	415	1,542	R0
4	65/M	groin・pubis (ST・B)	Undifferentated pleomorphic sarcoma	IV	10	Neoadj: AI×3 Adj: TRB	Postoperative 60Gy/30fr	431	7,613	R0
5	83/M	proximal thigh (ST)	Undifferentated pleomorphic sarcoma	III	15	-	-	359	1,288	R0
6	71/M	Groin (ST)	Dedifferentiated liposarcoma	III	7	-	-	386	1,370	R1
7	74/M	proximal femur (B)	Chondrosarcoma	III	30	-	-	372	1,720	R2

ST; soft tissue, B; bone, Neoadj; neoadjuvant, Adj; adjuvant, AI, Adriamycin and Ifosfomide; TRB, Trabectedin

Table 2. Complication, clinical and functional outcome

Case	Postoperative complication	Local recurrence	Metastasis (site)	Hospital stay (days)	Outcome (months of FU)	Preoperative PS	Preoperative ADL	Final PS	Final ADL	MSTS score	Prosthesis
1	Lymphocele formation, Wound infection, Urinary tract infection	-	+ (Lung)	74	DOD (19)	0	WF	-	-	-	No
2	-	-	-	84	CDF (24)	0	WF	2	WC	8/30 (26.7%)	No
3	DVT, Lymphocele formation	-	-	69	CDF (24)	1	CR	2	WC /CR	8/30 (26.7%)	No
4	PE, Lymphocele formation	-	+ (Lung)	48	AWD (16)	1	WF	2	WC /CR	8/30 (26.7%)	No
5	DVT, Lymphocele formation	-	+ (Lung, Brain)	74	DOD (6)	2	WF	-	-	-	No
6	Lymphocele formation	-	-	59	DOC (14)	0	WF	-	-	-	No
7	DVT, Pleural effusion/Atelectasis, Pneumonia	-	-	106	CDF (11)	1	WF	1	WK	7/30 (23.3%)	No

DVT; deep vein thrombosis, PE; pulmonary embolism, FU; follow-up, CDF; continuous disease free, AWD; alive with disease, DOD; dead of disease, DOC; dead of other causes, WF; ambulating without walking aid, CR; crutches, WK; walker, WC; wheelchair

Poster 285 3042529

RELATIVE PERCENTAGE OF CIRCULATING ACTIVATED EFFECTOR NKT CELLS FOLLOWING FIRST CYCLE OF CHEMOTHERAPY CORRELATES WITH HISTOLOGIC NECROSIS IN OSTEOSARCOMA PATIENTS

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Objective: Three previous studies have reported that osteosarcoma patients with higher absolute lymphocyte counts in peripheral blood two weeks after starting chemotherapy have improved outcomes. However, it is unclear which types of lymphocytes are associated with this therapeutic benefit. Therefore, we prospectively performed lymphocyte subpopulation analysis on peripheral blood samples from patients before and two weeks after their first cycle of neoadjuvant chemotherapy.

Methods: Patients with newly-diagnosed osteosarcoma from five institutions were treated with standard chemotherapy including cisplatin, doxorubicin, and high-dose methotrexate (MAP regimen). Blood counts and lymphocyte subpopulations were analyzed prior to starting therapy, and again two weeks after the first cycle of cisplatin and doxorubicin. Given the short median follow-up of this ongoing study, results were correlated with histologic necrosis at definitive surgery following neo-adjuvant chemotherapy, defining > 90% necrosis as favorable and $\leq$ 90% as unfavorable. Planned accrual is 34 evaluable patients, and we now report an interim analysis of results from the first 25 patients.

Results: Twenty-five patients are evaluable to date, including 8 females and 5 with metastatic disease. The median age was 15 years (range 11-34 years). With median follow-up of 627 days (1.7 years), the estimated 2-year progression-free and overall survival for the group was 59% and 78%, respectively. Ten patients (40%) had favorable necrosis at definitive surgery done 10 weeks after starting neoadjuvant chemotherapy. Following the first cycle of neoadjuvant chemotherapy, relative percentages of Granzyme B+ natural killer T (NKT) cells were significantly increased in those with favorable necrosis ($p = 0.0098$). In addition, there was a strong trend for increase in perforin+ NKT cells ($p = 0.06$) in patients with favorable necrosis. Interestingly, there was no significant difference in these cell populations prior to therapy, nor in other NK cell populations.

Conclusion: In the interim results from this prospective study, osteosarcoma patients with higher percentages of circulating

activated effector NKT cells (as demonstrated by granzyme B or perforin expression) following the first cycle of chemotherapy were more likely to have favorable histologic necrosis. These findings are consistent with preclinical work showing these cells potentiate the cytotoxicity of cisplatin in osteosarcoma cell lines, and suggest that this cell population in the peripheral blood may help mediate anti-tumor effects in osteosarcoma patients. Further analysis of additional patients is ongoing to confirm these preliminary findings.

Poster 286 3042815

IDENTIFYING JUDICIOUS APPLICATIONS FOR SPONTANEOUS BONE CANCER OF DOGS AS A MODEL FOR PEDIATRIC OSTEOSARCOMA

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Objective: Our goal was to define situations where the osteosarcoma of dogs provides a suitable model for the disease in humans.Comparative, cross-species studies can inform the basic biology of the disease, and animal models offer opportunities to test novel interventions. While osteosarcoma occurs in species of every vertebrate class from bony fishes to mammals, the disease is especially prevalent in domestic dogs. The natural history of the disease in dogs and humans is remarkably similar, so dogs have been advanced as an “excellent model” for pediatric osteosarcoma. Nevertheless, distinct differences in the epidemiology of these two diseases, including the stage of life when the disease is most common, raise questions about the strength of the model.

Methods: We used next-generation matched tumor and normal exome sequencing, RNA sequencing, and bioinformatic tools to define comparative landscapes of somatic mutations and gene expression profiles of canine and human osteosarcoma. Ninety-two samples were sequenced from dogs of both sexes and various breeds, ranging from 1 to 14 years of age. Exome data for human samples (n = 35) were obtained from the public domain (GEO Series GSE87624 and dbGap:phs000699.v1.p1). The analysis further relied on data from osteosarcomas of 25 mice with conditional mutation of *TP53* in osteoblasts, and from 67 mice with Sleeping Beauty transposon-accelerated osteosarcoma.

Results: Recurrent inactivation of *TP53* is a frequent mutational event in osteosarcomas from humans and dogs, but few additional abnormalities were found recurrently and none were extensively shared between the two species. Mutational signatures were distinctly different, with dogs showing predominance of the aging-associated signature that was absent in humans. Transcriptional profiles were conserved, with coordinated activation (or silencing) of cell cycle-related and immune response gene clusters seen in both species. A gene cluster expression summary score (GCESS) method allowed us to reduce transcriptional complexity and document that a cell cycle-GCESS was associated with outcome in both species. On the other hand, immune-GCESS were only predictive for outcome in human patients. This created a paradox, as canine osteosarcoma is an immunoresponsive tumor. The answer to this paradox may lie in the peculiar organization of the dog genome, which increases the probability of homozygous PTEN loss in the tumors. This PTEN loss, in turn, might ablate the protective effects of endogenous anti-tumor immunity, albeit preserving the capacity of the immune system to attack the tumor when given appropriate exogenous stimuli.

Conclusion: Distinct molecular mechanisms contribute to the risk of osteosarcoma in humans and dogs. The infrequent occurrence and predominance of the disease in children, adolescents, and young adults, points to syndromic predisposition and stochastic events as major risk factors in humans. In contrast, artificial selection for large size without compensatory protective mechanisms for longer lifespans seem to be the predominant risk factors in dogs. Inactivation of *TP53* pathways appear to be an important, causal event of osteosarcoma of both humans and dogs, likely contributing to genomic instability and the generation of chaotic genomes. Various additional, and generally patient-specific genomic alterations are responsible for the extensive molecular heterogeneity of the disease. Nonetheless, osteosarcomas of humans and dogs coalesce into a smaller number of clinical phenotypes with transcriptional homology, allowing for judicious applications of dogs as models to improve diagnostic precision, predict biological behavior, and develop effective strategies for treatment and prevention.

Poster 287 3042819

MODULATION OF MRNA TRANSLATION REGULATION IN HIGHLY METASTATIC OSTEOSARCOMA CELLS INHIBITS LUNG METASTASIS PROGRESSION

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Objective: The overall goal of the current work is to determine if targeting the mRNA translation machinery in highly metastatic osteosarcoma (OS) cells will inhibit lung metastasis progression. During the early phases of lung colonization, OS cells must quickly manage various cellular stresses (eg. redox stress) in order to survive and proliferate in a new microenvironment. In order to adapt quickly to a new extracellular environment, regulation of mRNA translation is known to facilitate a rapid change in the protein compliment of the cell. When comparing the mRNA translation machinery between clonally related human high and low metastatic OS cell lines, several components of the mRNA 5' capping complex, **e**ukaryotic **I**nitiation **F**actor **4F** (eIF4F), are differentially upregulated in high metastatic versus low metastatic OS cells (RNAseq data, previously published). In particular, **e**ukaryotic **i**nitiation **f**actor **4G** (eIF4G1) has been observed to be elevated (both mRNA transcript and protein levels) in high metastatic versus low metastatic OS cells. We hypothesize that the upregulation of translation initiation factors in highly metastatic OS cells, eIF4G1 in particular, contributes to their ability to adapt to redox stress. Moreover, an impaired ability to adapt to redox stress, via eIF4G1 inhibition, is predicted to diminish the ability of high metastatic OS cells to grow in the lung microenvironment.

Methods: Cell culture and materials: Human, eGFP-expressing high metastatic and low metastatic OS cell lines, MG63.3 and MG63 respectively, were used in the current study. O(2)-{2,4-dinitro-5-[4-(N-methylamino)benzoyloxy]phenyl} 1-(N,N-dimethylamino) diazen-1-ium-1,2-diolate (PABA/NO) is a nitric oxide donor compound, and was used to induce redox stress in OS cells *in vitro*. A small molecule inhibitor of eIF4G1, called SBI-756, was used as a pharmacological tool to perturb translation initiation in OS cells. An Incucyte cell culture system was used to monitor cell proliferation in response to vehicle, single-agent, and multi-agent drug studies. Cellular glutathione (GSH) levels were assessed by a GSH-dependent luminescence assay. Confocal microscopy: Vehicle-treated and PABA/NO-treated OS cells in chamber slides were immunostained for 3-nitrotyrosine (3-NT), a redox stress marker. Automated image acquisition was done on a confocal microscope with a computer-controlled stage. Images were analyzed in a semi-automated method via Image J. Pulmonary metastasis assay (PuMA): The growth of eGFP-expressing MG63.3 cells in viable mouse lung tissue sections (maintained *ex vivo*) was longitudinally over a period of 14 days. Protein mass spectrometry: Azidohomoalanine labelling, CLICK-chemistry, and pulse stable isotope labelling with amino acids, were used to identify which redox stress-induced, newly synthesized proteins were down-modulated by SBI-756 treatment *in vitro*.

Results: Nanomolar concentrations of SBI-756, by itself, resulted in no appreciable effects on MG63.3 cell proliferation compared to vehicle-treated controls. However, in the presence of redox stress (PABA/NO co-treatment), nanomolar concentrations of SBI-756 significantly inhibited the proliferation rate of MG63.3 cells. SBI-756 treatment in combination with PABA/NO resulted in a higher accumulation of 3-NT compared to vehicle treatment or single agent controls, as shown by quantitative immunofluoresence microscopy. MG63.3 cell treatment with increasing concentrations of SBI-756 resulted in dose-dependent decrease in GSH levels. SBI-767 was found to inhibit MG63.3 cell growth in the *ex vivo* lung explant PuMA model. Lastly, preliminary proteomic data suggests that enzymes in the glutathione (GSH) metabolism pathway are down-modulated by SBI-756. Current efforts are underway to validate these proteomic data.

Conclusion: Taken together, the data in the present work suggests that targeting specific components of the eIF4F complex in highly metastatic OS cells has translation potential as an anti-metastatic therapeutic strategy.

Poster 288 3004242

FACTORS ASSOCIATED WITH LIFE IN ADULTS WITH LOCALIZED OSTEOSARCOMA

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Objective: While the last two decades have seen significant advances in the treatment of many types of cancer, survival of patients with localized osteosarcoma has not changed significantly in several decades. Prognostic factors for survival in osteosarcoma have been well demonstrated in several studies and include age, size, margin status, chemotherapy regimen and tumor site. However, as the disease is uncommon, study sizes have been limited. Additionally, the degree of impact of specific factors on survival has been difficult to quantify. We investigated the largest registry of primary localized osteosarcoma, the national cancer database (NCDB). Our goal was to identify the factors most prognostic of survival

in adults. Specifically, we sought to identify the A) demographic B) tumor and C) treatment characteristics most highly correlated with survival.

Methods: We retrospectively analyzed patients in the NCDB from 2004 through 2015. Patients were included who had localized osteosarcoma. All patients with metastatic disease, or under the age of 18, were excluded. Unadjusted overall survival (OS) was estimated using the Kaplan Meier method, with statistical comparisons based on the log-rank test. A Cox proportional hazard model was used to estimate the association between demographic, pathologic, and treatment variables and OS after adjustment for known covariates.

Results: We identified 2,981 patients presenting with primary localized osteosarcoma. The patient cohort had a median age of 36 (range 18-90); 1,669 (56%) of the patients were males. Of the 2,981 patients with localized osteosarcoma, 2,294 had a tumor grade reported, of which 1,793 (78%) were high-grade, 259 (11%) were intermediate grade, and 242 (11%) were low-grade tumors. In a multivariate analysis, the factors that were most strongly correlated with survival in osteosarcoma included lower tumor grade, younger age, primary site in the limb, smaller tumor size, and negative margins. Amongst the demographic variables, younger age and female sex had the most significant impact on improved survival (Age >50 vs. <25 years hazard ratio [HR] 2.03 (1.69-2.44), p<0.001; male vs. female HR 1.18 (1.04-1.33), p=0.010). Amongst tumor characteristics, lower tumor grade, tumor site and smaller size had the largest impact on survival (high grade vs. low grade HR 4.34 (2.87-6.57), p<0.0001; site in pelvis or spine vs. limb HR 1.72 (1.44-2.07), p<0.001 and HR 2.12 (1.56-2.87), p<0.001, respectively; and size >5cm vs <5cm HR 1.94 (1.57-2.40), p<0.001). Amongst treatment characteristics, factors that were most associated with improved survival were surgery type, negative surgical margins and use of chemotherapy (amputation vs radical resection HR 1.34 (1.12-1.59), p=0.001; positive vs. negative margins HR 1.80 (1.48-2.19), p<0.001; no chemotherapy vs. chemotherapy HR 1.21 (1.04-1.42), p=0.013). Amongst high grade tumors, chemotherapy was correlated with dramatically improved survival (no chemotherapy vs. chemotherapy HR 1.61 (1.339-1.925), p=0.001). Factors that were not independently associated with survival included race, Hispanic ethnicity, insurance status, income, education and radiation use.

Conclusion: This is the largest patient cohort to date examining factors prognostic for survival in osteosarcoma. The most important overall factors prognostic of survival were younger patient age and lower tumor grade. Limb-sparing, margin negative surgery improves survival; chemotherapy use dramatically improves survival in high grade tumors. A better understanding of this uncommon disease is necessary if outcomes are to improve.

Table 1. Independent predictors of mortality in multivariate proportional hazards analysis

Variable	HR	Lower 95%	Upper 95%	P value
Patient variables				
Age (years) (Ref=0-25)	Ref			
25-50	1.28	1.09	1.51	0.0025*
>50	2.03	1.69	2.44	<.0001*
Male sex (Ref=Female)	1.18	1.04	1.33	0.0096*
Hispanic (Ref=Non-Hispanic)	0.89	0.71	1.12	0.31
Race (Ref=Caucasian)				
African-American	1.10	0.93	1.30	0.28
Asian	1.14	0.81	1.60	0.45
Comorbidity Score >1 (Ref=0-1)	1.60	1.10	2.34	0.0142*
Insurance (Ref=Private Insurance)				
Medicare	1.62	1.35	1.95	<.0001*
Medicaid	1.10	0.91	1.33	0.34
No insurance	1.21	0.94	1.55	0.14
Income below median ($48,000)	0.98	0.85	1.14	0.79
Education below median (87% HSD)	0.92	0.79	1.07	0.30
Tumor and treatment variables				
Size >5cm	1.94	1.57	2.40	<.0001*
Grade (Ref=Low grade)				
Intermediate grade	1.21	0.73	2.02	0.46
High grade	4.34	2.87	6.57	<.0001*
Location (Ref=Limb)				
Spine	2.12	1.56	2.87	<.0001*
Pelvis	1.72	1.44	2.07	<.0001*
Surgery (Ref=No surgery)				
All types	0.56	0.44	0.71	<.0001*
Amputation	0.73	0.55	0.97	0.0304*
Radical resection	0.55	0.43	0.71	<.0001*
Local resection	0.49	0.37	0.64	<.0001*
Surgical margins positive	1.80	1.48	2.19	<.0001*
Radiation use	1.06	0.87	1.28	0.58
Chemotherapy use	0.82	0.71	0.96	0.0129*

HR = hazard ratio; * indicates statistical significance (at alpha of 0.05)

Poster 289 3027652

HIGH GRADE INTRAMEDULLARY OSTEOSARCOMA: DOES HISTOLOGIC SUBTYPE AFFECT OUTCOME?

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Objective: Our understanding of osteosarcoma is limited by the rarity of this diagnosis, and the resultant difficulty in obtaining large enough patient populations for evaluation and analysis. The association between tumor necrosis rate and survival is of particular interest, as it may help guide treatment recommendations and improve future outcomes. The major subtypes of high grade intramedullary osteosarcoma may show differing responses to therapy, which may also affect survival. We evaluate outcomes of high grade intramedullary osteosarcoma in a large cohort.

Methods: We performed a retrospective review of 430 patients treated at our institution over a 25 year period. Descriptive statistics, survival analysis (overall, and recurrence-free survival) and Cox proportional hazards regression models were performed.

Results: The major histologic subtypes evaluated were: osteoblastic (52%), chondroblastic (20%), fibroblastic (20%), and telangiectatic (8%). Chondroblastic and telangiectatic subtypes were more commonly identified correctly at biopsy, compared to fibroblastic. The mean response to neoadjuvant therapy was 86%. On average, the percentage of necrosis was highest for telangiectatic and lowest for chondroblastic subtypes (P<0.001).
Disease specific mortality during the study period was 49%. The median time to death was 9.59 years [95% CI: (5.88; 13.90)]. Patients with less than 90% necrosis after neoadjuvant chemotherapy had significantly worse overall and recurrence-free survival (p<0.001), as did patients with metastatic disease at diagnosis (p<0.001). Chondroblastic subtype showed the worst overall survival, followed by osteoblastic. Telangiectatic subtype showed the best overall survival. Overall and recurrence-free survival by histologic subtype was not statistically significantly (p=0.09).
Multivariate analysis showed significantly worse overall and recurrence-free survival for patients with metastases at diagnosis, less than 90% necrosis after neoadjuvant chemotherapy, and with older age at diagnosis (p<0.01 for all factors).

Conclusion: Histologic subtype was significantly associated with response to neoadjuvant chemotherapy, with chondroblastic showing the least response, and telangiectatic the best. This correlated with a difference in overall and recurrence-free survival, but did not reach statistical significance. Overall and recurrence-free survival was significantly associated with the presence of metastatic disease at diagnosis, poor response to neoadjuvant chemotherapy (<90% necrosis), and older age at diagnosis.

Poster 290 3042179

THE CLINICAL OUTCOME OF THE OSTEOARTICULAR EXTRACORPOREAL IRRADIATED AUTOGRAFT FOR BONE SARCOMA

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Objective: Recycle autografts treated with extracorporeal irradiation or liquid nitrogen are an alternative operation technique to prosthetic devices or allografts for reconstruction after resection of bone malignancies. Recycle autografts have some advantages including no risk of viral transmission, no problems of prosthetic wear, the precise anatomical fit, re-attachment of muscle and tendons, or sparing of the growth plate in the surrounding healthy bone. Intercalary recycle autografts are reported as promising methods with good outcomes. However, there are few reports about osteoarticular recycle autografts. Especially, the difference in outcome among graft sites of osteoarticular recycle autograft has not ever been studied so far. The purpose of this study is to elucidate the clinical outcome of the osteoarticular extracorporeal irradiated autograft for bone sarcoma, to clarify the difference in complications among the sites of osteoarticular graft, and to find the way to utilize this technique.

Methods: We retrospectively reviewed the medical record of the 33 patients who underwent osteoarticular extracorporeal irradiated autograft for reconstruction after resection of bone malignancies including osteosarcoma, Ewing sarcoma,

chondrosarcoma, or bone metastasis from 1988 to 2014 in our hospital with a median age of 17 years (6 to 67). The graft bones were irradiated with a single dose of 50 Gy but 80 Gy for 2 patients with chondrosarcoma. The site of osteoarticular graft were 3 scapulas, 8 proximal humeruses, 2 distal humeruses, 1 proximal ulnas, 1 proximal radiuses, 1 distal radiuses, 1 metacarpals, 3 acetabulums, 1 proximal femurs, 3 distal femurs, 6 proximal tibias, and 3 distal tibias. We surveyed the survival, the recurrence, the infection, the additional procedures, the graft status, and the radiographic evaluation according to ISOLS graft evaluation criteria. For the patients who still had osteoarticular graft at the time of survey, we evaluated the Muscluoskeletal Tumor Society (MSTS) function score. Median follow up time was 8 years ranging from 5 months to 22 years.

Results: Of the 33 patients, 23 were continuously disease free (CDF), 3 no evidence of disease (NED), and 1 alive with disease (AWD), and 6 died of disease. Local recurrence was not observed at all. Additional procedures were needed for 15 patients (45 %) including 8 patients with infection, 5 patients with protrusion of the fixation implant, 2 patients with aseptic collapse of the grafted bone. The removal of the osteoarticular extracorporeal irradiated autograft was performed in 5 patients. One patient was treated with fibula graft for distal humerus, 1 patient with megaprosthesis for distal femur, 2 patients with autograft-prosthetic composite TKA for proximal tibia, and 1 patients with only debridement for proximal tibia due to systemic metastasis. The radiographic evaluation scores by ISOLS criteria of the osteoarticular extracorporeal irradiated autograft of the proximal humerus, proximal tibia, or distal tibia were significantly lower than that of the other locations (p=0.016). The MSTS functional score is median 23 (77 %) ranging from 16 (53 %) to 28 (93 %). The significant difference among the sites of autograft was not observed.

Conclusion: The osteoarticular extracorporeal irradiated autograft has a high complication rate. The radiographic results of this method for proximal humerus, proximal tibia, or distal tibia were poor. However, the functional outcomes were comparable to outcomes with the prostheses reported in the literature. The osteoarticular extracorporeal irradiated autograft can be an acceptable alternative especially for the case in which good prosthetic devices are not available such as acetabulum, scapula, or the first decade of life.

Poster 291 3042183

OSTEOBLASTOMA-LIKE OSTEOSARCOMA: IS GRADING USEFUL?

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Objective: Osteoblastoma-like osteosarcoma is an extremely rare variant of osteosarcoma, accounting for approximately 1% of all osteosarcomas. As histologically it mimics classic osteoblastoma, it represents a major diagnostic challenge. The main morphological differential diagnostic feature is the permeation in between the host bony trabeculae. In the latest WHO classification, osteoblastoma-like osteosarcoma in classified in the chapter of conventional high-grade osteosarcomas, however several cases have been described in the literature as low-grade malignant tumors. No strict criteria have been identified to distinguish between low-grade and high-grade tumors. We therefore reviewed our series of osteoblastoma-like osteosarcomas in order to verify if a grading scheme could be applied.

Methods: We retrieved 15 cases from the archives of our Institution. We used the criteria devised by Campanacci to discriminate between low-grade and high-grade osteoblastoma-like osteosarcomas. According to these criteria, histological features indicative of high-grade malignancy are the presence of areas of abudant osteoid, hyperchromatic nuclei, increased nuclear size, > 3 mitosis per 10 high power fields, aneuploid mitosis, necrosis, and areas of conventional osteosarcoma.

Results: Nine low-grade and 6 high-grade tumors were identified. Five patients developed metastasis, and 5 patients developed local recurrences following incomplete surgery. At last follow-up, 11 patients were alive without disease, while 4 patients died of disease. Statistical analysis revealed a statistically significant lower disease-free survival in patients with high-grade tumors (p = 0.0489).

Conclusion: Grading of osteoblastoma-like osteosarcoma indicates lower disease-free survival in patients with high-grade tumors. Campanacci's criteria can be used for this purpouse.

Poster 292 3042200

CXCR4 AS POTENTIAL MARKER IN OSTEOSARCOMA

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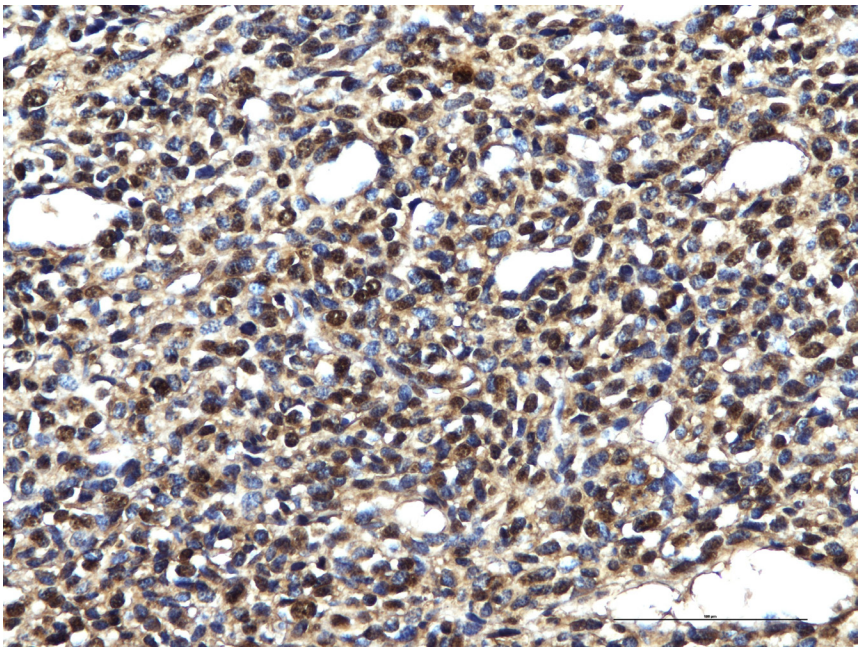
Objective: Osteosarcoma (OS) is a highly malignant bone tumour that predominantly affects young adults and pediatric patients. The low survival rate for patients with metastatic OS, due to the development of drug-resistance and high toxicity in treatment, has led us to focus on CXCL12/CXCR4 pathway, considered responsible for the development and progression of many malignant neoplasms.

Methods: CXCR4 gene and protein expression was analysed respectively by RT-PCR and immunohistochemistry (IHC) in 52 high-grade OS patients and 13 normal tissues. Statistics was used for clinical correlations. In vitro study was performed on OS cell lines cultured in BM-MSCs conditioned medium and treated by CXCR4 inhibitors, MDX1338 and AMD3100.

Results: A significant higher CXCR4 gene expression was found in OS samples when compared to normal tissues ($p<0.05$) and in metastatic compared to non metastatic patients ($p<0.05$). IHC showed that 45.5% of the OS presented a moderate to strong positivity for CXCR4 protein. Univariate Cox's analysis revealed that the risk of developing metastasis increased 2-fold (95% CI = 1.2-3.4; p=0.008) for each increase in the level of receptor expression. Accordingly, Kaplan Meier analysis showed that patients with a low and focal CXCR4 protein expression had a higher probability of disease-free survival than patients with a strong and homogeneous distribution.
We then analysed the effect of MDX1338 and AMD3100 on proliferation, apoptosis and migration in OS cell lines (U2OS, SAOS and 143B). Higher CXCR4 levels were seen in all cell lines when compared to osteoblasts (fold change =129.69, 17.38 and 33922.73 respectively). When the cells were treated with MDX1338 at the dose of 0.005 µg/mL and AMD3100 at the dose of 30 µg/mL, we found a decrease of cell proliferation up to 40% associated to an increased apoptotic fraction after 48h of treatment in U2OS and 143B. Concomitantly FACS analysis showed accumulation of cells in S/G2 phase. Finally, U2OS and 143B cells responded to 0.001 µg/mL of MDX1338 and 5 µg/mL of AMD3100 with a reduction of cell migration up to 24h of treatment.



CXCR4 protein expression in high-grade OS

Conclusion: Our data confirm the involvement of CXCR4 in OS progression and suggest that CXCR4 inhibitors are able to reduce tumour cell growth and migration. The delay in cell cycle progression might enhance the effects of agents controlling S/G2 checkpoints. In order to further support the role of CXCR4 as therapeutic marker, studies are on going on the evaluation of OS cell response to CXCR4 knockdown by using CRISPR/Cas9 technology.

Poster 293 3042729

ONCOLOGIC OUTCOME IN PATIENTS WITH OSTEOSARCOMA OF THE EXTREMITIES AND PATHOLOGIC FRACTURES: DIFFERENCES IN MICRO RNA PROFILE

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Objective: Prior to neoadjuvant chemotherapy and limb salvage surgery advances, pathologic fractures were considered a contraindication for limb-salvage. However, recent studies report good functional and oncologic outcomes. Subsequent literature reported higher local recurrence and metastatic disease rates and overall lower survival in osteosarcoma patients with pathologic fractures when compared to those without fracture.
Micro-RNA are small, non-coding RNA molecules that regulate post translational gene expression. Some micro-RNAs have proved to be poor outcome markers in osteosarcoma patients. Up to date, there has not been micro-RNA profiling comparison in osteosarcoma patients with and without pathologic fractures.

Methods: Eighty samples of high-grade osteosarcoma patients of the extremities were profiled for micro-RNA characteristics per standard methods for RNA sequencing data. Fourteen samples had a pathologic fracture. Differences between the pathologic fracture and the non-fracture groups were evaluated using the edgeR and DESeq test for differential expression. Once the micro-RNA profile was attained, comparison with other micro-RNAs known to be markers of poor prognosis in our cohort was performed. Additional comparison was performed with micro-RNA markers known to be predictors of poor outcome from previous research.

Results: mIR 155-5p was significantly more down-regulated in pathologic fracture patients. This is a marker of local aggressiveness in our cohort and in previously published research. This down-regulation decreases cell apoptosis and cell death. miR 455-3p was significantly down-regulated in fracture samples. This marker is also down-regulated in pathologic fractures in osteoporosis. The profile of pathologic fractures demonstrated a higher prevalence of micro-RNA markers associated with low survival and higher risk of metastasis but not local recurrence.

Conclusion: Pathologic fractures in osteosarcoma appear to be associated to low survival and higher risk of metastasis. Micro-RNA profiling demonstrated differences between both groups and a higher prevalence of micro-RNA markers of worse clinical outcome in extremity osteosarcoma patients with pathologic fractures.

Poster 294 3042782

CSF-1R IS A POTENTIAL PREDICTIVE BIOMARKER OF THE THERAPEUTIC RESPONSE OF OSTEOSARCOMA IN THE GSF-GETO OS2006 STUDY

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Objective: Osteosarcoma (OS) develops in a dynamic microenvironment rich in TAMs (tumor associated macrophage) and osteoclasts that play a regulatory function on OS cells, but low rate of TILs (tumor infiltrating T cells). Immunotherapy represents a promising new therapeutic option, but regulatory mechanisms need further investigations in osteosarcoma to improve its efficacy. T-cell specific immunosuppression could be amplified by TAMs and TAMs are associated with a better prognosis in osteosarcoma. Lower CD8-TILs levels were significantly correlated with less metastases and improved overall survival in osteosarcoma zoledronate-treated patients. Zoledronic acid could impair TAMs polarization. In the literature, it has been shown that CSF-1R (colony stimulating factor-1 receptor) overexpression enhances tumor growth in osteosarcoma cells and IDO (indoleamine 2,3-dioxygenase) promotes immunosuppression and is correlated with worse prognosis in osteosarcoma.

Methods: To better understand the interactions between the different potential candidates to be targeted in therapeutics, we measured by ELISA the CSF-1R and IDO levels in the serum of patients from the OS 2006 cohort (phase 3 trial combining zometa®, an inhibitor of the osteoclast activity, with chemotherapy and surgery). We then correlated the results with the expression of the markers (CSF-1R, IDO, TAMs, CD68, CD8) studied by immunohistochemistry in 124 OS 2006 biopsies, and with the response to chemotherapy and survival. RNA seq data were available for 16 patients and were correlated with CSF-1R and IDO staining.

Results: The median of CSF-1R and IDO levels in the OS serum patient was respectively 618 ng/mL (range: 102-1360) and 15 pg/mL (range: 0-959). CSF-1R was highly expressed in 80.6% of OS biopsies with an IRS>2 and the level of IDO was low in 77.3% of patients. No correlation was found between CSF-1R serum or RNAseq levels and its expression in biopsies by immunostaining (as for IDO expression).
CSF-1R staining was correlated with the level of CD68 (OCs and macrophages) (r=0.38; p= 0.0001), CD163 (Mph) (r=0.54; p< 0.0001) and CD8 (r=0.34; p= 0.0006) positive cells. IDO was inversely correlated with CD68 (r=-0.26; p=0.0096).
A higher level of the IRS CSF-1R staining was significantly associated with a poor response to chemotherapy, only in the group of zometa® treated patients (p=0.0332). No significant difference was notified with the expression of CSF-1R and IDO with overall and metastatic progression free survival.

Conclusion: The lack of correlation between CSF-1R and IDO RNAseq or serum levels and (over)expression on biopsies patients highlight the intratumoral heterogeneity of biological samples in osteosarcoma. This study demonstrates the potential interest of CSF-1R as predictive marker of therapeutic response in OS patients. In addition, this effect seems to be linked to the bone microenvironment as it is only observed in patients treated with zometa®. mCSF by binding its receptor CSF-1R activates osteoclast differentiation, and zometa® targets specifically cells from the monocyte lineage : macrophages and osteoclasts.

Poster 295 3042798

DO POSTOPERATIVE INFECTIONS INFLUENCE THE SURVIVAL OF OSTEOSARCOMA PATIENTS? RESULTS OF A MULTICENTER TRIAL

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Objective: The development of a deep infection is one of the gravest postoperative complications following the surgical resection of an osteosarcoma and endoprosthetic reconstruction. Recent retrospective studies suggested that patients developing a deep infection in the first year after surgery (DI1) developed no local recurrences. Two of these studies also showed a survival benefit for patients with a DI1, which could in theory be attributed to antitumor immunity. However another study suggested that this survival benefit was more likely to be related to the clinical characteristics of infected patients, rather than the effect of the infection itself. We therefore performed this study in order to examine the prognostic influence of a DI1 following wide resection and endoprosthetic reconstruction in osteosarcoma patients.

Methods: We performed a retrospective analysis of the files of 447 patients with a newly diagnosed, high-grade osteosarcoma of the extremities, which underwent multi-agent chemotherapy and limb-sparing surgery followed by endoprosthetic replacement between 1989 and 2016 in 5 centers in Germany and Austria and achieved a complete surgical remission of all detectable tumor foci. Survival curves were calculated with the Kaplan-Meier method and compared with the log-rank test.

Results: 49 patients developed a DI1. After a mean follow-up of 8.8 years for surviving patients, local recurrence (LR), event-free survival (EFS) and overall survival (OS) probability amounted to 5%, 67% and 78%, respectively. Pathological fractures and a poor response to neoadjuvant chemotherapy were associated with a higher LR ($p = 0.035$; $p < 0.001$) and a poorer EFS ($p = 0.002$; $p < 0.001$) and OS ($p < 0.001$; $p < 0.001$), while primary metastases were only associated with a poorer EFS ($p < 0.001$) and OS ($p < 0.001$).
No patient with a DI1 developed a LR. On the other hand, DI1 had no influence on EFS ($p = 0.395$) or OS ($p = 0.116$) in our entire cohort. A subgroup analysis showed that patients with a poor response to neoadjuvant chemotherapy and a DI1 had a significantly higher OS ($p = 0.027$) compared to patients without a DI1, while there was no association between DI1 and OS in patients with a good response to neoadjuvant chemotherapy ($p = 0.925$).

Conclusion: Our results confirm the observations of previous studies, that osteosarcoma patients with a DI1 do not develop local recurrences after wide resections, although it should be noted that we this does not establish causality. Contrary to the results of these previous, smaller studies, DI1 was only associated with an improved OS in patients with a poor response to neoadjuvant chemotherapy.

Poster 296 3042922

MYC AMPLIFICATION IN OSTEOSARCOMA PATIENTS IS A BIOMARKER FOR POOR OUTCOME AND VERY RAPID DISEASE PROGRESSION

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Objective: Osteosarcoma (OS) is the most common primary bone cancer. Currently, patients are categorized by clinical presentation at diagnosis as either localized or metastatic. While metastasis is well documented to correlate with a poor outcome, no biomarkers have previously been correlated with poor clinical outcome. We analyzed data from the Patient/parent Osteosarcoma genome-Wide Registry (POWR), comparing OS tumors with MYC amplification (25%) to non-MYC amplified (75%) in terms of genomics, clinical outcome, and disease progression.

Methods: Using data in POWR, genomic reports (primarily FoundationOne® Heme or MSKCC IMPACT) and medical history information from 80 relapsed/refractory (r/r) OS tumors were analyzed. Genomic reports identified genomic alterations (GA's, including base substitutions, indels, copy number alterations, and fusions/rearrangements, both pathogenic and variants of unknown significance (VUS). Medical history data included: % necrosis, time to relapse, time to death, and treatments received. Initial diagnosis tumors which were not r/r were excluded, as were tumors without sufficient medical history data. Only initial relapse medical history data was considered for % necrosis and time to relapse. A co-occurrence and statistical analysis of MYC and non-MYC amplified tumors was carried out.

Results: A comparison of the MYC amplified and non-MYC-amplified tumors found that 25% of the r/r tumors in POWR were MYC amplified. MYC tumors relapsed more quickly (mean of 3.4 months vs 6.5 months), were more likely to progress on the MAP chemotherapy (50% vs 36%), and barring Patient X, were all dead or dying (0% NED vs 23% NED). The most notable difference was median time to death (15 months vs. 39.5 months).
There was not much difference between MYC and non-MYC tumors in terms of gender and age. Response to MAP chemotherapy as defined by percent cell necrosis at surgery is somewhat lower for MYC tumors (47% vs. 58%), however the range is almost the same (0 to 95% vs 0 to 97%). While initial disease presentation for MYC and non-MYC tumors was the same in terms of localized disease (63% for each), all cases of multi-focal osteosarcoma in POWR were MYC-amplified. Additionally, MYC amplification and ATRX inactivation were found to be almost always mutually exclusive, as also seen in neuroblastoma. There is one MYC amplified patient (Patient X) who was excluded from this analysis because the patient also had the CD274 (PDL-1 protein gene) and PDCD1LG2 (PDL-2 protein gene) genes deleted, a unique occurrence in POWR's 140+ tumors. This patient is to date still in remission with no evidence of disease. All MYC amplified individuals with the exception of Patient X are dead or on hospice. Of these, we identified 5 who showed clinically stable disease while on hospice with very heavy tumor burdens for anywhere from 4-12+ months after being on one of the following non-traditional treatment combinations: Nivolumab + Ipililumab; Nivolumab + Denosumab; Ifosfamide + Olaratumab; Ifosfamide + Etoposide + Lenvatinib; and 223Ra+pazopanib+denosumab, then gemcitabine + NAB-paclitaxel +denosumab.

Conclusion: R/r OS tumors commonly show MYC amplification (25%). As in neuroblastoma, MYC amplification and ATRX inactivation are almost always mutually exclusive. Although not different in metastases at diagnosis, MYC amplified patients had particularly poor outcomes involving multi-focal nature, rapid disease progression, and inability to achieve a low disease burden (NED). OS patients with MYC amplification showed a much shorter time to relapse and death than seen in OS patients without MYC amplification. This data provides compelling evidence that all patients diagnosed with OS, should have their tumor screened for MYC amplification at diagnosis. MYC amplification is implicated in aggressive disease with rapid disease progression on upfront therapy. Additional novel therapies should be considered in the MYC amplified patient.

Table 1

Description	MYC	Non-MYC
% Male	62.5%	56.0%
% Female	37.5%	44.0%
Ave Age (range of 8 to 52 years)	15.3	19.1
Ave # Genomic Anomalies (range of 1 to 41)	21	14.5
At Dx, %		
Localized	62.4%	63.0%
Metastatic	18.8%	37.0%
Multifocal	18.8%	0%

Table 2

Description	MYC	Non-MYC
Avg Necrosis	47.0%	58.0%
Progressed on chemo	50.0%	36.0%
Never NED	44.0%	34.0%
Positive Surgical Margins	13.0%	8.0%
Mean time to relapse (mths)	3.4	6.5
Current Status		
Dead	56.0%	54.8%
On Hospice	38.0%	22.6%
NED	6.0%*	22.6%
Median time to death (mths)	15	39.5

*See more under Patient X in results section.

Poster 297 3027666

A PHASE II STUDY OF PAZOPANIB WITH ORAL TOPOTECAN IN PATIENTS WITH METASTATIC OSTEOSARCOMA

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Objective: Topotecan and pazopanib individually have clinical benefit in patients with sarcomas. Pazopanib is a multi-tyrosine kinase inhibitor and topotecan affects endothelial cells, and inhibits HIF-1, an upstream regulator of VEGF expression. The utilization of pazopanib with topotecan is anticipated to produce anti-tumor synergism in patients with osteosarcomas.

Methods: A phase II study of pazopanib/topotecan in patients with metastatic and non-resectable osteosarcomas was conducted by the Midwest Sarcoma Trials Partnership. Age >18, ECOG ≤1, adequate organ function, measurable disease and 1 prior therapy were required. Patients were treated with pazopanib 800mg oral daily, Topotecan 8mg orally day 1, 8, 15 on a 28-day cycle until disease progression or unacceptable toxicity. Primary endpoint: progression-free rate (PFR) at 12 weeks. Secondary endpoints: overall response rate (ORR), clinical benefit rate (CBR), OS, median progression free survival (PFS), and 3, and safety and tolerability. Lab correlates evaluated PFR and OS to levels of VEGFR2 and PDGF. Simon 2-stage design was used.

Results: A total of 21 pts were enrolled at 6 sites, with 17 evaluable for response. Mean age was 41 years, 48% of patients were female and 95% had metastatic disease. PFR at 12 weeks is 59% with a median PFS of 4.5 months and OS of 11.1 months. ORR is 6 % and CBR is 85%. Grade 3-4 adverse events (%): neutropenia (42), thrombocytopenia (29), hypertension (16) and anemia (12). Correlative data will be presented.

Conclusion: The combination of pazopanib/topotecan proved extremely promising for patients with unresectable or metastatic osteosarcoma. To date 10 patients have met the primary endpoint. If an anticipate 11 or more patients/ 36 will have disease control at 4 months, the agent would be considered sufficiently efficacious for additional study.

Poster 298 3033727

MULTI-ARM TRIAL IN LOCALIZED OSTEOSARCOMA: MOVING FROM A DREAM TO REALITY

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Objective: Chemotherapy and surgery achieve a 5-year event-free survival of 60-70% in localized osteosarcoma, but little additional progress has been made since the 1980s. All recent large randomized trials in localized osteosarcoma have failed to further improve long-term outcomes.

Clinical research in osteosarcoma is hampered by its rarity and by a limited pipeline of new agents. Globally, only 4 randomized trials with a survival endpoint are currently recruiting patients with localized osteosarcoma (last verified on 12 June 2018): 3 in China and 1 in Japan.

To accelerate the pace of clinical research in localized osteosarcoma, we proposed the establishment of a trial infrastructure (platform) which combines two concepts:
A trial design allowing the addition of new arms and the removal of arms for futility, within the same trial;
The testing of drugs already approved for other indications in 2 phases, a screening phase & a confirmation phase.

We have named the proposed trial PRESTO (Platform for the Rapid Evaluation of Several Treatments in Osteosarcoma). Our objective was now to gather feedback about the necessary criteria and the main issues to be overcome to be able to conduct such a multi-arm multi-stage (MAMS) platform trial in localized osteosarcoma.

Methods: A successful implementation of a MAMS platform trial is dependent on five key criteria:
1- The feasibility of sufficient patient accrual
2- A surrogate endpoint to guide the selection of first phase interventions
3- Interventions with a positive risk/benefit ratio for a population undergoing curative treatment
4- The existence of a network of osteosarcoma centres
5- The availability of large scale funding
An initial assessment of these criteria was performed.

Results: For criteria 1, we summed up the number of patients randomized in trials performed by various collaborative groups in localized osteosarcomas and found a capacity of randomizing 340 patients a year, within EURAMOS countries, France, Italy & Latin-America.

For criteria 2, we identified possible surrogate candidates for each of the key treatment period:
- good histological response (GHR) for the neoadjuvant period,
- circulating tumour cells for the perioperative period,
- early DFS for both the adjuvant and the maintenance period.
Using a frequentist approach, aiming at improving GHR from 50% to 70% would require 53 patients per arm for a 80% power and a relaxed alpha of 20%. Another 214 patients in each arm would need to be included to evaluate the effect of the intervention on EFS with a power of 80%, an alpha of 5% and a target HR of 0.70, assuming accrual over 3 years and 3 years of additional follow-up.

For criteria 3, our literature review indicated 87 existing drugs with some evidence of activity against osteosarcoma. We selected sirolimus as the first drug to undergo a systematic review of safety, efficacy and rationale. Results show that mTOR inhibition has been tested in 16 trials in sarcoma patients with 13 of them having included osteosarcoma patients. The evidence indicates a possible role for sirolimus in the neoadjuvant, adjuvant or maintenance period.

For criteria 4, European and US centres have built EURAMOS. Other networks exist in China, France, Italy, Japan & Latin-America.

For criteria 5, several funding sources have been identified such as the new Horizon Europe program, Cancer Research UK and private philanthropists.

Conclusion: Despite the multiple challenges to conducting randomized trials in localized osteosarcoma, our evaluation shows it might be feasible to run a MAMS platform trial within an international collaboration. Learning from the results of EURAMOS and other negative trials, it seems more efficient to stop trials early for futility, particularly when new arms can be instituted in their place. Using surrogate endpoints – even imperfect endpoints – represents an important avenue for future clinical trials in osteosarcoma.

Poster 299 3039394

ANGIOPOIETIN LIKE 2: A POTENTIAL NOVEL BIOMARKER FOR PATIENTS WITH OSTEOSARCOMA

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Objective: Osteosarcoma is the most common bone tumor in children and young adults with an incidence of approximately 400 new diagnoses per year. Standard of care treatment includes a combination of neoadjuvant chemotherapy and aggressive local control surgery. Recent Children's Oncology Group clinical trial also showed no improvement in 5 year Event free survival despite use of intensification of chemotherapy for patients with poor necrosis of <90% after neoadjuvant chemotherapy. There's a dire need for improved biological and molecular mechanisms to improve overall outcomes for patients with osteosarcoma. The aberrant expression of ΔNp63, an oncogenic variant of a p53 family member protein, is

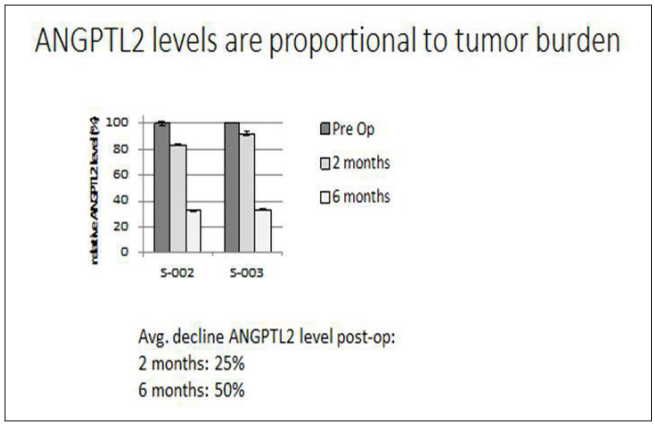
associated with metastatic behavior in osteosarcoma. ΔNp63 has been implicated in chemotherapy resistance by inhibiting apoptosis as well as in metastasis by driving ANGPTL2 expression. Additionally, inhibition of ANGPTL2 signaling diminishes metastatic load and the size of the nodules in lungs in preclinical models. In summary, the expression of a secreted glycoprotein, Angiopoietin-like Protein 2 (ANGPTL2) plays an important role in osteosarcoma biology. ANGPTL2 has also been shown to be a potential serum biomarker for colorectal, gastric and esophageal cancer. We hypothesize that serum ANGPTL2 will serve as a non-invasive, real time marker of treatment response for patients with osteosarcoma.

Methods: A single institutional IRB approved study was performed at Nationwide Children's Hospital, a tertiary children's hospital. Patients with localized or metastatic osteosarcoma were enrolled at the time of diagnosis, while receiving active treatment or during post therapy follow up periods. Blood samples were collected at diagnosis, pre and post local control, approximately every 3 months while receiving chemotherapy and at the time of any clinical change such as relapse or progression of disease. ANGPTL2 levels in extracted plasma were measured using the Human ANGPTL2 Assay Kit from IBL following the manufacturer's instructions.

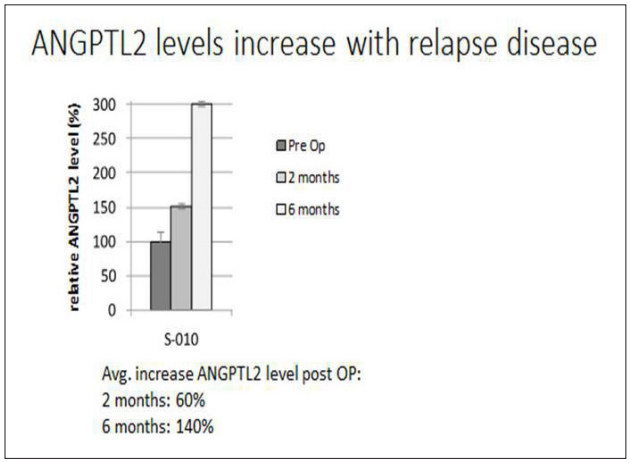
Results: Eighteen patients were enrolled over a 20 month period. Age at the time of enrollment ranged from 8-31 years. Of the 18 patients, 3 had metastatic disease at diagnosis. Two withdrew from study and 1 died of progressive disease. Blood samples were collected per study protocol ranging from 2-7 time-points for these patients. ANGPTL2 levels were found to be proportional to degree of tumor burden. Data from two patients with blood samples collected at diagnosis, at the time of neoadjuvant chemotherapy and then post local control are demonstrated here with an average decrease in ANGPTL2 levels by 25% at 2 months and decrease by 50% at 6 months. (Figure 1) Conversely, ANGPTL2 levels also increase with occurrence of relapse disease. (Figure 2) ANGPTL2 levels remain stable for patients who are in continued remission. (Figure 3) Incidentally, transient increases in ANGPTL2 levels were also noted in relation with concurrent infections.

Conclusion: Our study shows evidence that increasing levels of ANGPTL2 post local control for patients with osteosarcoma correlates with relapse of disease. There is a direct association with ANGPTL2 level and tumor burden as demonstrated by decreased ANGPTL2 levels post local control surgery. Monitoring serum ANGPTL2 levels can be used as a potential novel biomarker to support treatment response and possibility of identifying early relapse of osteosarcoma.

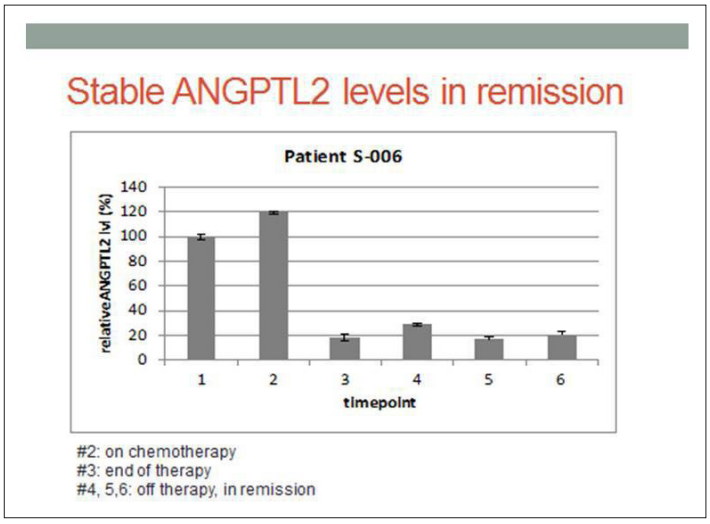
ANGPTL2 levels are proportional to degree of tumor burden



ANGPTL2 levels show signigicant increase with the presence of relapse disease



Steady ANGPTL2 levels are seen with patients in remission



Poster 300 3042556

EVALUATION OF THE EFFICACY AND TOXICITY OF HIGH DOSE OF THIOTEPA (HDT) AS ADJUVANT TREATMENT TO STANDARD CHEMOTHERAPY (SCT) IN RELAPSED OSTEOSARCOMA: FINAL RESULTS OF THE MULTICENTRIC RANDOMIZED PHASE II TRIAL OSIITTP

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Objective: Osteosarcoma is an aggressive malignancy that affects both children and adults. Relapse following a first treatment occurs in 40% of patients within a median delay of 20 months. There is no standard regarding relapse treatment. In France, high dose thiotepa 900 mg/m^2 (HDT) with stem cell rescue has been used after standard chemotherapy (SCT) for many years. A retrospective survey conducted from 2004 to 2006, reported that 30% of relapsing osteosarcomas are treated with HDT in the SFCE (French Society of Children Cancer) centers. We aim to evaluate efficacy and tolerance of this HDT administration in a prospective randomized trial.

Osteosarcoma is an aggressive malignancy that affects both children and adults. Relapse following a first treatment occurs in 40% of patients within a median delay of 20 months. There is no standard regarding relapse treatment. In France, high dose thiotepa 900 mg/m^2 (HDT) with stem cell rescue has been used after standard chemotherapy (SCT) for many years. A retrospective survey conducted from 2004 to 2006, reported that 30% of relapsing osteosarcomas are treated with HDT in the SFCE (French Society of Children Cancer) centers. We aim to evaluate efficacy and tolerance of this HDT administration in a prospective randomized trial.

Methods: This randomized open label phase II study assigned patients in a 1:1 ratio (stratification on 1 vs >1 lesion) to receive 4 courses of SCT followed by HDT and autologous transplantation or SCT alone. Main inclusion criteria were patients aged over one year and less than 50 years, with a Lansky score ≥60% or PS≤2, with a local or metastatic relapse of a high grade osteosarcoma, for whom a SCT indication was confirmed by a multidisciplinary committee and a complete resection could be achieved prior or after SCT. Patients should not have previously received a high dose of chemotherapy. Only patients who were non-progressive after 2 SCT courses were eligible for randomization. The resections had to be performed as soon as feasible. Primary endpoint was Overall Survival (OS) from randomization date. 37 deaths were required to detect an improvement in 2-year Overall Survival rate (2y-OS) from 20% (SCT) to 45% (SCT+HDT) with 10% one-sided α and 80% power, corresponding to an estimated sample size of 44 patients followed up between 2 and 6 years. Secondary objectives included Progression Free Survival (PFS), and safety.

Results: From Sept 2009 to Nov 2016, 44 patients were randomized. Arms were well balanced; median age was 16y (9-32y), 54.5% males and 30 (68.2%) with >1 lesion. The intent-to-treat analysis showed a 2y-OS rate of 66.7% (95%CI 42.5-82.5) for SCT+HDT *vs* 46.6% (95% CI 24.2-66.3) for SCT. The median OS was respectively 27.4 and 22.5 months (HR: 0.823, 95% CI 0.385-1.756; p=0.6174).

The median PFS reached 15.6 (8.9-24.9) months in SCT+HDT *vs* 7.2 (4.8-33.3) months in SCT, p=0.3693. The 1y-Progression free rate was 55.3% (31.6-73.7) *vs* 31.8% (14.2-51.1). The average length of stay in hospital for HDT administration was 15 days. Among the 22 pts treated with SCT+HDT, 16 (72.7%) experienced grade ≥3 adverse events (AE) compared to 18/22 (81.8%) among SCT patients. Nine patients experienced serious AEs; 5 among SCT+HDT (including one Suspected Unexpected Serious Adverse Reaction) versus 4 among SCT. No toxic death occurred.

Conclusion: SCT followed by HDT and autologous transplantation allows a prolongation of OS and PFS in relapsed osteosarcomas with acceptable toxicity. The clinical benefit did not reach the statistical significance, probably due to a lack of power with a number of required events not reached. Nevertheless, considering these results and as new targeted therapy haven't yet demonstrated a clear benefit in osteosarcoma, and are not available in children, HDT could be an alternative for second line treatment in a selected group of patients with relapsed osteosarcoma.

Poster 301 3042677

EFFICACY AND SAFETY OF CHEMOTHERAPY IN RELAPSED OSTEOSARCOMA

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Objective: Although multiagent chemotherapy and surgical resection has improved the outcome of patients with localized primary osteosarcoma, the prognosis for patients with relapse is still dismal. Complete resection of relapsed lesions is mandatory for long-term survival, but no promising treatment strategy has been established and role of chemotherapy at relapse is controversial. The purpose of this study is to evaluate the efficacy and safety of chemotherapy for patients with relapsed osteosarcoma.

Methods: We retrospectively reviewed fifteen patients who experienced local recurrence or distant metastasis after completion of the primary treatment in our institute and underwent chemotherapy for relapse from 2000 to 2017. The median age was 19 years (range 11-68). Total of 35 regimens were performed. Regimens included ifosfamide and etoposide for 12 cases, gemcitabine and docetaxel (GD) for 8 cases, temozolomide and etoposide (TE) for 4 cases, pazopanib (Pazo) for 3, ifosfamide (IFO) for 3, and others for 5. Relapsed lesions were located at lung (n=27), bone (n=4), lung and bone (n=2), lung and brain (n=1), intravenous tumor embolisms (n=1). Surgical resection was performed in 10 patients. Progression free survival, best response rate, adverse effects were evaluated.

Results: The median follow-up period was 16 months (range 7-56). The median progression free survival for all patients was 7.0 months (95%CI: 4-12). Best responses were as follows: no complete response, 8 stable disease (23%), 11 stable disease (31%), 16 progression disease (46%). Response rates according to regimens were as follows: 50% in TE, 33% in IE, 25% in GD, Pazo, IFO, and 0% in others. Frequency of serious adverse events (CTCAE grade >=3) were 100% in IE and IFO, 88% in GD, 33% in Pazo, and 25% in TE. There was no treatment-related death. Final prognosis for all patients was NED in 4, AWD in 4, and DOD in 8.

Conclusion: Taking response rate and adverse effect into consideration, temozolomide and etoposide regimen could be promising treatment option for relapsed osteosarcoma.

Poster 302 3042898

UTILIZING A NOVEL FORMULATION OF NICLOSAMIDE TO TREAT CANINE METASTATIC OSTEOSARCOMA

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Objective: Osteosarcoma (OS) has seen few therapeutic and survival advances in the past three decades. There is a significant clinical need to identify novel therapies to treat OS without the treatment-derived morbidity of cytotoxic chemotherapeutics. The anthelminthic drug niclosamide has demonstrated inhibitory effects on several pathways known to be dysregulated in OS. However, the extremely low bioavailability and need for solubilizing agents pose substantial *in vivo* therapeutic obstacles. To overcome these challenges, we developed a novel niclosamide stearate prodrug therapeutic (NSPT), which is made of a lipid nanoparticle formulation of esterified niclosamide stearate. Translation to humans, where OS is uncommon, would benefit from correlative studies in dogs with OS, as the incidence of canine OS approximately 10 times that in humans and the diseases are virtually identical in terms of molecular pathogenesis and behavior. Using a canine and human cross-species approach, we sought to evaluate the efficacy of these NSPTs *in vitro*, *ex vivo*, and *in vivo*. Further establishing the efficacy and survival benefits of NSPTs will be crucial for clinical translation of this work with the ultimate goals of improving survival and decreasing morbidity for OS patients.

Methods: Nanoparticles were prepared by solvent-solvent exchange of niclosamide stearate dissolved in acetone with water in a 1:9 v/v ratio and concentrated using centrifugal ultrafiltration. Dose-response assays and western blot analyses were performed on cultured canine (Abrams, Moresco, D17, and D418) OS cells after treatment with various concentrations of NSPTs and pure niclosamide solubilized in DMSO. OS cells were transduced with lentiviruses encoding firefly luciferase, NLS mCherry, and cytoplasmic zsGreen. NSPT effects on OS proliferation and apoptosis cells were studied *in vitro* using live-cell multiplexed imaging and *ex vivo* using a lung explant pulmonary metastasis assay (PuMA). For the *in vivo* experiments, mouse models of osteosarcoma metastasis were generated via tail-vein injection of $1x10^6$ luciferase-labeled D418 OS cells

into 6-week-old SCID/beige (Prkdc^{scid}, Lyst^{bg-J}) mice. Mice were randomized to PBS (200 µL i.v.), NSPT (50 mg/kg i.v.), and doxorubicin (1.2 mg/kg i.p). Bioluminescence in average radiance (p/s/cm^2/sr) was measured as an indicator of intravital tumor burden. These results were compared to prior work completed with human OS cells.

Results: Dose-response assays demonstrated that both NSPT and pure niclosamide in DMSO inhibited canine OS cell growth *in vitro.* Cell lines were more sensitive to N-DMSO vs. NSPTs (Mean IC_{50}: 0.786 µM vs. Mean IC_{50}: 1.268 µM, respectively; p=0.04). Western blot analysis showed reductions in phospho-S6, with cell line-specific reductions of phospho-STAT3, phospho-Akt, and mTOR. Multiplexed proliferation/apoptosis assay corroborated time- and dose-dependent inhibition of OS cell growth and caspase 3/7-mediated cell-kill. *Ex vivo,* NSPT treatment groups significantly reduced lung tumor burden at 5 days vs. PBS in D418 OS cells. *In vivo*, mice treated with NSPTs had significantly lower overall tumor burden. Similarly, NPSTs significantly delayed metastatic colonization of the lungs by D418 cells as compared to control mice. No sequalae of NSPT therapy were observed at this higher dosage, while doxorubicin treated mice lost weight.

Conclusion: NSPTs represent a novel and effective therapy for OS *in vitro*, *ex vivo*, and *in vivo* in a mouse model of metastatic OS. In mice, NSPTs are able to modulate antitumor effects without the treatment-derived morbidity of standard-of-care chemotherapeutics, such as doxorubicin. This is in concordance with our prior work in human OS cells, suggesting that canine and human OS will respond similarly. Leveraging the similarities between canine and human OS biology and treatment response provides a unique opportunity to develop NPSTs clinically in pet dogs with OS prior to human trials.

FIGURE 1: Decreased *ex vivo* lung tumor burden.

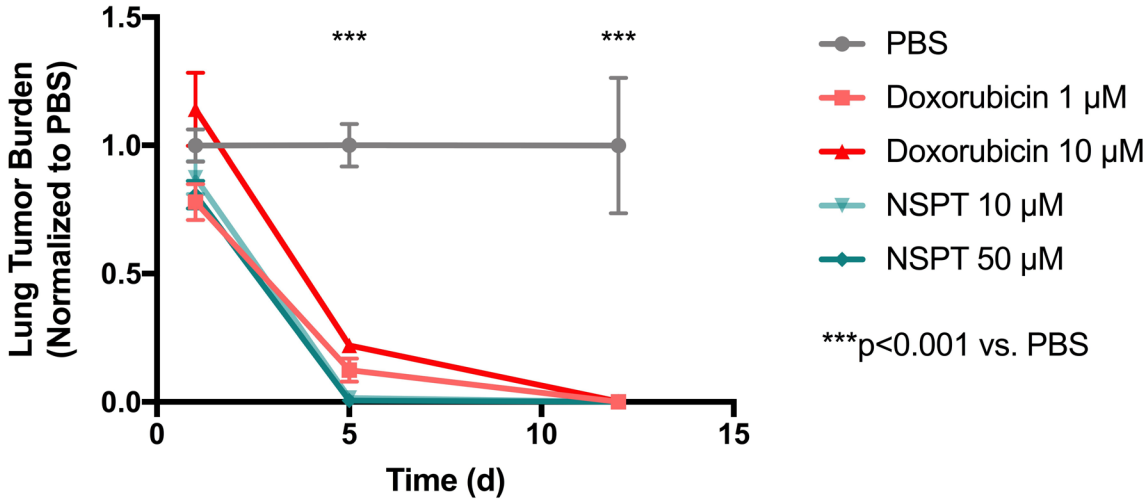
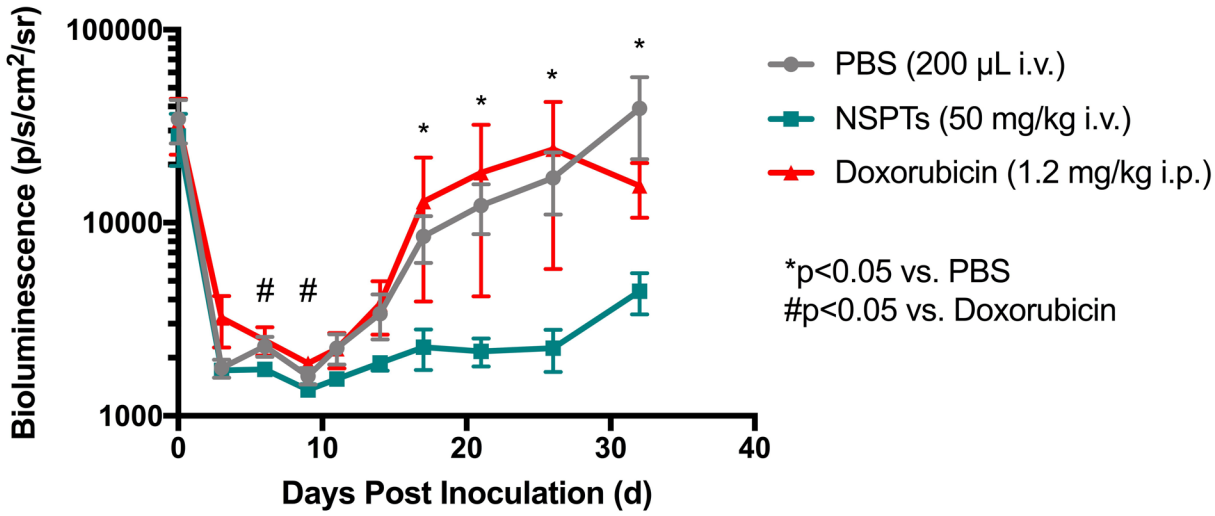


FIGURE 2. Delayed metastatic progression *in vivo.*



Poster 303 3030032

COMBINED RADIATION THERAPY AND SURGERY PROVIDE EXCELLENT LOCAL CONTROL FOR PATIENTS WITH EXTRASKELETAL OSTEOSARCOMA

Andrew J. Bishop[1]*; John A. Livingston*[2]*; Dejka M. Araujo*[2]*; Bryan Moon*[3]*; Shreyaskumar Patel*[2]*; Wei-Lien Wang*[4]*; Alexander J. Lazar*[4]*; B. Ashleigh Guadagnolo*[1]

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Objective: While patients with bone osteosarcomas commonly do not receive radiation therapy (RT) as part of the standard treatment algorithm, our practice typically regards extraskeletal osteosarcomas as soft tissue sarcomas where RT is incorporated into the multidisciplinary management. We sought to evaluate the outcomes in this rare tumor type for patients with localized extraskeletal osteosarcomas treated with RT in combination with surgery.

Methods: We reviewed the records of 21 patients with non-metastatic, extraskeletal osteosarcomas treated with RT in combination with surgery at our institution from 1984 to 2015. All histologic diagnoses were confirmed by our sarcoma-specific pathologists. The Kaplan-Meier method was used to estimate rates of overall survival (OS), disease-specific survival (DSS), local control, and distant metastatic free survival (DMFS). Log-rank tests were used to assess for significance of differences between curves.

Results: Median follow-up time was 120 months (range, 6-200). The median patient age was 62 years (range, 21-80) with the cohort mostly comprised of male patients (n=14, 66%). The most common tumor location was the lower extremities (n=15, 71%; UE n=4, 19%; trunk n=2, 10%) with a median tumor size of 8 cm (range, 1-20), and the majority were >5cm (n=15, 71%). After the final definitive excision of their tumor, 19 patients (90%) had negative final surgical margins, and only 2 patients (10%) had positive/uncertain margins. Postoperative RT was used for 10 patients (48%) to a median dose of 60 Gy (range, 60-68 Gy). The other 11 patients (52%) received 50 Gy preoperatively. Seven patients (33%) were treated with neoadjuvant or adjuvant chemotherapy, which was determined at the discretion of the treating medical oncologist. Larger tumor size (>5 cm) was associated with chemotherapy use (P=0.046). Among the patients who received chemotherapy, all were treated with doxorubicin and ifosfamide for a median of 6 cycles (range, 4-6).
The 5-year and 10-year OS rates were 55% and 49%, respectively. There were 12 deaths (57%), of which 7 were attributable to cancer, resulting in a 5-year DSS rate of 62%, which was unchaged at 10 years. The median DSS was 36 months (range, 2-279 months). There were no treatment or tumor-related factors associated with improved DSS, including chemotherapy use (P=0.29). All patients who died from disease had metastases (P<0.001).
The 5-year and 10-year LC rates were both 93%. Only 1 patient (5%) had a local recurrence at 22 months. Given the limited number of local recurrences, statistical analyses were limited. Nine patients (43%) developed distant metastases, of which all were in the lung, at a median time of 9 months (range, 1-30 months) with an observed 1- and 3-year distant metastatic free survival (DMFS) of 64% and 53%, respectively. No disease- or treatment- related factors influenced DMFS including tumor size (≤5cm: 3-y 60% vs. >5cm: 3y 50%, P=0.49) or use of chemotherapy (chemo: 3-y 36% vs. no chemo: 3-y 65%, P=0.23). Following disease relapse, the median DSS was 14 months (range, 5-190 months). Of the 9 patients who relapsed distantly, 7 patients received salvage chemotherapy and 4 underwent metastasectomy. There were two patients who were ultimately salvaged, both of whom were treated with chemotherapy and surgery.

Conclusion: Extraskeletal osteosarcoma represents a rare soft tissue sarcoma diagnosis. Despite the presumed radioresistant nature of osteosarcomas, the risk of local recurrence for these extraskeletal tumors following combined RT and surgery was low. These data provide support for combined modality therapy for localized disease. Unfortunately, these patients have a high risk of distant relapse.

Poster 304 3030493

CLINICAL OUTCOME OF PERIOSTEAL OSTEOSARCOMA: A SINGLE INSTITUTIONAL STUDY

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Objective: Periosteal osteosarcoma is a rare, nonmedullary chondroblastic osteosarcoma arising on the surface of long bones. They account for 1-2% of all osteosarcoma patients. Treatment is by surgical excision but the role of chemotherapy is still controversial due to their rarity. We retrospectively reviewed the clinical outcome of periosteal osteosarcoma treated at our institute.

Methods: We identified out of 370 osteosarcoma patients treated at our institute between 1970 and 2015, 8 patients (2.2%) with periosteal osteosarcoma. Gender was male 2, female 6; age at presentation was 12-53 years (median 18.5 years); site of tumor was tibia 5, femur 3. All patients were treated with wide resection surgery. Chemotherapy with regimen of conventional osteosarcoma was planned for all patients. Follow-up period was 53-219 months (median 130 months).

Results: At last follow-up, the clinical outcome was CDF 5, NED 1, DOD 2. Five-year event-free survival was 62.5% and 5-year overall survival was 75%. The two patients who died, one discontinued chemotherapy after one course due to malaise and age (53 years) but had lung metastasis at 31 months and died at 53 months. The other patient had only neo-adjuvant chemotherapy and had lung metastasis at 37 months and died at 53 months. One patient who had recurrence did not initially receive chemotherapy due to pregnancy at diagnosis. Only local treatment was administered after delivery by Cesarean section. Local recurrence, bone and lung metastasis were observed at 6 months. She was then treated with chemotherapy, amputation and metastasectomy. She is presently disease free for 154 months.

Conclusion: Patients with periosteal osteosarcoma had good outcome when treated with surgery and chemotherapy. Patients with insufficient chemotherapy had poor outcome. Due to the rarity of periosteal osteosarcoma, a multi-institutional study is needed to clarify the role of chemotherapy in treatment of this tumor.

Poster 305 3042661

THE EFFECT OF RADIOTHERAPY COMBINED WITH IRON OXIDE-BASED NANOVEHICLE AND PHOTOSENSITIZER IN OSTEOSARCOMA

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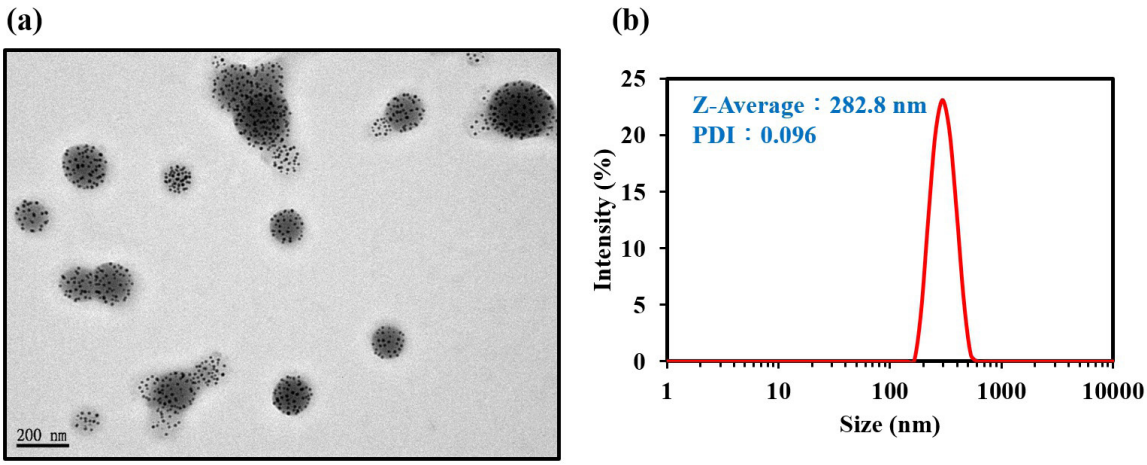
Objective: Osteosarcoma is not sensitive to radiation, resulting in poor efficacy on radiotherapy. In this study, iron oxide-based nanovehicle and photosensitizers were used to improve the radiotherapy efficacy of osteosarcoma. We used iron oxide as a radiation dose enhancing agent while using low-dose radiation induced photosensitizers to generate more reactive oxygen species (ROS), leading to cell apoptosis. From the past literature, this kind of combination has not been studied. Therefore, this is worth exploring.

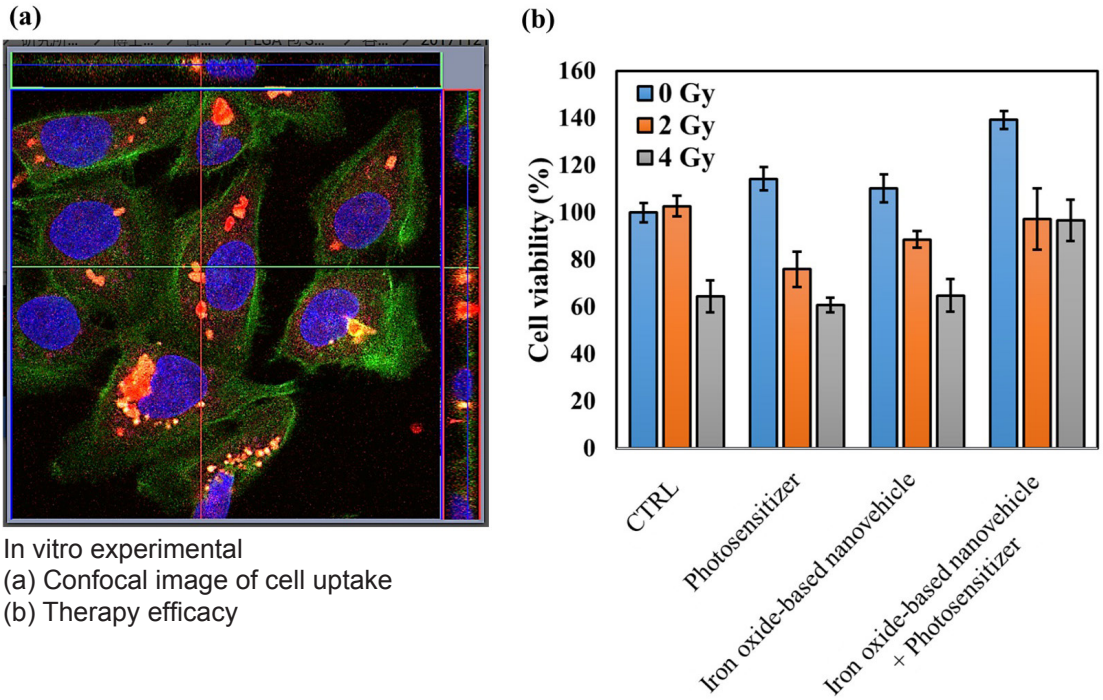
Methods: In this study, the preparation method of iron oxide is based on Hyeon's method. Briefly, first, mix ferric chloride hexahydrate (40 mmol), sodium oleate (120 mmol) with ethanol (80 ml), deionized water (60 ml), and hexane (140 ml). Afterwards, the iron-oleate complex was prepared by reacting at 70 °C for 4 hours. Then, iron-oleate complex (40 mmol), oleic acid (20 mmol) and 200 g 1-octadecene were mixed and reacted for 30 minutes at 325 °C, and then the product was precipitated with ethanol to obtain iron oxide. Next, an iron oxide-based nanovehicle was formed using PLGA as an iron oxide coating material by an emulsification method. In vitro test, we compared the interaction effects of different photosensitizers and iron oxide-based nanovehicle in radiotherapy. The possible effects of these results were analyzed from cell viability, ROS production, and cell cycle data, respectively. In vivo test was explored the accumulation and metabolism of photosensitizers in mice.

Results: From the experimental data, it could be found that iron oxide-based nanovehicle and photosensitizers had a slight toxic effect on osteosarcoma. However, there was a slight interaction between the photosensitizer and iron oxide-based resulting in reducing the amount of ROS. In addition, the amount of ROS seems to be related to the PLGA encapsulation that affected the slow release of iron oxides. On the other hand, in vivo test, we found the accumulation of photosensitizer in solid sarcomas was very poor and it seem to have a relationship with the vasculature perfusion and tissue distribution of the inherent sarcoma. The different injection method was used in it and there was showed the application of photosensitizer was limited.

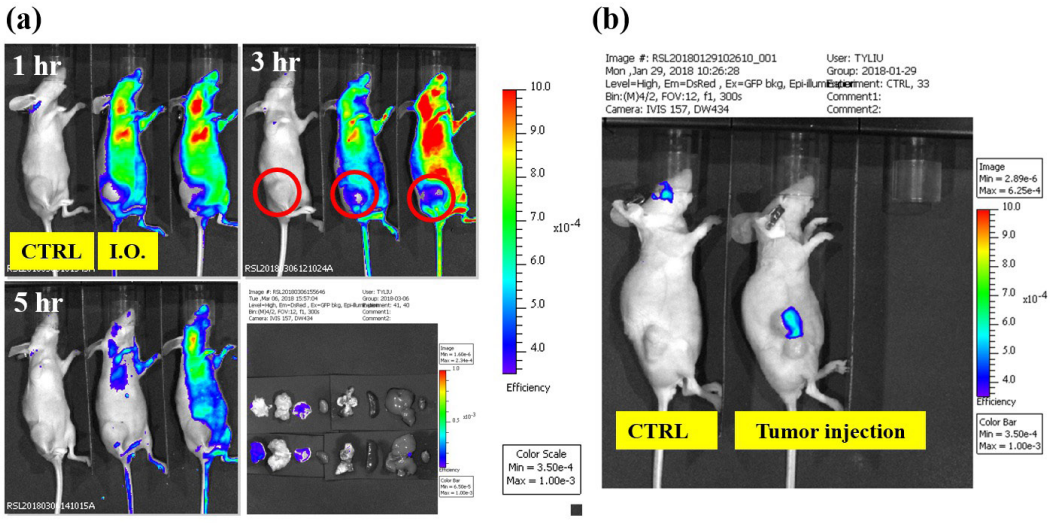
Conclusion: In this study, although the radiotherapy of efficacy combing an iron oxide-based nanovehicle and photosensitizer on osteosarcoma is not very obvious. Many details can be learned from this study. For example, we can disscus how the interaction between the iron oxide-based nanovehicle and the photosensitizer affects ROS production and how the release of the iron oxide-based nanovehicle is promoted, making the cytotoxic effect even more pronounced. In vivo experiments, we also learned that due to the special tissue structure and distribution of blood vessels in solid sarcoma, the accumulation of small molecule photosensitizers in the body is limited. Therefore it is very important to prepare a nanovehicle with drugs. These data provide a good basis for our future research in this area.



Iron oxide-based nanovhicle (a) TEM image (b) DLS analysis



In vitro experimental
(a) Confocal image of cell uptake
(b) Therapy efficacy



In vivo accumulation of photosensitizer (a) I.O. injection (b) intratumor injection

Poster 306 3042663

OSTEOFIBROUS DYSPLASIA LIKE ADAMANTINOMA IS NOT ADAMANTINOMA

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Objective: The primary purpose of this study was to summarize the treatment and long term outcomes for the osteofibrous dysplasia (OFD), osteofibrous dysplasia-like adamantinoma (OFDLA), and admantinoma (AD) cohorts. The secondary purpose was to characterize the clinical evolution of OFD and to determine if a spectrum exists among OFD, OFDLA, and AD.

Methods: We conducted a single institution prospective cross-sectional study and retrospective medical record review of 59 patients with a diagnosis of OFD (43), OFDLA (9), AD (5), OFD/OFLDA (1), and OFDLA/AD (1) between 1958 and 2016. The 2 pathologically indeterminate cases were excluded from all analyses. Patients were mailed questionnaires to assess long-term outcomes. Median follow-up was 4 years for OFD, 3 years for OFDLA, and 8 years for AD. For each group, we recorded the rate of metastatic disease and the rate of surgical intervention, as well as associated recurrence and complications. Available pathology was reviewed in light of current classification of these tumors.

Results: The mean age at presentation was 9 years (1 to 21 years). Histological diagnosis was confirmed by a pathologist at our institution in 78% of cases (46/59) with biopsy or excision specimens. Of the 43 OFD patients, 26 were treated conservatively (60%), while 17 were managed surgically: 12 underwent intralesional curettage, 4 were treated with excision, and 1 was treated with a Taylor spatial frame. No differences were detected between OFD and OFDLA patients with respect to age, sex, bone affected, tumor volume, or cortical involvement (all $p>0.3$). However, patients with OFDLA were more than 4 times as likely to have surgery compared to OFD (OR=4.5; 95% CI = 1.1 to 26.6; $p=0.04$). Of the 9 OFDLA patients, 5 were treated with excision (3 at an outside institution), 2 underwent intralesional curettage, and 2 were treated conservatively. Of those who underwent surgical intervention, there were no differences across the two groups with respect to recurrence ($p=0.34$) or complications ($p=0.07$). Lastly, none of the 7 OFD and OFDLA patients that underwent reoperation for local recurrence were found to have a change in histological diagnosis. Four out of 5 patients with AD were treated with wide excision, 1 of which was managed at an outside institution. There was 1 local recurrence that was treated with re-excision. One AD patient had metastatic disease after treatment, whereas none of the OFD or OFDLA patients metastasized. Almost half of the patients who underwent operative treatment experienced at least one complication (13/28, 46%). Of the patients with a clear diagnosis, 20/57 (35%) returned the follow-up questionnaire at a median of 5.6 years. There were no differences in patient reported pain, limitations, assistance, or limp across tumor types (all $p>0.15$).

Conclusion: We did not observe any patients who progressed from OFD or OFDLA to AD. Conservative treatment of OFD is adequate and curettage and bone grafting can be reserved for extensive and symptomatic lesions. AD should be treated with wide excision, as is widely accepted within the literature. While optimal treatment of OFDLA has yet to be clearly defined, our study results support the contention that the clinical behavior of OFDLA is similar to OFD. This is inconsistent with OFDLA's name, as the autological nature suggests a closer proximity to AD and may in fact influence treatment decisions. However, initial careful observation of OFDLA is appropriate and supported by previous literature. Additional studies with a greater number of OFDLA patients are needed to draw any meaningful conclusions.

Poster 307 3037697

REFERRAL PATTERNS OF SOFT TISSUE SARCOMAS TO A TERTIARY SARCOMA CENTER OVER A 20 YEAR PERIOD

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Objective: Soft tissue sarcomas (STS) are rare malignancies often falsely presumed as benign pathologies. A mistaken diagnosis will initiate a cascade of errors leading to unplanned resection (UR) of the malignancy. These URs carry significantly higher recurrence rates and added morbidity. Patient-related obstacles such as distance and economic hardships can delay or prevent proper referral to tertiary sarcoma centers (TSC). Early referral to a TSC is shown to improve outcomes for primary STS. Evaluating physicians should have the requisite knowledge and training for early diagnosis and proper referral to avoid UR. There is a need to identify the specialties most commonly encountering these diseases so as to direct education efforts toward those fields. The primary aim of this study is to characterize the medical specialties that diagnose and refer STS patients to a tertiary sarcoma center and determine if there is a correlation between the type of referring provider and unplanned resection. Secondary aims include determining effect of distance of referring physician to the TSC on unplanned resection status and determining if published economic hardships (2008 Recession) had any historical correlation with increased UR rates or tumor size at presentation.

Methods: A retrospective review was performed on all patients that presented to the University of Michigan Comprehensive Cancer Center with a diagnosis of STS between January 1st, 1996 and January 1st, 2017. Using EMERSE (Electronic Medical Record Search Engine), 2,600 patients were identified with "soft tissue sarcoma" search term. Inclusion criteria: untreated, primary extremity STS including axilla or buttocks. Exclusion criteria: prior treatment, metastatic disease or axial location. We collected histology, grade, size, resection status, patient demographics and referral information. Referral information (referring physician, credentials, zip code, and specialty) was obtained from the medical record and supplemented with an internet search engine (Google). Distance from the TSC was obtained using the referring physician's zip code at the time of referral and online mapping software (Google Maps).

Results: 848 patients were identified. The mean age was 54 years (range: 2-94), with 41.9% female and 58.1% male. Mean sarcoma size was 8.44cm (range: 0.4 to 59). 36 unique histopathology types were identified. The overall rate of UR was 26.2% (217 of 827). Grade distribution: 21.4% grade 1; 4.1% grade 2; 74.6% grade 3. General Medicine, General Surgery, Orthopedic Surgery, Internal Medicine and Oncology were the most common referral specialties with UR rates of 19.2%, 42.0%, 24.6%, 13.0% and 30.1% respectively. There was no significant correlation between specialty or credentialing and UR rate. UR status showed a statistically longer distance of referring physician to the TSC compared to primary resection (PR) (122.6mi vs 79.7mi, p = 0.04). Over the twenty years reviewed, there was no significant change in UR rate or tumor size for any specific year, including the 2007-2009 timespan of the 'Great Recession'.

Conclusion: Soft tissue sarcomas remain a challenge for primary providers and oncologic specialists alike. With national UR rates exceeding 30%, a better understanding of STS presentation and diagnosis is necessary to minimize UR rates, local recurrence, and morbidity associated with re-excision. Additionally, physicians located farther from TSCs should be mindful of biases that exist for local treatment of tumors. Further research is needed to establish more accurate and sensitive diagnostic criteria for soft tissue sarcomas. We recommend evaluating physicians with suspicion of malignancy refer for evaluation of masses at a TSC with formal biopsy and pathologic analysis before local resection is considered. It is our ultimate goal to ensure proper education for primary providers in accurate diagnosis and initial referral to TSC for patients with a soft tissue sarcoma.

Specialty	UR	Total	% UR	% Total
Gen Med	41	213	19.2	25.1
Gen Surgery	68	162	42.0	19.1
Oncology	28	93	30.1	11.0
Internal Med	15	115	13.0	13.6
Ortho	30	122	24.6	14.4
Self	1	10	10.0	1.2
Unknown	8	28	28.6	3.3
Sports	0	5	0.0	0.6

Total number of unplanned resections (UR), unplanned resection percentage (% UR) and total percentage of referrals (% total) based on referring specialty.

Poster 308 3041866

THE INFLUENCE OF HEALTH INSURANCE STATUS ON OUTCOMES IN SOFT TISSUE SARCOMA

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Objective: Numerous studies in a variety of malignancies have demonstrated that health insurance status is linked to differences in clinical presentation, types of treatment received, and survival. The effect of insurance status on the management of soft tissue sarcoma is unknown. We assessed the impact of insurance status on 1) stage at diagnosis, 2) receipt of standard therapy, and 3) overall survival in patients with soft tissue sarcoma.

Methods: Patients with stage I–IV soft tissue sarcomas of various histologies diagnosed from 2004-2015 were identified from the National Cancer Database (NCDB). Patients were stratified by insurance status into cohorts of commercial insurance, Medicare, Medicaid, and no insurance. Analysis was performed after dichotomizing the population, based on age of eligibility for Medicare coverage, into those ≥65 and those <65 years. In the <65 years subgroup, patients with Medicare

were excluded, as Medicare enrollment in that age group signifies the presence of disability or comorbidities that we were not able to control for. In the ≥65 years subgroup, only patients with Medicare and commercial insurance were compared as these were the dominant insurance types in this age group. The associations between insurance status and stage at diagnosis as well as receipt of standard of care surgery plus radiotherapy for stage II/III disease were examined with multivariable logistic regression analyses. The impact of insurance status on survival was assessed using Kaplan-Meier and multivariable Cox proportional hazards analyses.

Results: 49,754 patients were identified of whom 23,677 (48%) had commercial insurance, 20,867 (42%) had Medicare, 3,229 (6%) had Medicaid, and 1,918 (4%) were uninsured. In patients <65 years, those with Medicaid (OR=1.74, 95% CI: 1.57–1.93, P<0.001) and no insurance (OR=1.71, 95% CI: 1.51–1.94, P<0.001) were more likely to present with stage IV disease at diagnosis compared to those with commercial insurance. In patients <65 years with stage II/III disease who had limb sparing surgery, Medicaid (OR= 0.88, 95% CI: 0.78–1.00, P=0.046) and no insurance (OR= 0.75, 95% CI: 0.64–0.87, P<0.001) were associated with a decreased likelihood of receipt of neoadjuvant or adjuvant radiation compared to commercial insurance (Table 1). In the cohort of patients <65 years, Medicaid (HR=1.26, 95% CI: 1.17–1.34, P<0.001) and no insurance (HR=1.30, 95% CI: 1.20–1.41, P<0.001) were associated with an increased hazard of death compared to commercial insurance. The increased risk of death associated with insurance status remained significant after propensity score matching (Table 2). In patients, ≥65 years, there were no statistically significant differences between Medicare and commercial insurance with regards to disease presentation receipt of perioperative radiotherapy or survival (Tables 1 and 2).

Conclusion: In this large modern cohort identified from the NCDB, insurance status impacted early diagnosis, receipt of standard treatment, and survival for patients with soft tissue sarcoma. Further efforts to understand disparities of care based on health insurance in the United States are needed.

Table 1.
Adjusted Odds of Metastatic Disease at Presentation and Receipt of Peri-Operative Radiation by Insurance Status

Patients				
	Metastatic Disease at Presentation (n=25,587)*		Receipt of Peri-Operative Radiotherapy (n=13,488)**	
	OR [95% CI]	p	OR [95% CI]	p
Commercial Insurance	-	-	-	-
Medicaid	1.74 [1.57, 1.93]	<0.001	0.88 [0.78, 1.00]	0.046
Uninsured	1.71 [1.51, 1.94]	<0.001	0.75 [0.64, 0.87]	<0.001
Patients ≥65 years				
	Metastatic Disease at Presentation (n=21,759)*		Receipt of Peri-Operative Radiotherapy (n=12,101)**	
Commercial Insurance	-	-	-	-
Medicare	0.96 [0.86, 1.07]	0.48	0.94 [0.89, 1.06]	0.31

* Metastatic disease at presentation comparison is stage I-III vs stage IV. ** Receipt of peri-operative radiotherapy analysis completed only for patients with stage II-III soft tissue sarcoma who underwent limb sparing surgery.

Table 2. Factors Associated with Overall Survival

Patients				
	Multivariable		Propensity Score-Matched Cohort	
	HR [95% CI]	p	HR [95% CI]	p
Commercial Insurance	-	-	-	-
Medicaid	1.26 [1.17, 1.34]	<0.001	1.19 [1.13, 1.25]	<0.001
Uninsured	1.30 [1.20, 1.41]	<0.001	1.23 [1.16, 1.32]	<0.001
Patients ≥65 years (n=19,959)				
	Multivariable		Propensity Score-Matched Cohort	
Commercial Insurance	-	-	-	-
Medicare	1.05 [0.99, 1.11]	0.14	1.02 [0.97, 1.07]	0.13

Poster 309 3042750

CLINICOPATHOLOGIC FEATURES,TREATMENT UTILIZATION TRENDS AND OUTCOMES OF PRIMARY BREAST SARCOMA :A POPULATION BASED ANALYSIS

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Objective: Primary breast sarcoma (PBS) is a rare cancer accounting for less than 1% of all breast malignancies. Complete surgical resection is the primary treatment for PBS. Although perioperative radiation therapy (RT) and chemotherapy (CT) are used frequently, their impact on overall survival (OS) is not clear. We performed a large population based study to evaluate the current treatment utilization patterns, and outcomes in patients with PBS in the United States of America.

Methods: We queried the National Cancer Database (NCDB) to identify patients with PBS(T1-T4, N any, M0) between 2004and 2015. Patients with phyllodes histology and M1 disease were excluded. Patients were grouped based on treatment received:surgery alone,surgery+chemotherapy, and surgery+radiation. Impact of treatment on OS was investigated in univariate models and as main effect in multivariable analysis after adjusting for other covariates.

Results: A total of 1840 patients were identified from the database. Median age was 65 years with 99% of cases being female. Tumors had a slight preponderance on the left side 967 (53%) as compared to right 865 (47%). The most common histology was Angiosarcoma 980 (53%) and 737 (53%) patients had poorly differentiated tumor. T staging was based on AJCC 8th edition. 58% had <5cm tumor followed by 28% with 5-10 cm , 8% with 10-15cm and 6% patient with T >15 cm.1564 patient underwent surgical resection with 1164 (74%) of them underwent mastectomy whereas 400 (26%) patients underwent breast conserving surgery(BCS). Lymph node (LN) staging was not available for 1021 (55%) patients. Among patients who had LN staging 113(15%) had LN+ disease. R0 resection was done in 1556 (90%) of patients. We used sequence of systemic therapy as a surrogate for chemotherapy administration. 109(7%) patients underwent neoadjuvant CT, 354(24%) patients underwent adjuvant CT and 23 (2%) underwent both neoadjuvant and adjuvant therapy . Radiation therapy data was used in 491(27%) of patients . In univariate analysis age, size, grade, adjuvant chemotherapy ,BCS and radiation were found to be associated with survival benefit. In multivariate analysis BCS (HR 0.733, with 95% CI 0.558, 0.963 p=.0259), Adjuvant CT (HR 0.54 with 95% CI 0.35, 0.84) and radiation therapy (HR 0.53 ,p=.0006) was associated with statistical benefit on OS.

Conclusion: PBS is an extremely rare tumor. Surgical resection of the tumor was the most common treatment modality used. Adjuvant CT and RT were utilized in a minority of patients and were associated with improved OS. Multi-disciplinary is essential for optimal management of patients with this rare disease.

Poster 310 3042849

INDETERMINATE PULMONARY NODULES AT DIAGNOSIS IN PEDIATRIC RHABODMYOSARCOMA: ARE WE UNDERTREATING PATIENTS? A REPORT FROM THE EUROPEAN PAEDIATRIC SOFT-TISSUE SARCOMA STUDY GROUP-RMS-2005 STUDY

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Objective: Finding indeterminate pulmonary nodules in patients with newly diagnosed rhabdomyosarcoma (RMS) can pose a diagnostic dilemma, since differentiation between malignant and benign nodules can be very difficult. In previous European study protocols staging for pulmonary metastases was usually done by a chest radiograph. With the introduction

of the European *paediatric* Soft-tissue sarcoma Study Group (E*p*SSG)-RMS-2005 study chest radiographs were replaced by a chest CT.
In the E*p*SSG-RMS-2005 study patients with 4 or less pulmonary nodules smaller than 5 mm or 1 nodule ranging from 5 to less than 10 mm were considered to have indeterminate pulmonary nodules. The assumption was made that these nodules were micro-metastases and that these indeterminate pulmonary nodules did not affect survival. Therefore, patients with indeterminate pulmonary nodules were treated according to localized disease protocol. However, this was solely based on a theoretical assumption. If this assumption was wrong, it might have impaired survival for this patient group.
We aimed to assess the clinical significance of indeterminate pulmonary nodules at diagnosis in patients with pediatric rhabdomyosarcoma (RMS), by comparing event-free and overall survival for patients with indeterminate pulmonary nodules to those without such lesions.

Methods: We selected patients with supposed non-metastatic RMS treated in large oncology centers in the United Kingdom, France, Italy and the Netherlands and enrolled in the E*p*SSG-RMS-2005 study. Patients who were diagnosed between September 2005 and December 2013, in whom chest CTs at diagnosis were available for review were included. Local radiologists were asked to review chest CTs for the presence of pulmonary nodules, recording findings on a standardized case report form. In the E*p*SSG-RMS-2005 study, patients with indeterminate pulmonary nodules were treated identically to patients without pulmonary nodules, enabling us to compare event-free survival (EFS) and overall survival (OS) between groups by log-rank test.

Results: In total, 316 patients were included; 67 patients showed indeterminate pulmonary nodules (21.2%), 249 patients showed no pulmonary nodules at diagnosis (78.8%). Median follow-up for survivors (n=258) was 75.1 months; 5-year EFS and OS rates [95% CI] were 77.0% [64.8-85.5%] and 82.0% [69.7-89.6%] for patients with indeterminate nodules and 73.2% [67.1-78.3%] and 80.8% [75.1-85.3%] for patients without nodules at diagnosis (*p*=0.68, *p*=0.76, figure 1 and 2) respectively.

Conclusion: Our study indicates that indeterminate pulmonary nodules at diagnosis do not affect outcome in patients with localized RMS. There is no need to biopsy or upstage patients with indeterminate pulmonary nodules at diagnosis in future rhabdomyosarcoma protocols.

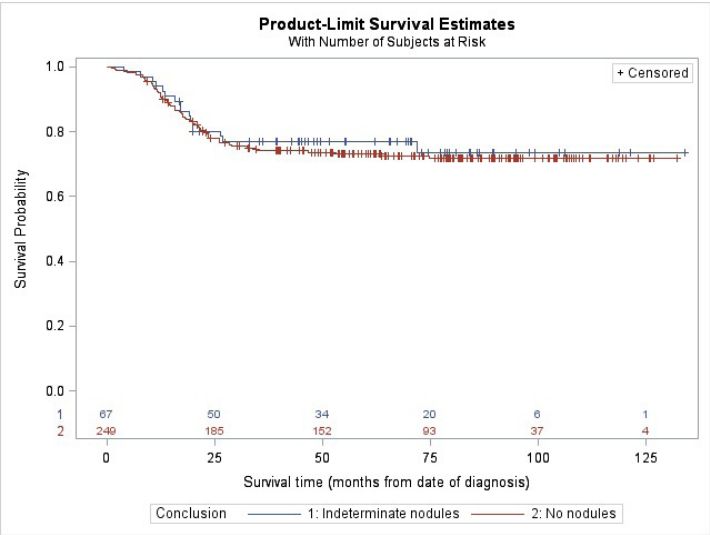

Figure 1: Kaplan-Meier curve showing Event-Free Survival for included patients based on the presence of indeterminate pulmonary nodules.

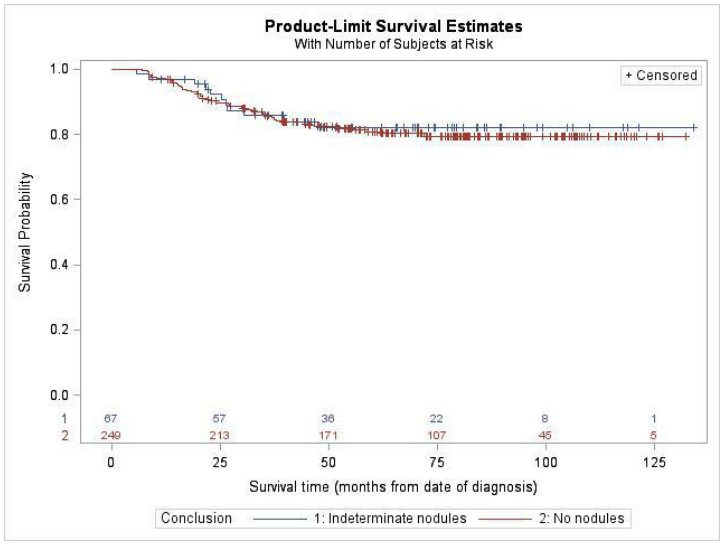

Figure 2: Kaplan-Meier curve showing Overall Survival for included patients based on the presence of indeterminate pulmonary nodules.

Poster 311 3042865

THE USE OF HEALTHCARE SERVICES TWO YEARS BEFORE DIAGNOSIS IN DANISH SARCOMA PATIENTS, 2000-2013

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Objective: Sarcoma is a rare type of cancer with non-specific symptoms and uncertain aetiology. Thus, timely diagnosis of sarcomas is a clinical challenge. The aim of this study was to investigate the use of healthcare services 24 months preceding a sarcoma diagnosis compared to a matched cohort.

Methods: The study was a retrospective, population-based, matched cohort registry-study. Patients with sarcoma in Denmark 2000-2013 were identified in the Danish Sarcoma Registry (n=2167) and matched 1:10 on gender, age and listed general practice. Using a binomial regression model, incidence rate ratios (IRRs) were calculated for face-to-face contacts in general practice, inpatient and outpatient visits, surgery, paraclinical examinations, and diagnostic imaging. Analyses were stratified for sarcoma subtypes, grade, stage, gender, and presence of comorbidity.

Results: The sarcoma patients had a significantly increased use of healthcare services compared to the matched cohort a year before their diagnoses. An increase in consultation rates was seen 11 months before diagnosis for inpatient visits, 9 months before diagnosis in general practice and outpatient visits, 8 months before diagnosis for paraclinical examinations, and 4 and 3 months before diagnosis for diagnostic imaging and surgery, respectively. There were no clinical significant differences in length of increased consultation rates between sarcoma type, stage and grade. Sarcoma patients with comorbidity had continuous higher consultations rates compared to patients without comorbidity.

Conclusion: The use of healthcare services among sarcoma patients increased several months before diagnosis in all healthcare sectors. The results reveal a diagnostic time window and a potential to refer, diagnose, and treat sarcoma patients in a more timely manner.

Poster 312 3042880

THE ASSOCIATION BETWEEN SOCIOECONOMIC POSITION AND TUMOUR SIZE, GRADE, STAGE, AND MORTALITY IN DANISH SARCOMA PATIENTS – A NATIONAL, OBSERVATIONAL STUDY FROM 2000 TO 2013

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Objective: An optimal outcome in sarcoma patients depends on a range of prognostic factors. An association between cancer survival and socioeconomic position is known for other cancers. We examined the relation between three socioeconomic factors and risk of presenting with known prognostic factors, and the overall mortality of the different socioeconomic and prognostic factors in 1919 patients treated for sarcoma in Denmark 2000-2013.

Methods: Sarcoma patients aged 30 year or over at diagnosis were identified in the Danish Sarcoma Registry, and linked on an individual level to Danish national registries. We obtained data on educational level, disposable income and cohabitation status. Odds ratios (ORs) were estimated for the association between the socioeconomic factors and the likelihood of receiving a diagnosis of high-grade sarcoma against low-grade, disseminated stage against localised stage, and a large tumour against a small tumour, respectively. Survival analyses were performed using Cox proportional hazard models and Kaplan Meier survival curves.

Results: In adjusted analyses, educational level, income and cohabitation status were not associated with grade, stage or tumour size at the time of diagnosis, but were significantly associated with mortality. Patients with a short education, low income, who live alone, comorbidity or a large tumour had a significantly higher mortality.

Conclusion: Low socioeconomic position was associated with increased overall mortality. No association between socioeconomic position and grade, stage or tumour size, at time of diagnosis was seen.

Poster 313 3042903

NODAL INVOLVEMENT AND SURVIVAL IN SYNOVIAL, CLEAR CELL, ANGIO, RHABDO AND EPITHELIOID SARCOMA

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Objective: Synovial, Clear cell, Angiosarcoma, adult Rhabdomyosarcomaand Epithelioidsarcoma are often referred to by the mnemonic SCARE as soft tissue sarcoma subtypes with higher risk of lymph node involvement(LNI). This study is to identify the incidence of LNI, prognosis and predictors of LNI, treatment and patterns of failure.

Methods: We identified 829 patients with the diagnosis of the above 5 histologieswho were treated in our institution. We retrospectively reviewed 332 patients who were diagnosed from 2000 to 2017. Statistical significance was assessed with Chi-square or Fisher's exact test. Kaplan-Meier analysis and Cox proportional hazards regression were used to analyze survival outcomes and prognostic factors.

Results: Primary SCARE sarcoma sites include head and neck(71, 21%), upper extremity(57, 17%), lower extremity(90, 26%), thorax, abdomen and pelvis(47, 14%), trunk and retroperitoneum(44, 13%), GU, GYN and other(34, 10%). 152 present with Stage 2 and 109 with Stage 3 disease (AJCC7). Primary tumor size was =< 5 cm in 123, 5-10 cm in 77 and >10 cm in 57.LNI was found in 54(16%) patients, of whom 48 werepositive at diagnosis and 6 were found during follow up. LNIrates differed significantly (table 1). Tumor size(p=0.05), histology(p<0.001), metastasis(p<0.001) were found as predictors of LNI. 282(82%) patients underwent resection with R0 in 177 patients. Sentinel lymph node biopsy was performed in a limited number of patients. 171(50%) patients received chemotherapy. 247(72%) patients received radiation therapy. Median follow up is 44 months. 5-year overall survival(OS) in SCARE histology is 69.6%, 41.7%, 34.5%, 29.0%, 51.9% respectively. Synovial sarcoma(SS) has better survival compared to others(p<0.001). LNI was associated with worse OS (p=0.001) and PFS(p=0.001). Multivariate analysis identified age, LNI, large tumor size, thoracic, abdomen and pelvis, metastasis, as significant negative prognostic factors affecting OS. Incomplete surgery (R2) and no surgery both negatively affects OS. Radiation treatment independently improves OS. LNI was associated with CARE histology (p<0.001), metastasis (p<0.001), and larger tumor size (p=0.008).

Conclusion: LNI is significantly higher in clear cell, angiosarcoma, rhabdomyosarcomaand epithelioidsarcoma than SS. It is associated with larger tumor size and metastasis status. It predicts worse OS and PFS.

	synovial	clear cell	angio	adult rhabdo	epithelioid
Total 332	125	18	79	73	37
LNI at diagnosis %	5.6	33.3	14	20.5	24.3
LNI overall %	7.2	55.6	16.5	23.3	37.8

Poster 314 3042961

SARCOMA TREATENT IN ONTARIO: A POPULATION-BASED STUDY

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Objective: Due to the low prevalence of sarcoma, most of the evidence in sarcoma care is based on uncontrolled and relatively small case series. Evidence-based information on outcomes following sarcoma care requires larger studies. Our objective is to leverage the large number of sarcoma patients available through a comprehensive provincial administrative database to better inform the evidence regarding outcomes after sarcoma treatment.

Methods: We used administrative data from the Institute for Clinical Evaluative Sciences (ICES) database. All patients in Ontario with biopsy-confirmed sarcoma between 1993-2015 were identified with ICD-10 codes. We report patient demographics, tumor characteristics, comorbidity and mortality data on this cohort. We determined treatment patterns for soft tissue sarcomas (STS) and bone sarcomas (surgery, chemotherapy, radiation therapy, and any combination of the above). We generated survival curves for each stage of sarcoma and report 5, 10, and 15-year survival rates. A Cox regression analysis was performed to evaluate the association between sex, income quintile, or treatment at academic or rural center and survival.

Results: Demographics

A total of 10,627 [AB1] Ontario Sarcoma patients were eligible for analysis, 8706 STS and 1921 Bone sarcomas. Males comprised 56% of our cohort. Incidence of STS was highest in patients in their 5th, 6th and 7th decades of life who comprise 17%, 18%, and 19% of the cohort respectively. Patients aged less than 35 years comprised 49% of the Bone sarcoma cohort.

The three most common STSs based on coding were: Sarcoma, NOS (1385, 16%), Leiomyosarcoma (1121, 13%) and Liposarcoma (1062, 12%). The most common bone sarcomas are Osteosarcoma (677, 35%), Chondrosarcoma (618, 32%) and Ewing's Sarcoma (410, 21%). The most common location for sarcoma was lower Limb with 3019 cases (22.4%). The number of sarcoma cases reported each year increased steadily from 364 in 1993 to 514 in 2004 and 910 in 2015, an average increase of 11% annually, most likely related to more efficient capture by the linked databases. The majority of sarcomas were treated in academic centers (86.5%) and the average sarcoma patient received 2.5 lung surveillance CT scans in the two years following sarcoma surgery.

Treatment Patterns and Survival

Patients with STS were treated with surgery in 75% of cases, received radiation therapy in 60% of cases, and chemotherapy in 27% of cases. Patients with Bone sarcomas were treated with surgery in 65% of cases, received radiation therapy in 26% of cases, and chemotherapy in 61% of cases. Please see **Table 1** for complete treatment information.

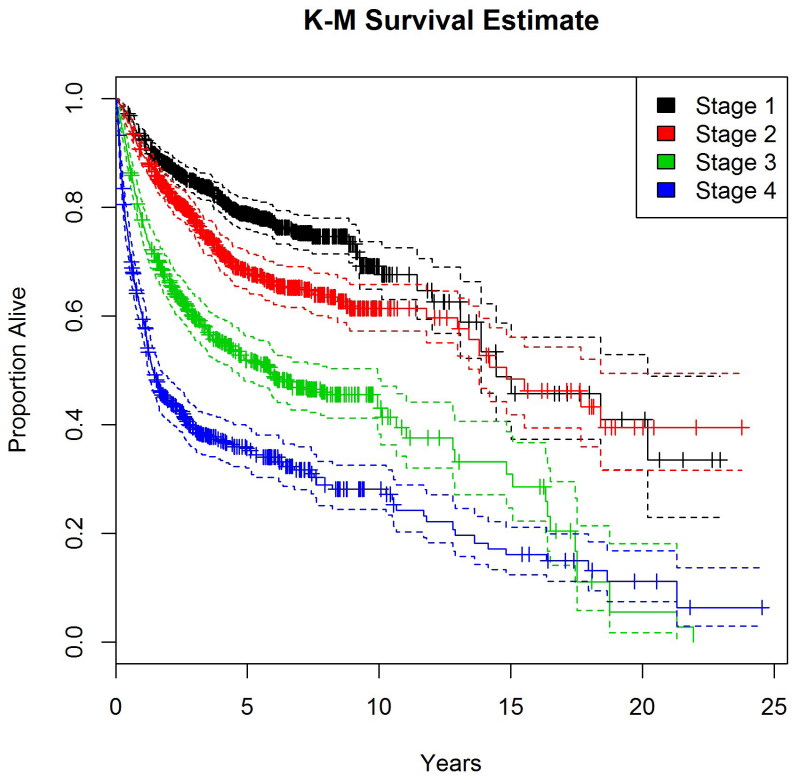
The 5, 10 and 15-year survival rates for Stages 1-4 are displayed in **Figure 1.** No differences in overall survival were seen between patients from different income quintiles, rural vs urban patients, males or females.

This number is with all the carcinomas and unknown ICD-10 codes removed. It is the sum of clear STS and clear Bone Sarcoma cases.

Conclusion: Our analysis of a very large cohort of sarcoma patients reveals treatment patterns and outcomes for sarcoma patients in Ontario, Canada. In this Canadian healthcare setting, the vast majority of sarcoma patients are treated at academic high-volume specialty centers. Specific knowledge on outcomes based on stage or other disease, patient and treatment factors can be helpful for sarcoma care providers in Ontario as well as in other healthcare environments.

Sarcoma Treatment

	SOFT TISSUE SARCOMA	BONE SARCOMA
	N (%)	N (%)
Total patients with treatment information	5646	1546
Surgery Alone	1864 (33%)	428 (27.7%)
Surgery + Radiation Therapy	1169 (20.7%)	67 (4.3%)
Radiation Alone	1001 (17.7%)	114 (7.3%)
Chemotherapy Alone	453 (9.5%)	303 (20%)
Chemotherapy + Radiation Therapy	385 (6.8%)	129 (8.3%)
Surgery + Chemotherapy + Radiation Therapy	361 (6.4%)	108 (7.0%)
Surgery + Chemotherapy	668 (15%)	397 (25.7%)



Poster 315 3030594

THE ROUTE TO DIAGNOSIS (RTD) OF SARCOMA PATIENTS: A QUALITATIVE STUDY IN THE NETHERLANDS (NL) AND THE UNITED KINGDOM (UK)

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Objective: Sarcomas are rare mesenchymal tumours that have considerable heterogeneity with respect to age of onset, presentation, anatomic location, tempo of progression and outcome. Early and adequate diagnosis is difficult, but important for local control, survival and quality of life. To improve the RtD it is important to understand patients' appraisal, help-seeking behaviour and the diagnostic process. Limited knowledge is available on the sarcoma patient experience of the RtD. The aim of this qualitative study was to examine the diagnostic pathway and factors that contributed to the duration of the RtD from a patients' perspective.

Methods: We conducted semi-structured interviews with sarcoma patients diagnosed within the past 4 months in one of the participating sarcoma centres in NL(Radboudumc, Nijmegen) and the UK(Royal Marsden Hospital, London). The RtD was defined as the time of the first symptoms until the time the patient was informed of the pathological diagnosis. The interviews were analyzed according to qualitative content analysis. Topics were derived from the data and from literature. These were based on Walter's Model of Pathways to Treatment, which provides a framework for research of the RtD. The last interval, pre-treatment, falls beyond the scope of our research and experiences were thus attributed to one of three categories: (1) appraisal, (2)help-seeking, and (3)diagnostic. Appraisal refers to the time interval between detecting bodily changes and help-seeking of a healthcare provider(HCP), whereas help-seeking is the period between the decision to consult a HCP until the actual appointment. The diagnostic phase refers to the period from diagnostic tests to histological diagnosis.

Results: Seven Dutch and eight English patients with a time to diagnosis(TtD) varying between 10-145 weeks participated(Table 1). They reflect the heterogeneity of the population.

Themes that prolonged appraisal were (1)alternative explanations for bodily changes; (2)normalising symptoms; (3)other life priorities. Triggers for help-seeking were (1)interference of symptoms with daily life; (2)persistence or increase of symptoms.

'I had a bit of a bulge on my leg and I first thought: "fluid" and then I thought: "maybe it is an old bruise"'(patient nr5).

Two types of patients could be identified during the help-seeking interval: those who received diagnosis after first HCP consultation and those who experienced repeated cycles of appraisal and help-seeking. In this last group reassurance without a safety-net, absence of a lead HCP, or HCPs who did not start a new cycle of clinical reasoning on 2nd request were factors that prolonged TtD.

'I was made this appointment at a back specialist clinic and again he completely examined me and he quite 100% told me that you have got a class-3 classic sciatica. He just said, keep taking your medication, you're on the best medication that you can get. Well, with that I then continued'(patient nr13).

During the diagnostic phase patients mentioned waiting times as the factor contributing most to a long TtD. Waiting caused distress, decreasing the quality of life.

'I suppose the most difficult part was not knowing, or waiting, knowing that in all these investigations would obviously help towards the diagnosis and just waiting and not knowing'(patient nr8).

Conclusion: Three phases of the RtD were identified (appraisal, help-seeking, diagnostic), all with room for improvement to decrease TtD. This study suggests that awareness of patients that their symptoms may be caused by something serious could accelerate appraisal and help-seeking, and awareness of HCPs about the possibility of sarcoma could shorten the diagnostic phase which could reduce distress due to waiting times as well. The study lays the groundwork for future research into improving RtD for sarcoma patients. Quantitative, prospective studies are needed to quantify TtD, examine risk factors for prolonged TtD and assess the impact on clinical and patient-reported outcomes.

Participants

	Age	Sex	Diagnosis	TtD (weeks)
1	24	M	OS	26
2	68	M	MPNST	49
3	40	F	SFT	32
4	65	F	MS	10
5	41	F	OS	22
6	54	F	SFT	137
7	18	M	ES	15
8	69	F	SFT	13
9	85	F	LMS	22
10	51	F	ESS	99
11	50	M	ES	64
12	48	F	ES	145
13	61	M	LS	24
14	56	F	UPS	16
15	69	M	LS	10

Participant 1-7 were Dutch, participant 8-15 were English. Abbreviations: OS: osteosarcoma; ES: Ewing Sarcoma; SFT: solitary fibrous tumour; LS: liposarcoma; LMS: leiomyosarcoma; MPNST: malignant peripheral nerve sheath tumour; UPS: undifferentiated pleomorphic sarcoma; ESS: endometrial stromal sarcoma.

Poster 316 3021215

OUTCOUME DATA OF ADVANCED SOFT TISSUE SARCOMA PATIENTS FROM A TERTIARY REFERRAL CENTER: NOT SO BAD AS OFTEN REPORTED?

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Objective: Soft tissue sarcomas (STS) are rare cancers which tend to develop metastases or local relapses in more than half of the cases impairing patients' life expectancy dramatically. The objective of this study was to analyse outcome data of STS patients with relapsed, locally advanced or metastatic disease challenging the historically reported 12 months overall survival (OS) limit.

Methods: A retrospective analysis was conducted including all STS patients with advanced disease treated between 2010 and 2016 in a tertiary referral Sarcoma Unit at the Mannheim University Medical Center, Germany. Recorded characteristics were age, gender, disease status, tumor and metastatic localisations, tumor size, grading according to FNCLCC, time from initial diagnosis to relapse and death, surgical margins and type of adjuvant/neoadjuvant treatment. The prognostic relevance of these characteristics were analysed using a Kaplan-Meier and Cox model.

Results: 327 patients were included; median follow-up was 31 months. Mean age was 54.9 years (range 2-88). Most cases showed metastatic disease (n = 193) predominantly in the lungs (n = 110) whereas 129 patients had local relapse. Most common histologies were leiomyosarcomas (n = 48) and undifferentiated pleomorphic sarcomas (n = 26). Most common tumor locations were the lower limbs (n = 84) and retroperitoneum (n = 63). Median OS of the whole patient cohort was 37 months; those suffering from local relapse had a median OS of 59 months and those with advanced/metastatic disease 24 months, respectively. The OS rates at 12, 24 and 60 months were 76 % (71-81 %, CI 95 %), 61 % (55-66 %, CI 95 %) and 35 % (29-43 %, CI 95 %), respectively. Unfavourable characteristics found to be independent prognostic factors in the univariate analysis were presence of metastasis ($p = 0.000003$), especially initial or early (within 12 months after first diagnosis) metastasis ($p = 0.001$), localisation ($p = 0.01$), grading ($p = 0.00004$) and tumor size > 5 cm ($p = 0.04$). Characteristics not showing any prognostic significance regarding OS were sex ($p = 0.05$), age at primary diagnosis ($p = 0.6$) and surgical margins ($p = 0.1$).

Conclusion: The current analysis could demonstrate that further progress in the outcome of patients suffering from advanced STS could have clearly been made exceeding the often cited 12 months OS boundary of this patient cohort characterised by a usually unfavourable prognosis.

Poster 317 3027342

A CLINICOPATHOLOGIC EXAMINATION OF MYXOFIBROSARCOMA. RATES OF LOCAL RECURRENCE, METASTASES AND PATIENT SURVIVAL FROM A SINGLE INSTITUTION

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Objective: Identify if a difference exists in local recurrence, metastases and survival rates between patients with positive and negative margins. Determine if any other patient variables recorded have an association with disease related outcomes.

Methods: In this retrospective study, disease related outcomes were recorded in 40 patients surgically treated for MFS over 10 years at a single institution.
Demographic data include: age at diagnosis, age at surgery, tumor location, tumor depth, histological grade, histological margin of the surgery, adjuvant treatments, local or metastatic recurrence, period until recurrence or metastasis, and total time of disease free survival. Size, grade, depth and location of initial myxofibrosarcoma and subsequent recurrences were recorded.
Kaplan-Meier estimator was used to determine recurrence-free survival for patients diagnosed with myxofibrosarcoma. Multivariable analyses of recurrence, metastases and survival were based on cause-specific hazards and evaluated with Cox regression models. Fischer-exact tests were used to determine differences between categorical groups with p value set at 0.05.

Results: Forty patients were surgically treated for MFS in this study. Of the 40, 3 (7.5%) had a tumor with histological grade I; 18 (45%) grade II; and 19 (47.5%) grade III. Out of all 40 cases, 33 (82.5%) had negative surgical margins while 7 (17.5%) had positive surgical margins. Eighteen patients (45%) received post-operative radiation, 8 patients (20%) received pre-operative irradiation, 4 patients (10%) received both post-operative and pre-operative radiation treatments, 6 patients (15%) were treated with chemo-radiation, and 1 patient (2.5%) received only chemotherapy. Average tumor size was 7.04 cm, and average tumor depth was 4.31 cm.
Four patients (10%) were diagnosed with local recurrence. Two were histological grade II and 2 were grade III, while 0 were grade I (P-value = .162). Of the cases with local recurrence, 2 (50%) had negative surgical margins and 2 (50%) had positive surgical margins (p=.131). All 4 cases received post-operative radiation therapy. Three of the patients with local recurrence had metastatic disease at presentation.
Metastatic disease was diagnosed preoperatively in 4 patients and postoperatively in 3 for a total of 7 cases (17.5%). All postoperatively diagnosed cases of metastatic disease had negative surgical margins. Two received post-operative radiation and 1 received pre-operative radiation. Patients were diagnosed with metastatic disease on average of 3.75 years post-surgery. Of the 3 patients diagnosed with post-operative metastatic disease, 1 was histological grade II, and 2 were grade III, while 0 were grade I (P-value=.785).
Overall survival at 5.11 years follow-up was 80%. Of these patients, 4 (50%) received pre-operative radiation, 3 (37.5%) received post-operative radiation, and 1 (12.5%) did not undergo any adjuvant therapy. Of the 8 deceased patients, all had negative surgical margins (P-value=.197). Five of these cases (62.5%) were histological grade II, 3 (37.5%) were histological grade III, and 0 were grade I (P-value=.356).
No clinical correlations were found between demographics (i.e. gender, race and age at surgery) and disease-related outcomes.

Conclusion: The results of this study are in line with current literature regarding local recurrence rates (10%), metastases (17.5%) and overall survival (80%). No difference was found in local recurrence rates between patients with positive and negative margins, which is contrary to most published series on surgical margins in soft tissue sarcoma. Our study also shows trends toward decreased rates of recurrence, metastases and mortality for grade I tumors compared to grade II/III tumors. Limitations to this study include small sample size and a relatively short follow-up period. Additional research with a larger sample size as well as further histopathological studies may be able to elucidate these findings.

Patient Outcomes

	Number of Patients	Percent
Local Recurrence	4	10%
Metastases	7	17.5%
Overall Survival	32	80%
Total	40	100%

Poster 318 3029786

METASTASECTOMY IN SOFT TISSUE SARCOMA IS ASSOCIATED WITH A POST-METASTASIS SURVIVAL BENEFIT. RESULTS FROM A BI-CENTRE STUDY INCLUDING 135 PATIENTS

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Objective: Metastasectomy is a frequently practiced treatment in metastatic soft tissue sarcoma (STS). Evidence in favour of this approach derive from non-controlled, retrospective single arm studies possibly liable to a selection bias, though. The aim of the present study was therefore to apply advanced comparative effectiveness methods in order to investigate the benefit of metastasectomy vs. a non-invasive treatment approach with chemotherapy ± radiotherapy or best supportive care in patients with metastatic STS.

Methods: In the present study, 135 patients who had primarily undergone surgery for localised STS and later on developed metastatic disease, were retrospectively included. Patients were selected out of a database of over 1000 STS-patients treated at two tumour centres over a time period of 17 years.
A propensity score (PS) was generated in order to compensate for prognostic factors differing between metastasectomy- and non-invasively-treated patients at time of treatment decision (in an MDT). Based on the PS, an inverse probability of treatment weight (IPTW) was calculated to estimate the efficacy of metastasectomy on post-metastasis survival (PMS).

Results: In those 68 patients (50.4%) who had undergone metastasectomy post-metastasis survival was significantly better in comparison to the 67 patients (49.6%) treated non-invasively (5-year PMS: 34% vs. 11%; log-rank test: p<0.0001; hazard ratio (HR): 0.34, 95% confidence interval (CI): 0.22-0.53, p<0.0001). However, several positive prognostic factors at baseline were prevailing in the metastasectomy-group, including a better ECOG performance status, better Haemoglobin- and Albumin-levels, fewer number of metastases and rather lung metastases than metastases to other sites. After weighting the data for the IPTW, and thus adjusting for these imbalances, the positive association of metastasectomy in terms of PMS prevailed (5-year PMS: 31% vs. 10%; log-rank-test: p<0.0001; HR: 0.33, 95%CI: 0.20-0.52, p<0.0001).

Conclusion: According to our results, metastasectomy is effective in metastatic soft tissue sarcomas, even presence of poor prognostic parameters. Therefore, the option of surgery in the metastatic setting should be provided to STS-patients as often as possible.

Poster 319 3037787

SOFT TISSUE SARCOMA OF THE EXTREMITY: ASSOCIATION BETWEEN TREATMENT DELAY, TUMOR FEATURES AND SURVIVAL

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Objective: The effect of delay in initial treatment on outcomes of patients with soft tissue sarcoma (STS) of the extremity is unclear. The goal of this study was to determine the association between treatment delay, tumor characteristics and survival.

Methods: We evaluated patients diagnosed with soft tissue sarcoma of the extremity between 2006 and 2015 using the National Cancer Database. Treatment delay was defined as 30, 60 or 90 days between the date of diagnosis and the date of initial treatment (surgery, radiation, systemic, or other therapy). Characteristics of patients who experienced a treatment delay were compared to those who did not experience a treatment delay using Chi-square tests. The odds ratios of treatment delay were calculated using logistic regression. Kaplan-Meier analysis estimated survival rates. The risk of death associated with a treatment delay was calculated using Cox regression. Both crude hazard ratios and hazard ratios adjusted for tumor features and treatment types were calculated. A p-value of < 0.05 was used for all tests to determine statistical significance.

Results: The study sample included 17,987 patients with STS of the extremity. The mean age was 64.4 years, 54.7% were male and 84.7% were white. With treatment delay defined as ≥ 30 days, patients who experienced a delay were more likely

to have undifferentiated rather than well differentiated tumors (OR = 1.62; 95% CI: 1.45 – 1.82), and stage IV rather than stage I disease (OR = 1.82; 95% CI: 1.60 – 2.07) compared to those who did not experience a treatment delay. Similarly, with treatment delay defined as ≥ 60 days, patients who experienced a delay were more likely to have stage IV rather than stage I disease (OR = 1.52; 95% CI: 1.26 – 1.84) compared to those who did not experience a treatment delay. In contrast, with treatment delay defined as ≥ 90 days, patients who experienced a delay were less likely to have undifferentiated rather than well differentiated tumors (OR = 0.74; 95% CI: 0.56 – 0.99), but more likely to have stage IV rather than stage I disease (OR = 1.37; 95% CI: 1.01 – 1.84) compared to those who did not experience a treatment delay. When stratified by disease stage, survival was equivalent for patients who experienced a treatment delay ≥ 90 days compared to those who did not for stage I (HR = 1.31; 95% CI: 0.89 – 1.92), stage II (HR = 1.18; 95% CI: 0.74 – 1.88), stage III (HR = 1.31; 95% CI: 0.94 – 1.81), and stage IV (HR = 0.98; 95% CI: 0.71 – 1.37). Results were similar with a delay of ≥ 60 days and ≥ 30 days.

Conclusion: Patients who experienced a treatment delay ≥ 90 days were more likely to have lower grade disease compared to those who did not experience a delay. Further research into the factors that permit patients who experience a treatment delay to achieve comparable outcomes to patients who do not experience a delay is warranted.

HAZARD RATIOS (HR) AND RESPECTIVE 95% CONFIDENCE INTERVALS (CI) ESTIMATING RISK OF DEATH, STRATIFIED BY STAGE

Stage	Treatment Delay		
	≥ 30 days, HR† (95% CI)	≥ 60 days, HR† (95% CI)	≥ 90 days, HR† (95% CI)
All Stages	1.13 (1.05 – 1.20)*	1.14 (1.03 – 1.26)*	1.22 (1.04 – 1.44)*
Stage I	1.16 (0.98 – 1.38)	1.21 (0.95 – 1.54)	1.31 (0.89 – 1.92)
Stage II	1.12 (0.94 – 1.32)	1.24 (0.95 – 1.62)	1.18 (0.74 – 1.88)
Stage III	1.13 (1.01 – 1.26)*	1.08 (0.89 – 1.30)	1.31 (0.94 – 1.81)
Stage IV	0.94 (0.81 – 1.10)	0.93 (0.75 – 1.16)	0.98 (0.71 – 1.37)

Notes: referent is no delay. *p-value significant at < 0.05. †Adjusted for age, grade, histology, surgery type, radiation, and chemotherapy.

Poster 320 3041954

DESCRIPTIVE ANALYSIS OF LONG-TERM SURVIVORS AMONG PATIENTS WITH METASTATIC SOFT TISSUE SARCOMA

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Objective: Soft tissue sarcomas (STS) are a group of rare and heterogeneous mesenchymal tumors. Half of patients with STS present *de novo* or will develop metastases. Metastatic STS are considered incurable disease with a median overall survival (OS) ranging between 12 to 18 months. Although poorly described, a proportion of patients with metastatic STS are still alive 5 years after diagnostic of metastasis and defined as “long-term survivors”. Clinical characteristics of these patients and pathologic features of their tumors as well as therapeutic modalities administered are poorly assessed. The aim of this study was to evaluate the incidence of long-term survivors and describe their presentation and management in a large cohort of patients with metastatic STS.

Methods: We retrospectively collected information of patients with metastatic STS ≥18 years old managed in Centre Leon Berard between 1985 and 2015. Clinical information of patients, tumor characteristics and therapeutic management were gathered from NetSarc database and electronic medical records. These data were compared between the “long-term survivor” group, defined as the group of patients alive 5 years after the diagnosis of metastases, versus the “control group” defined as the group of patients who died within 5 years after metastatic diagnosis. Prognostic value of patients and tumors characteristics was investigated by logistic regression analysis. For “long-term survivor” group, we explored treatment administered at metastatic stage.

Results: Out of 436 patients with metastatic STS, 39 (9%) were still alive 5 years after diagnostic of metastases with a median OS of was 146 months (12 years). This “long-term survivors” group included, when compared to the control group, more female, younger patients, patients with better performance status, more patients with synovial sarcoma or endometrial stromal sarcoma, more patients with simple genomic sarcomas and whose genomic alteration was a translocation, lower

tumor grade, and smaller tumor. In multivariate analysis, age below 55 years old at metastatic stage (p=0.0002) and grade 1 tumor (p<0.0001) were significantly associated with the “long-term survivors” group. The therapeutic management of “long-term survivors” group was usually aggressive. Five patients received intensified chemotherapy as first-line treatment. Combination of systemic treatment and local treatment of metastases (surgery, radiotherapy, radiofrequency or cryotherapy) was frequently performed, leading to 62% of complete response in first line setting. Local destruction of metastasis was frequent, even in 2nd (48% of patients), 3rd (52%) and 4th (35%) lines of treatment. Nearly 60% of patients in the “long term survivors” group had been enrolled in clinical trial. The growth modulation index between first and second line was 1.3 [0.03-24.9].

Conclusion: Very long-term survivors are observed in metastatic STS. Selection of patients in good condition with less aggressive tumor and administration of intensive treatment may lead to obtain these motivating results in a poor prognosis disease.

Poster 321 WITHDRAWN

Poster 322 3042697

THE CLINICAL CHARACTERISTICS AND OUTCOMES OF PRIMARY BREAST SARCOMA: RETROSPECTIVE STUDY OVER 20 YEARS FROM A SINGLE, TERTIARY CENTER

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Objective: Primary breast sarcoma (PBS) is extremely rare disease, with less than 1% of all malignant tumor of breast. There are many controversies concerning the biological characteristics, prognosis and optimal treatment of these tumors due to rare incidence. The aim of this study was to assess the clinico-pathologic characteristics, outcomes and prognostic factors in PBS.

Methods: We retrospectively analyzed the results of 27 consecutive patients with PBS, identified and treated at the Asan Medical Center, Seoul, Korea between January 1998 and December 2016. Kaplan-Meier method was used to calculate overall survival (OS) and disease-free survival (DFS). Prognostic factors in survivals were analyzed by Cox proportional hazard model.

Results: The median age was 45 years (range: 14-66) and patients were one man and 26 women. The mean tumor size was 5.4 cm (range: 0.8-13) and the most common histologic subtype was angiosarcoma (n=8) followed by leiomyosarcoma

(n=4), liposarcoma (n=3) and others. All patients were treated by surgery. The mastectomy was performed in 12 patients and lumpectomy in 15 patients. Seven patients underwent axillary staging, but the lymph node stagings were all negative. Sixteen patients received adjuvant therapy including chemotherapy (n=7) and radiotherapy (n=13) and both therapies (n=4). After median follow-up of 30 months (range: 4-196), 11 patients developed recurrent diseases. The loco-regional recurrence was observed in 7 patients, while distant metastasis was observed in 6 patients. The common metastasis sites were bone (n=5) and liver (n=3). Five-year OS was 81% and five-year DFS was 60%. Six patients died and 4 patients died from the disease. Potential prognostic factors (tumor size, histologic subtype, tumor grade, type of surgery, adjuvant therapy) were analyzed by Cox model. Even though there was no statistical significance, there were trends toward worse DFS with histologic subtype of angiosarcoma (HR=3.45, 95% CI, 0.65-18.3 p-value=0.146), large size (HR=1.55, 95% CI, 0.26-9.33 p-value=0.63) and high grade tumors (HR=2.03, 95% CI, 0.37-11.5 p-value=0.41).

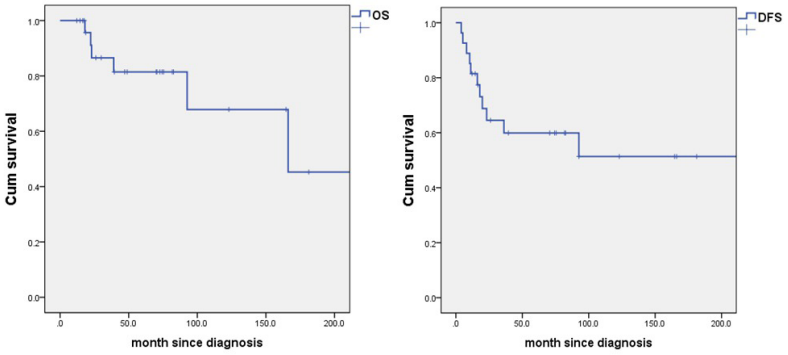
Conclusion: Our study showed that histologic subtype of angiosarcoma had a poor prognosis in PBS, and tumor size and grade were also prognostic factors. To improve survival in patients with PBS, aggressive surgical resection with the multidisciplinary approach might be needed.

Table 1.
Patient characteristics and treatment

	No.	%
Age		
< 45	13	48
≥ 45	14	52
Median age	45	
Tumor size		
< 5cm	15	56
≥ 5cm	12	44
Grade of tumor		
Grade 1	9	33
Grade 2+3	16	60
Missing data	2	7
Previous radiotherapy		
Yes	1	4
No	26	96
Type of surgery		
Lumpectomy	15	56
Mastectomy	12	44
Axillary staging		
Yes	7	26
No	20	74
Adjuvant radiotherapy		
Yes	13	48
No	14	52
Adjuvant chemotherapy		
Yes	7	26
No	20	74
Recurrence		
Yes	11	41
No	16	59

Table 2.
Univariate analysis of factors influencing disease-free survival

Variable	Hazard ratio (CI)	p-value
Histologic subtype		
Non-angiosarcoma	1	-
Angiosarcoma	3.45 (0.65-18.32)	0.146
Tumor size		
< 5cm	1	-
≥ 5cm	1.55 (0.26-9.33)	0.632
Grade		
Grade 1	1	-
Grade 2+3	2.03 (0.37-11.15)	0.415
Type of surgery		
Lumpectomy	1	-
Mastectomy	1.26 (0.18-8.76)	0.814
Adjuvant therapy		
No	1	-
Yes	1.254 (0.23-6.91)	0.795



Poster 323 3042704

TWENTY-EIGHT-YEAR EXPERIENCE OF SOFT-TISSUE AND BONE SARCOMAS AT A TERTIARY CARE HOSPITAL IN KOREA

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Objective: Sarcomas are rare and heterogeneous cancer of mesenchymal origin, that constitute less than 1 percent of all adult cancer. The rarity and the various subtypes of the disease have made it difficult to study sarcomas. The epidemiology and etiology of sarcomas are not well-understood. In our study, we performed a statistical analysis of all sarcoma patients who visited a 2700-bed-tertiary care hospital in Korea for 28 years.

Methods: A total of 4349 histologically diagnosed sarcoma patients, over 16 years old, were identified at Asan Medical Center in Korea from June 1989 to January 2017. Data about patient's demographics, clinicopathological characteristics, treatment pattern, and survival outcomes were extracted using Asan Biomedical Research Environment (ABLE). Of the total patients, 909 patients without treatment records were excluded. The overall survival and hazard ratio was estimated using the Kaplan-Meier analysis and the Cox proportional hazards regression analysis.

Results: In the registry, sarcomas were slightly female patients predominant (n=1822, 53.0%). The age distribution peaked in the 50s (n=727, 21.1%) and the number of elderly (≥65 years old) patients were 545 (15.9%). The fibroblastic myofibroblastic tumor (n=566, 16.5%) was most frequent histologic subtype and the undifferentiated/unclassified sarcoma (n=395, 11.5%) was second. The extremities and skeleton (n=1285, 37.4%) was the most common primary tumor site. The 5-year survival rate for all sarcoma patients was 79.3% and for soft-tissue sarcoma and bone sarcoma patients were 78.4% and 82.0%, respectively. Surgical resection was performed in 3220 (93.6%) patients and the 5-year survival rate was better in those patients compared to patients who did not receive surgery (81.2% vs. 38.0%; p<0.01). When survival rate was analyzed by treatment pattern, the 5-year survival rate for patients who received surgical resection with or without chemotherapy was 92.9% and palliative chemotherapy without surgical resection was 30.5%. Age, sex, histologic subtype, primary site, and treatment pattern was significantly associated with overall survival (Table 1).

Conclusion: This study has provided a baseline statistical information about the epidemiology, treatment, and prognosis for patients with sarcoma in a tertiary care hospital of Korea. Further large-scale, multicenter studies are needed to have a more comprehensive understanding and improved prognosis of this heterogeneous disease.

Table 1. Cox proportional hazards models for overall survival (OS)

	5yr OS (%)	Univariate analysis		p-value	Multivariate analysis		p-value
		Hazard ratio	95% CI		Hazard ratio	95% CI	
Age							
16-29 years (n=587)	81.9%	1			1		
30-64 years (n=2308)	81.5%	1.05	0.83-1.33	0.673	1.25	0.97-1.62	0.09
≥65 years (n=545)	64.3%	2.11	1.59-2.77	<0.01	2.08	1.54-2.82	<0.01
Sex							
Female (n=1822)	82.2%	1			1		
Male (n=1618)	76.1%	1.40	1.19-1.66	<0.01	1.27	1.06-1.52	0.01
Histologic subtype							
Fibroblastic myofibroblastic tumors (n=566)	92.9%	1			1		
Adipocytic tumors (n=394)	88.4%	1.59	0.98-2.59	0.06	1.58	0.97-2.59	0.07
Smooth muscle tumors (n=353)	72.0%	4.24	2.79-6.44	<0.01	4.11	2.66-6.33	<0.01
Tumors of uncertain differentiation (n=360)	68.3%	5.23	3.48-7.86	<0.01	5.78	3.81-8.78	<0.01

Undifferentiated/unclassified sarcomas (n=395)	64.1%	6.07	4.05-9.07	<0.01	5.96	3.95-8.98	<0.01
Osteogenic tumors (n=172)	73.3%	4.07	2.53-6.57	<0.01	5.73	3.47-9.47	<0.01
Ewing sarcoma (n=135)	57.5%	7.92	5.06-12.40	<0.01	6.76	4.24-10.78	<0.01
Primary tumor site							
Head and neck (n=222)	77.4%	1.54	1.09-2.17	0.01	1.17	0.82-1.67	0.39
Thorax (n=475)	70.8%	2.02	1.58-2.59	<0.01	1.65	1.27-2.15	<0.01
Abdomen (n=808)	74.6%	1.67	1.34-2.09	<0.01	1.70	1.1.32-2.19	<0.01
Extremities and skeleton (n=1285)	84.7%	1			1		
Treatment							
Surgical resection ± chemotherapy ± radiotherapy (n=3196)	81.6%	1			1		
Chemotherapy ± radiotherapy (n=202)	30.5%	5.54	4.35-7.07	<0.01	3.57	2.74-4.65	<0.01
Other treatment (n=42)	54.6%	3.19	1.59-6.43	<0.01	2.62	1.28-5.37	0.01

Poster 324 3042875

MULTIMODAL TREATMENT IN PATIENTS (PTS) WITH ADVANCED/METASTATIC SOFT TISSUE SARCOMA (A/M STS): IMPROVMENT IN OVERALL SURVIVAL (OS) IS MAINLY ASSOCIATED WITH COMBINATION OF CHEMO-THERAPY (RX) AND SURGERY (SX).

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Objective: MT is considered as standard of care in a selected group of pts with a/m STS, although the impact of MT on prognosis remains undefined. Here, we report on a/m STS pts. with palliative medical treatment (Rx) with MT(+) or without MT(-), retrospectively.

Methods: 181 a/mSTS pts were identified from medical records (observation period: 12/1998–05/2016). Throughout the course of palliative treatment all pts received Rx, as well as MT(+) pts received in addition either surgery (Sx) or radiotherapy (RTx), or both. Overall survival (OS) was defined as time from first palliative treatment until death. Response rates were defined by clinical and radiological evaluation. Descriptive statistics Kaplan-Meier and Log-rank analysis, as well as Cox-regression and Land-mark analyses were applied.

Results: Out of 181 a/mSTS pts 111 (61.3%) pts received MT(+). Herein, in both subgroups number of Rx lines where similar. According to first administered Rx, response rates in all pts tends to be superior for doxorubicin/ifosfamide (n=56) compared to doxorubicin (n=61) (p=0.018), while in MT(+) pts difference was not significant (p=0.31). MT(+) pts received a median of 1 RTx (r: 0-8) and 1 Sx (range (r):0-7). Median OS was 18 (95%CI:14.1-21.9) months (mo) for all pts, while MT(+) pts showed a superior OS of 22 (95%CI: 15.2-28.8) mo compared to MT(-) with 15 (95%CI:8.8-21.2) mo (log-rank p=.029). OS improvement was associated with the use of Rx+Sx±RTx (log-rank p≤.001) in MT(+) pts, which remained significant at land-marks 3- (log-rank p=.001) and 6-mo (log rank p=.004). Rx+Sx±RTx showed an independent association with decreased risk of death (HR: 0.45 (95%CI: 0.4-0.8); p=.004), while Rx+RTx was not identified as independently associated with risk of death.

Conclusion: MT in a/mSTS within the palliative treatment sequence was performed in a relevant proportion of pts at our center. MT was associated with superior OS, mainly in pts receiving Rx+Sx ±RTx within 6 months upon first palliative treatment, rendering additive surgery the preferred approach within the multimodal strategy. However, identifying parameters for intensive treatment of a/m STS remains to be defined for optimal pts selection.

Poster 325 3017541

PROGNOSTIC SIGNIFICANCE OF SARCOPENIA IN PATIENTS WITH SOFT TISSUE SARCOMA

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Objective: Sarcopenia, loss of skeletal muscle mass, is considered as a poor prognostic factor in patients with various malignancy. However, the association between sarcopenia and oncological outcomes in patients with soft tissue sarcoma (STS) is not well understood. We aimed to identify the prevalence and prognostic implications of sarcopenia on oncological outcomes after surgery for STS.

Methods: We reviewed 536 patients with STS in extremities and trunk who were surgically treated at our institution between 2004 and 2016. We enrolled 359 patients after we excluded patients with metastasis at diagnosis, age under 18 years old, and follow-up period less than 12 months. Sarcopenia was assessed by calculating skeletal muscle index using CT scan at the level of L3 vertebrae. Patients were dichotomized according to the presence of sarcopenia. Clinicopathological, surgical, and oncological outcome data were analyzed to evaluate prognostic significance of sarcopenia in terms of overall survival (OS), local recurrence free survival (LRFS), metastasis free survival (MFS), and event free survival (EFS). The median age of the patients was 52 years and the mean follow-up period was 48 months.

Results: Sarcopenia was present at 126 of 359 patients (35.1%). Among the patients who developed distant metastases, prevalence of sarcopenia was present in 22 of 50 patients (44.0%). On univariate analysis, sarcopenia was not significant poor prognostic factor for OS (p=0.318), MFS (p=0.489) and EFS (p=0.217). However, it was statistically poor prognostic factor for LRFS (p=0.018). On multivariate analysis, sarcopenia was not a significant prognostic factor for OS (p=0.529), LRFS (p=0.076), MFS (p=0.378), and EFS (p=0.892). In a subgroup analysis among patients who developed metastases, sarcopenia was not a significant factor for post-metastasis survival (p=0.890).

Conclusion: Sarcopenia was identified in about one-third of patients with STS, and the prevalence was higher in patients who developed metastases. However, sarcopenia was not a significant prognostic factor predictive of OS, LFRF, MFS, and EFS, nor was it a significant factor for post-metastasis survival.

Poster 326 3025847

REAL-WORLD TREATMENT PATTERNS AND OUTCOMES FOR PATIENTS WITH ADVANCED SOFT TISSUE SARCOMA RECEIVING SYSTEMIC THERAPY IN BRAZIL

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Objective: Soft tissue sarcomas (STSs) are a group of cancers with more than 50 different histological types that develops from specific soft tissues in any part of the body. In the US and European countries, incidence rates vary from 1.8 to 5.6 cases per 100,000 annually. In Brazil, real-world information regarding STS is scarce, difficulting evidence-based decisions. This study aimed to describe the disease course, treatment patterns, and healthcare resource use, for advanced STS in Brazil. We present preliminary results that include 46 patients.

Methods: This retrospective, multicenter, observational study reviewed medical charts from patients diagnosed with advanced STS between January 1st, 2005 to December 31th, 2015. Patients included were ≥18 years at the initial diagnosis, with a histologically confirmed diagnosis of advanced STS (locally advanced or metastatic STS, excluding Kaposi's Sarcoma, gastrointestinal stromal tumor [GIST] and bone sarcoma, and not amenable to curative treatment with surgery or radiotherapy). Patients must have started the first cycle of the first line of systemic therapy to treat advanced STS. The total sample size will be 200 patients. Medical records are reviewed retrospectively from the date of study inclusion, regardless of the time of diagnosis. No information will be collected prospectively. Demographic information, comorbidities and risk factors, disease information, treatment patterns and healthcare resource utilization are collected and described.

Results: Approximately 45% of patients were men and mean age was 51.2 (±15.71) years. The most frequent histologies were leiomyosarcoma (23.9%), undifferentiated pleomorphic sarcoma (10.9%) and synovial sarcoma (8.7%). The most common primary tumor locations were leg (39.1%), arm (8.7%) and shoulder (8.7%). The majority of patients were treated in the public sector (40, 87 %). In the private sector, 4 patients had medical insurance and 2 paid out-of-pocket. Comorbidities were reported by 56.5% of patients, being high blood pressure (69.2%) and diabetes (7,7%) the most common comobirdities. Approximately 57% of the patients completed only the first-line of treatment, while 28.3% and 6.5% performed up to the second and third-lines, respectively. In the first-line therapy, the most common regimen were doxorubicin+ifosfamide (34.8%), doxorubicin (23.9%), paclitaxel (8.7%) and docetaxel+gemcitabine (8.7%). The most common regimes in the second-line were docetaxel+gemcitabine (30%),doxorubicin (10%), paclitaxel (10%) and doxorubicin +ifosfamide (10%). Regarding third-line, the reported regimens were dacarbazine (42.9%), docetaxel+gemcitabine (28.6%), ifosfamide (14.4%) and trabectedin (14.3%). The proportion of patients receiving single-drug therapy was 37%, 40% and 71% in the first, second and third line of treatment, respectively. In first-line therapy, the most used drugs were doxorubicin (65.2%) and ifosfamide (45.6%). In the second-line, gemcitabine, doxorubicin, and docetaxel were received by 40%, 30% and 30% of patients, respectively. The proportion of STS staging at initial diagnosis was 4.3%, 2.2%, 32.6% and 45.6% at stage I, II, III and IV, respectively. Staging was unknown in 15.3%. of patients. In first line ECOG status information was reported in 78% of charts. Among them, the ECOG score was 0 in 13.9% of patients, 1 in 66.7%, 2 in 11.1%, and 3 in 8.3% of patients. Metastasis were reported at the time of diagnosis for 48% of patients. Approximately 39.1% of patients received supportive care, with blood transfusion (57.7%), oxygen therapy (23.1%) and nutritional support (11.5%) the most frequent ones.

Conclusion: STS treatment shows increased use of single-drug therapies in later treatment lines and high variability among of regimens. Patients were generally diagnosed in late stages and experienced low to moderate functioning disabilities as measured with ECOG.

Poster 327 3027452

NETWORK META-ANALYSIS OF RANDOMIZED TRIALS FOR SECOND OR LATER-LINE TREATMENTS OF METASTATIC LIPOSARCOMA

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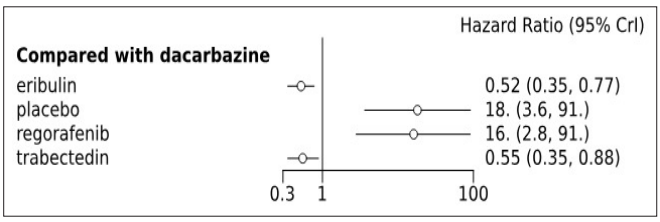
Objective: Soft tissue sarcomas (STS) are heterogeneous diseases and span a broad range of differentiation including adipocytes, smooth or striated muscles, and other several origins. It is well known that different treatment sensitivity to chemotherapy for different histological subtypes. Current guideline usually recommends anthracycline-containing regimens for systemic treatment of locally advanced or metastatic STS. However, the vast majority of advanced STS undergo progression after first-line anthracycline-based chemotherapy. Many chemotherapeutic agents have been tested and approved for patients with STS who have failed anthracycline-based chemotherapy. However, only a few direct comparisons have been performed between those agents. We focused on liposarcoma, one of the most common and relatively chemotherapy sensitive STS. We performed a network meta-analysis (NMA) to compare and rank the regimens available for second or later line treatment for advanced liposarcoma in terms of progression-free survival (PFS).

Methods: We conducted a systematic literature review to identify eligible randomized trials meeting the following criteria: trials comparing the efficacy of second or later-line treatment for advanced sarcoma and trials including information of hazard ratios(HRs) for PFS of liposarcoma histology. A Bayesian NMA based on PFS with a fixed-effect model was performed to determine the ranking of second or later-line treatments and compare relative efficacies of the regimens. One of the most commonly used drugs, dacarbazine, was used as reference treatment.

Results: Five randomized trials were identified including five treatments: dacarbazine, eribulin, regorafenib, trabectedin, and placebo (best supportive care). One of the most commonly used regimen in practice, gemcitabine with docetaxel, was not included in this study because of not forming network framework with other several regimens. Two out of five drugs were significantly better in terms of PFS than dacarbazine; eribulin (HR, 0.52; 95% credible intervals (CrIs), 0.35-0.77) and trabectedin (HR, 0.55; 95% CrI, 0.35-0.88). The probability of being best treatment was 57% and 43% for eribulin and trabectedin, respectively.

Conclusion: Eribulin and trabectedin showed superior efficacy regarding PFS over dacarbazine for second or later-line treatment of advanced liposarcoma, and these two drugs could be recommended than dacarbazine or regorafenib. Network meta-analyses could provide a thorough overview of each treatment's relative efficacy in case of lacking head-to-head comparisons.



Poster 328 3027524

DESCRIPTIVE EPIDEMIOLOGY AND CLINICAL OUTCOMES OF SOFT TISSUE SARCOMAS IN ADOLESCENT AND YOUNG ADULT PATIENTS IN JAPAN

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Objective: The prognosis of Adolescent and young adult (AYA) patients with cancer, from ages 15 to 39 years, have not improved comparing to younger children or older adults. In this study, we focused on soft tissue sarcoma of AYA patients. The purpose of this study was 1) to derive nationwide statistics of AYA patients with soft tissue sarcoma and compare them to other age groups, 2) to determine whether a correlation exists between the AYA age group and poor DSS and 3) to clear up the cause of poor results of AYA patients.

Methods: We identified the records of 7759 patients with soft tissue sarcomas (4309 male and 3450 female) from the Bone and Soft Tissue Tumor (BSTT) registry that was a nationwide registry in japan during 2006 -2013. We analyzed and compared the epidemiological features of AYAs with other age groups. Histologic subtypes that have many cases and have a high ratio of AYA patients were selected. The rest appointed to high-grade sarcoma and low-grade sarcoma.

Results: Among AYA, myxoid/round cell liposarcoma was predominant (19.5%), followed by synovial sarcoma(17.7%). The DSS rate of AYA patients with soft tissue sarcoma was worse than that of other age groups. The DSS rate of AYA patients with only malignant peripheral nerve sheath tumor (MPNST) and rhabdomyosarcoma (RMS) in histologic subtypes were worse than that of other age groups. However, multivariate analysis demonstrated that poor prognostic factors of soft tissue sarcoma were Age >65 years, Male, high tumor grade, tumor size >10 cm, multiple tumor location, amputation, positive surgical margins, metastasis and deep tumor depth.

Conclusion: Our findings demonstrated that the DSS rates of AYA patients with soft tissue sarcoma were inferior to those of other age groups in Japan. This is probably related to the worse DSS rate of AYA patients with MPNST and RMS.

Poster 329 3038308

PATTERNS OF CARE OF ADVANCED SOFT TISSUE SARCOMAS (STS) NON-GIST IN FOUR EUROPEAN COUNTRIES (EU4)

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Objective: Soft-tissue sarcomas (STS), a heterogeneous group of rare solid tumors of mesenchymal origin, account for approximately 1% of adult cancers. Real-life data are needed to understand the current medical approach and the impact of the advances in the clinical research on the routine clinical practice.

Methods: A cross-sectional survey that collected anonymized patient-level data from a panel of physicians (approximately 60 per year) in France, Germany, Spain, and Italy. Patient cases were reported if they had a diagnosis of stage IV Soft Tissue Sarcoma. Case information was generated from secondary data and captured full retrospective treatment information, patients' profile, surgical interventions and radiotherapy. Physicians were enrolled in the survey if they had personally treated STS patients during the most recent 3-months period. Each respondent was asked to report the most recent consecutive STS patients managed during the reporting period. The study population consisted in 4,492 cases collected from January 2015 to March 2018.

Results: Anthracyclines were the class of cytotoxic drugs used the most used across all EU4 countries in 1st line (~70%), led by doxorubicin in monotherapy (~36%) or combined with ifosfamide (~21%). Epirubicin in combination with ifosfamide was given to 2% of patients, while ~1% received it as monotherapy. Taxanes were the second most used class of drugs in 1st line: docetaxel as preferred option (~15%) followed by paclitaxel (~7%). Other 1st-line treatments prescribed included gemcitabine-based regimens (~13%), dacarbazine (~5%), trabectedin (~4%), and anti-VEGFR/VEGF (<1%). Trabectedin dominated the 2nd line treatment (~30%), followed by gemcitabine (mainly in combination with other drugs alike 1st line treatment, 6% in monotherapy or ~17% in gemcitabine-based protocols), pazopanib (~20%), taxanes (~20%), anthracyclines (~11%) and ifosfamide (~9%). Although the use of trabectedin was still high in 3rd and subsequent lines (~25%), pazopanib was the most frequently used drug in later lines (~34%). The use of gemcitabine increased to ~28%, while anthracylines' decreased by 7%; a ~2% use of eribulin was also noted in 3rd line. Most patients in 1st line stopped their treatment due to completion (>50%), while in later lines, 2nd and subsequent, distant progression was the most common reason (up to 45%) for stopping treatment.

Conclusion: Anthracyclines are still the backbone of the first-line treatment, and other cytotoxic drugs like gemcitabine and taxanes are mainly used as rescue therapy alone or in combination in the pre-treated setting. Targeted therapies are most used in pre-treated settings, with trabectedin as the agent most used in second-line, and pazopanib as the agent most used in third line. These patterns of care are reflecting the state of the art of the STS clinical research, with novels that are currently established agents in pre-treated setting moving forward the front-line setting that is still dominated by the use of classic cytotoxic agents, mainly anthracyclines. Real-Life data are very important in describing the impact of the clinical research into the routine clinical practice, to provide a measure of the application of a treatment strategy to the daily clinical practice and to provide a historical reference to evaluate changes over time.

Poster 330 3042802

A MATCHED COHORT STUDY OF ADJUVANT RADIO-CHEMOTHERAPY VERSUS RADIOTHERAPY ALONE IN SOFT TISSUE SARCOMA PATIENTS

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Objective: Surgery is the main treatment of high risk soft tissue sarcomas (STSs) patients. Postoperative radiotherapy after conservative surgery increases local control, in selected cases chemotherapy is indicated to reduce the risk of local recurrence. The safety and efficacy of neoadjuvant radiochemotherapy (RT-CT) in STSs is well established, radiochemotherapy association in postoperative setting is still debated due to the risk of increased toxicity. We performed a matched cohort analysis in high risk soft tissue sarcoma patients, to evaluate if there are differences in terms of clinical outcomes and toxicity between patients treated with concomitant radiotherapy and chemotherapy (RT-CT group), and those treated with radiotherapy alone (RT group).

Methods: Ninety STSs patients treated at our Institution with postoperative intent were selected; 50% of them received adjuvant concomitant radiotherapy and chemotherapy and 50% of them received adjuvant radiotherapy alone. Patients in the two groups were matched according to age, T stage and grading. Overall survival, recurrence free survival and distant metastases free survival were analyzed and results were compared between the two groups. Acute and late toxicities were recorded.

Results: Acute toxicities were represented by dermatitis. We recorded Grade 3 dermatitis during treatment in 15 (16.7%) patients, of which 6 (6.7%) were in the RT-CT group. Late toxicities were represented by late fibrosis, joint stiffness and bone fracture, in 12 (13.3%), 3 (3.3%) and 1 (1.1%) patients, respectively. We didn't find any differences in the rate of acute and late toxicities between RT-CT and RT group. Local recurrence was observed in nineteen (21.1%) patients; overall 5-year local relapse free survival was 83%, without any differences between the two groups. Twenty-nine patients developed distant metastases, of which 14 (15.6%) were in the RT-CT group and 15 (16.7%) were in the RT group. Sixty (67%) patients were free from distant metastases after 5 years. The only independent factor affecting distant recurrence was found to be age >65 years (HR=5.7, 95% CI 2.7-11.9; p=0.001). At the time of analysis 15 (16.7%) patients were dead, of which 6 (6.7%) were in the RT-CT group and 9 (10%) were in the RT alone group. 5-year overall survival was 88%. Age >65 years at the multivariate analysis was found to be an independent prognostic factor of overall survival (HR=3.7, 95% CI 1.2-12.1, p=0.037).

Conclusion: In this report adjuvant radiochemotherapy resulted in a good local and distant control and acceptable toxicity. Elderly population had an increased risk of distant metastases and worse survival. Being a high risk and fragile population, in elderly soft tissue sarcoma patients tailored treatment has to be considered, to obtain better outcomes. Prospective randomized studies are needed, with large size populations and subgroup analysis subdivided by histotype subtypes, to clarify the role of adjuvant chemotherapy in soft tissue sarcoma patients.

Poster 331 3042925

RISK STRATIFICATION OF SOFT TISSUE SARCOMA FOR PREDICTION OF LOCAL RECURRENCE

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Objective: The purpose of this study is to determine what factors influence the STS local recurrence rate and to develop a risk stratification system that will help to predict the risk of local recurrence in patients with resected STS. In this investigation we aimed to answer the following questions

1. What are the risk factors associated with local recurrence following soft tissue sarcoma resection?
2. Can we implement a risk stratification system for local recurrence following resection of a soft tissue sarcoma?

Methods: This is a retrospective analysis of patients treated surgically for STS at 10 different institutions. Patients with atypical lipomatous tumor/well-differentiated liposarcoma were excluded. Data recorded included: demographic characteristics, medical comorbidities, body mass index, smoking status, tumor characteristics , surgical margins, use of adjuvant radiation and chemotherapy. Data was recorded for 444 patients (203 female, 229 male) with a mean age of 55.0 years (+/- 20.19 years) patients. Proportions were compared between independent groups using a Chi-square test or Fisher's exact test for small expected frequency counts. Means were compared between groups using a 2-sample t-test and medians were compared using a Wilcoxon rank sum test. Ordered categorical variables were compared between groups using a Cochrane-Armitage test for trend. A log-rank test was performed for any study variable that was significant at 0.05 alpha level based on the univariate model to compare the time to local recurrence. In order to identify risk groups for local recurrence, a recursive partitioning method was used. The goal of the recursive partitioning algorithm is to group participants together according to their risk for local recurrence.

Results: Of 444 patients, 65 (14%) had a local recurrence of STS following wide resection. There was difference in age with the mean age of 63.3 years +/- 16.2 in those with a recurrence and 53.6 years +/- 20.5 in those without (p=0.0003). There was no statistical significant difference in any other patient demographics or medical comorbidities. There was no difference in tumor size, anatomic location, depth, or presence of distant metastases in those with a local recurrence. Undifferentiated pleomorphic histology (p=0.0250), metastatic regional lymph nodes at diagnosis (p=0.0043), and histologic grade (G1 compared to G2, G3) (p=0.0076) were all associated with a statistically significant increase in local recurrence. There was no statistically significant difference in local recurrence based on MSTS margin classification or distance of the tumor to the resection margin. There was a statistically significant increased risk of recurrence (p=0.0224) in those who received postoperative radiation.

Based on these results, a predictive model based on risk stratification was developed to help predict the risk of local recurrence using histologic subtype (UPS vs. Other), grade, margin, and use of post-op radiotherapy (XRT). Three risk groups were identified. The low risk group (<5% predicted probability to local recurrence) were those with Grade G1 tumors. The intermediate risk group (14% predicted probability of recurrence) had two arms combined: Grade G2 or G3 tumors and no post-op XRT, or Grade G2 or G3 tumors and post-op XRT and histologic subtype other than undifferentiated/unspecified. The high risk group (32% probability of recurrence) were those Grade G2 or G3 tumors who also had post-op XRT and undifferentiated/unspecified histologic subtypes.

Conclusion: Our data indicate most important factors to predict local recurrence were age, grade, histology and post-operative radiation status. The lack of correlation of margin status with local recurrence in our data set may be influenced by the inclusion of many low grade tumors as well as the judicious use of radiotherapy. These results indicate that local recurrence is a multifactorial problem, not solely related to margins, and is deserving of further careful investigation.

Poster 333 3042160

CLINICAL IMPLEMENTATION OF A NANOSTRING-BASED PANSARCOMA FUSION ASSAY

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Objective: Background: Molecular pathology is increasingly being considered the gold standard for diagnosis of fusion gene sarcomas. Recently, we developed a NanoString-based assay that detects 178 sarcoma fusions with 96% sensitivity and 100% specificity, at lower cost and with faster turn-around than FISH or next generation sequencing (Chang KTE et al,

J. Mol. Diagn. 2018). This non-proprietary, non-commercialized testing solution is now being used as the first-line clinical assay for sarcoma molecular diagnosis in British Columbia and Singapore.

Aim: We report the first year of real-world experience implementing the NanoString pan-sarcoma platform for clinical use, as performed in two accredited molecular diagnostic laboratories (Vancouver Hospital and KK Women's and Children's Hospital).

Methods: RNA is extracted from six 5-micron scrolls for FFPE core biopsies or three scrolls from excision samples (target input: 200 ng) and hybridized overnight with a sarcoma fusion oligonucleotide probe pool ("codeset") and corresponding fluorescent barcode tags. Codeset/sample RNA complexes are counted on a NanoString Digital analyzer based on bound fluorescent reporter probe barcode tags. RNA sample quality is assessed by expression of four housekeeping genes. An analysis pipeline was developed using standard R functions for data processing and R Markdown for report generation. For external proficiency testing, cases are exchanged between Vancouver and Singapore.

Results: For clinical accreditation in Vancouver, 25 validated cases were repeated in a verification study in the clinical molecular laboratory; results were concordant for all 23 cases where sufficient RNA quantity and quality was available. For external quality assurance, 3 samples obtained through a College of American Pathologist QA program are analyzed every six months in Vancouver, with 100% accuracy based on 6 samples run to date.
Formal clinical accreditation was completed in Vancouver in 2017. Since clinical testing commenced in February 2018, 254 cases have been tested where a sarcoma subspecialty pathologist considered a fusion-associated sarcoma in the differential diagnosis, including 57 incident clinical cases and 89 research cases in Vancouver, and 108 total cases in Singapore (Table 1). Vancouver samples have been collected from 5 sarcoma centres in Canada and 3 sites internationally. Singapore received samples from 3 local hospitals and via referral from additional hospitals across Asia. At the Vancouver site, 132/146 cases met RNA quality control input metrics, and in these the overall sensitivity was 97.0% (vs. PCR) and specificity 97.7%. The assay is currently run weekly as batches of 3-6 cases, providing results a day ahead of weekly provincial tumor board meetings. In Singapore, 101/108 cases had sufficient RNA for analysis, with these cases showing 97.0% sensitivity and 99.0% specificity; the assay is currently being run every second week with 4-8 cases per batch. The runtime per batch was 36 hours. Our total cost per case was USD$270, including reagent cost, technologist time and overhead. Test availability has however increased overall use of molecular diagnostics, including challenging cases that usually turn out to be fusion-negative.

Conclusion: This Nanostring-based PanSarcoma assay continues to perform with high sensitivity and specificity in practice and has become the standard assay for sarcoma molecular diagnosis in British Columbia and Singapore. Costs are lower and turnaround time faster than alternatives we have tested. The nature of the test means it does not cover very rare or novel fusion variants. A 3rd-generation of the assay is in active development to increase coverage for clinically-important new variants of small blue round cell tumors.

Table 1. Case Summary

Sarcoma Entity	Vancouver Research	Vancouver Clinical	Singapore
ACTB-GLI1	0	0	2
ATIC-ALK	0	0	1
COL1A1-PDGFB	8	0	0
COL1A1-USP6	1	0	0
ETV6-NTRK3	2	0	1
EWSR1-ATF1	1	0	6
EWSR1-CREB1	0	0	1
EWSR1-ERG	0	3	3
EWSR1-FLI1	4	3	6
EWSR1-NFATc2	0	1	0
EWSR1-NR4A3	0	0	1
EWSR1-WT1	0	1	2
FUS-DDIT3	1	0	1
HAS2-PLAG1	0	1	0
HEY1-NCOA2	1	1	1
MYH9-USP6	3	1	1
PAX3-FOXO1	1	1	1

PAX3-FOX04	0	0	1
PAX7-FOXO1	0	0	1
RBP56-NR4A3	1	0	0
SS18-SSX1/2/4	8	2	4
YWHAE-NUTM2	0	1	1
ZC3H7B-BCOR	0	1	4
No fusion detected	45	37	62
False positive	3	0	1
RNA fail/ not analyzable	10	4	7
Total cases	89	57	108

Poster 334 3041833

VIRTUAL BIOBANKING FOR RETROPERITONEAL SARCOMA – A TARPSWG INITIATIVE

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Objective: Members of the Trans-Atlantic Retroperitoneal Sarcoma Working Group (TARPSWG) from expert sarcoma centers across four continents were surveyed to define current biobanking efforts and long-term goals. Our aim was to determine if members thought centralized biobanking would be a sensible and feasible next step to facilitate translational research.

Methods: Using SurveyMonkey, 21 questions were posed on current clinical data collection, biobanking procedures and level of interest to collaborate on research using a shared biobank. Initial surveys were sent to the TARPSWG membership list in February 2018. Reminders were sent twice and responses were collected until May 2018. Preliminary findings were discussed at the TARPSWG meeting held in Chicago, IL, March 2018.

Results: A total of 49/134 members from 42/59 centers (71%), 14 countries and 4 continents responded to the survey. The majority of subjects were surgical oncologists (76%), and over 58% of all responders have clinical practices comprised of at least 50% sarcoma. Most respondents (80%) have an ethics board approved prospective clinical database for sarcoma patients (date established ranged from 1995-2018, accrual 10-500 patients per annum). Biobanking is undertaken in 88% of centers and was established as early as 1988 in one center. Almost all centers store their surgical specimens (97%) as FFPE samples, fresh frozen samples or both, while only 18% of responders also store germline tissue. The biobanks are managed centrally by the department of pathology in 55% of centers, directly by clinical faculty in 40%, and centrally by the government in 5%. Funding sources for biobanking varied worldwide, with 25 (74%) having primarily institutional funding; while 3 centers relied solely on philanthropy and 4 centers on grants. Although 95% of centers biobank pre-treated sarcoma specimens, standardized operating procedures to ensure tissue quality of the samples was not uniform. Lack of funding, limited infrastructure and legal and ethical consideration were perceived barriers for the 6 centers that do not routinely biobank. Finally, 89% of respondents were willing to share biobanked specimens with TARPSWG members depending on the protocol proposed, however with more formal group discussion. Overall, a virtual biobank with tissue storage at local centers is preferred over a more centralized TARPSWG biobank.

Conclusion: Collaboration of TARPSWG to date has focused on clinical management and outcomes in retroperitoneal sarcoma patients, which has expanded to over 14 countries worldwide. Virtual biobanking for translational research projects is enthusiastically supported by TARPSWG members, and potentially will ensure large availaibility of rare tumors tissues. Nevertheless, more comprehensive standard operating procedures need to be generated and implemented to ensure specimen quality.

Poster 335 3041966

IDENTIFICATION OF RECURRENT FUSIONS WITHIN SUCCINATE DEHYDROGENASE A (SDHA) IN WELL DIFFERENTIATED RETROPERITONEAL LIPOSARCOMA

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Objective: Well differentiated retroperitoneal liposarcoma (WD-RPLS) is a rare tumour, with a poor response to neo-adjuvant chemotherapy and a significant five-year mortality. A large number of sarcomas have been found to have consistent chromosomal abnormalities, with translocation being the most common type of cytogenetic abnormality. We aimed to carry out a comprehensive multi-platform molecular characterisation of WD-RLPS.

Methods: 8 WD-RPLS samples underwent whole genome sequencing of three tumour:normal pairs and five tumour only samples to an average of 85x read depth. Gene fusion prediction via analysis of WGS data demonstrated recurrent fusion events in succinate dehydrogenase A (*SDHA*). HMGA2 and MDMA amplification have been well described in liposarcoma, however *SDHA* fusion has not been previously identified.

We aimed for orthogonal validation using a targeted RNA sequencing fusion panel. 31 FFPE samples of WD-RPLS (8 paired: normal, 6 tumour only, 10 normal tissue only) underwent RNA extraction. RNA was concentrated using a column-based purification protocol. Samples were taken through a QIAgen RNAscan fusion panel targeted against SDHA. This used a single extension primer designed to target each exon of SDHA with a universal primer at each end. Raw sequences were mapped to the GrCh38 transcriptome, and fusions called using STAR.

Results: Recurrent fusions between SDHA and other fusion targets were identified as the result of an unstable breakpoint. 8 out of 13 liposarcoma samples had evidence of a gene fusion, with five of these showing a fusion between SDHA and MIR6087. Other fusion targets included ELN, SNORD10 and PTGIR. Importantly, none of the normal samples showed evidence of an SDHA fusion.

Conclusion: We have successfully demonstrated recurrent fusions within SDHA using WGS and a targeted RNA fusion panel, which we believe to cause loss of function. SDHA encodes a major complex in the mitochondrial respiratory chain and has recently been found to act as a tumour suppressor gene in paraganglioma. SDHB is implicated in phaeochromocytoma and GIST tumourigenesis and there is evidence to suggest these tumours, due to a truncated TCA cycle have a limited ability to produce key amino acids vital for cell proliferation and survival. They exhibit synthetic lethality, which is a potential for targeted drug therapy. Further study is required to understand the effect of the changes in this gene and its relevance in WD-RPLS. Work is currently ongoing to validate this loss of function in vitro with mitochondrial dysfunction experiments, with a view to in vivo validation using C13 isotope tracing.

Poster 336 3025780

SENSITIVITY OF DIFFERENT BIOPSY METHODS IN SOFT TISSUE AND BONE SARCOMAS: CORE NEEDLE VS. INCISIONAL BIOPSY

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Objective: The importance of a conclusive tissue sample for a fast and precise diagnostic in soft tissue and bone sarcomas is well known. In principle, there is the option of minimally invasive core needle biopsy (also CT-controlled) or an open incisional biopsy. Sensitivity and validity of minimally invasive methods are known to be limited. The aim of our study was to evaluate sensitivity of both mentioned biopsy methods regarding entity and grading.

Methods: A total of 365 patients with confirmed diagnosis of a bone (BS) or soft tissue sarcoma (STS) had been evaluated between 2006 and 2017. All tumors were finally resected after biopsy in our institution. In total 415 consecutive biopsies were performed. Core needle biopsies were performed either image-based (ultrasound-, image- or CT-guided) or by clinical findings (after MRI imaging). The open biopsy was performed in general anesthesia. The entity of the tumor and, as if possible, grading had been evaluated.

Results: Of all performed biopsies, 276 were core needle biopsies (66.5%) and 139 (33.5%) incisional biopsies. The diagnosis of the tumor entity could not be obtained in 2,6% of cases. A benign tumor was diagnosed in 6.9%, in 90.5% of the

cases a malignant tumor was described. Multiple biopsies (repetition of core needle biopsy or a switch to incisional biopsy) was required in 12.9%.

The rate of correct final results in the group of core needle biopsies was 98.4% regarding the entity. Grading was correctly evaluated in 63.7%. An upgrading after resection was seen in 33,3% of G1 sarcomas, a downgrading in 2,8% of G2 or G3 sarcoma. In sarcomas 96% of BS and 89.1% of STS were diagnosed correctly regarding the entity.
In the group of incisional biopsies, the proportion of correct diagnosis regarding the entity was 87%. In 81.8% of the cases, grading could be evaluated correctly. In this group, the initial low-grade sarcomas were significant more frequently upgraded (30.8%). In sarcomas the entity was correctly diagnosed primarily in 96.4% of BS and 97.9% of STS. There was no significant difference between incisional and core needle biopsy in the sensitivity of entity (p=.443) and grading (p=.909) diagnosis.

		STS	
Kind of biopsy	Inzision		Core needle
Sensitivity entity	97.9 %		89.1 %
Sensitivity G	81.8 %		63.7 %
		BS	
Sensitivity entity	96.4 %		96.0 %
Sensitivity G	78.8 %		72.9 %

Conclusion: Both biopsy methods represent valid diagnostic procedures. Incisional biopsy seems to be more advantageous regarding the evaluation of differentiation, grading and entity of STS. The poorer result of incisional biopsies regarding the sensitivity is due to the preselection of patients in this group (bias).

Poster 337 3028837

UTILITY OF CORE NEEDLE BIOPSY IN RETROPERITONEAL LIPOSARCOMA: A FIFTEEN YEAR REVIEW

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Objective: In the retroperitoneum, adipocytic neoplasms are considered to be liposarcoma (LPS) until proven otherwise. Management of retroperitoneal masses varies depending on the histology, ranging from observation to a wide multivisceral en bloc resection, with or without pre-operative radiation. Accurate diagnosis is thus essential and surgical oncology literature recommends core needle biopsy (CNB) for management planning. Limitations of CNB of retroperitoneal (RP) adipocytic neoplasm include inadvertent sampling of normal fat, fibrous tissue, or necrosis, sampling of dedifferentiated component only and sampling bias where classic histologic features are absent. We aim to determine 1) how frequently CNB of RPLPS provides a useful diagnostic result and 2) if the CNB diagnosis is representative of the subsequent resection. Few studies have examined the utility of CNB specifically in RPLPS and, knowing its limitations, one must consider the possibility of improved biopsy techniques which may be necessary to improve accuracy of these biopsies.

Methods: A retrospective review of the pathology laboratory information system (LIS) at The Ottawa Hospital (Ontario sarcoma designated tertiary care center) was performed to identify all CNB and resections of RPLPS from 2002 to 2017. In addition, for each of the resections, the patient's history was reviewed to identify if a pre-operative CNB had been performed. Data was collected on CNB adequacy, histologic features, and diagnosis, and on the subtype and grade of the resections.

Results: Review of the LIS for RPLPS found 26 patients that had both a CNB and resection, 49 that had resection alone (these patients went straight to surgery due to their imaging charcteristics of well-differentiated LPS (WDLPS) thus not requiring a neo-adjuvant treatment), 9 that had CNB alone, 4 that had alternative forms of biopsy and resection, and 4 that were consult cases for which biopsy status was unknown. CNB cases with LPS confirmed on subsequent resection were categorized based on utility of biopsy (Table 1). Sensitivity of CNB for LPS was 81%. FISH for *MDM2* was used in 4 CNB with equivocal features; 3 resembled normal fat and 1 was dedifferentiated. Of the 15 cases diagnosed as LPS on CNB, subtype was given in 12 (80%). Three cases (2 WDLPS and 1 pleomorphic LPS) were reclassified as dedifferentiated LPS on resection.

Conclusion: Over the past 15 years in our institution, RPLPS was definitively diagnosed on 58% of CNB and listed in the differential diagnosis for an additional 23% for a dignosis in 81% of cases. Utility was improved in recent cases with equivocal features when FISH for *MDM2* was used. *MDM2* seems to improve diagnostic ability as seen in other studies.

The main challenge in diagnosing fatty tumours is the size and amount of the tissue received from CNB. These biopsies were all done with 18G needles and larger needles (14-16G) in different parts of the tumour, with more cores may improve diagnostic ability. A minimal number of cores to allow for a diagnosis is currently unknown and is currently being evluated by our group. Even with the known limitations, CNB remains a viable tool for diagnosis and aids in the management in RPLPS and thus remains recommended in the mangament of these complex cases.

Table 1: Diagnosis on CNB

Diagnosis	Number	Percentage (%)
LPS or “favor LPS”	15	57.7
Descriptive only; LPS included on differential diagnosis (DDX)	1	3.8
Other diagnosis favored; LPS included on DDX	5	19.2
LPS not given on DDX	4	15.4
No lesional tissue	1	3.8

Poster 338 3035429

WHAT IS THE DIAGNOSTIC ACCURACY OF BIOPSIES OF SOFT TISSUE SARCOMAS?

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Objective: Accurate pathologic diagnosis of an extremity soft tissue mass is essential as it guides the proper treatment paradigm for the patient. Two sampling modalities are commonly used: core needle biopsy and incisional/open biopsy. The goal of this study was to examine the diagnostic accuracy of needle and open biopsies performed at our institution over the last 5 years.

Methods: Three hundred fifty-nine patients who had a biopsy of a soft tissue sarcoma at our institution from Jan 2012 to May 2017 and who did not have a prior unplanned excision were identified from our prospectively collected database. Type of biopsy performed (image-guided needle, Tru-cut or open), whether a diagnosis/subtype or grade was reported, and if a second biopsy was required were determined. Results for type of biopsy were compared with the chi-square test. The type of biopsy performed was at the discretion of the treating surgeon. Tru-cut and open biopsies were performed by fellowship trained orthopaedic oncologists or oncology fellows. Image-guided needle biopsies were performed by musculoskeletal interventional radiologists.

Results: Initial biopsies were open in 129 patients, Tru-cut in 109, and image-guided needle in 121. Overall, 49/359 (13.6%) patients underwent a second biopsy: 8.5% of open biopsies (11/129), compared to 15.6% (17/109) of Tru-cuts and 17.4% (21/121) of image-guided biopsies (p=0.1). A definitive histologic subtype was given in 64.3% of open biopsies (16 no subtype and 30 equivocal), 49.5% of Tru-cuts (22 none and 33 equivocal), and 57.0% of image-guided biopsies (31 none and 21 equivocal) (p=0.02). A grade was given for 79.8% of open biopsies (103/129), 71.6% of Tru-cuts (78/109), and 58.9% of image-guided biopsies (p=0.001). Open biopsies had both a definitive subtype and grade reported in 56.5% of cases (73/129), compared to 43.1% (47/109) of Tru-cuts and 41.3% (50/121) of image-guided biopsies (p=0.03).

Conclusion: Open biopsies remain the most reliable method of diagnosing a soft tissue sarcoma. However, a definitive subtype and grade may only be reportable in 57% of cases. With the use of neo-adjuvant therapies, this has implications for determining patient prognosis.

Poster 339 3035892

DIAGNOSTIC ACCURACY OF PERCUTANEOUS BIOPSY IN RETROPERITONEAL SARCOMA

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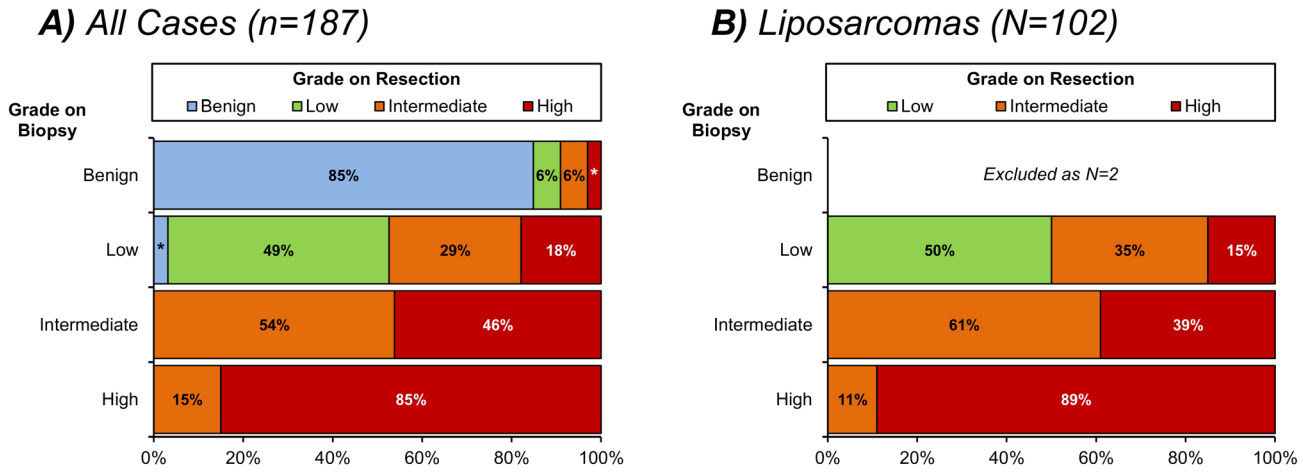
Objective: Percutaneous biopsy is recommended prior to surgery in suspected retroperitoneal sarcoma (RPS) to confirm the histological diagnosis and guide surgical strategy. The present study aimed to establish diagnostic accuracy of percutaneous core biopsy with respect to histological diagnosis and tumour grade.

Methods: Data on patients with a suspected RPS who underwent percutaneous biopsy followed by resectional surgery between 2005 and 2016 at Istituto dei Tumori, Milan, Italy and at University Hospital Birmingham, UK were reviewed.

Histological tumour type and FNCLCC grade on biopsy were correlated with post-operative histology to evaluate diagnostic accuracy.

Results: A total of 239 patients underwent percutaneous core biopsy followed by resectional surgery in Milan (N=163, 68%) and Birmingham (N=76, 32%). Diagnostic accuracy varied with histological diagnosis (p<0.001), but demonstrated overall concordance with final pathology in 67% of biopsies (Kappa = 0.606). The majority of discrepencies occurred in dedifferentiated liposarcoma (DDLPS), due to under-recognition of dedifferentiation in this group. Concordance between pathology on biopsy and resection improved to 81% when both DDLPS and WDLPS were grouped as liposarcoma. Tumour grade on biopsy was concordant with grade on resection in 60% of cases (Kappa = 0.640). Diagnosis of high-grade tumours on biopsy had a high specificity (98%) and moderate PPV (85%) and NPV (78%).

Conclusion: A diagnosis of DDLPS or leiomyosarcoma on percutaneous biopsy is highly reliable. High-grade sarcomas can be identified with high specificity, which could support an experimental neoadjuvant strategy in these patients, since over-treatment of low or intermediate grade lesions would appear highly unlikely.



Poster 340 3042770

MDM2 AMPLIFICATION AND FUSION GENE *SS18-SSX* IN A POORLY DIFFERENTIATED SARCOMA: A RARE BUT PUZZLING CONJUNCTION

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Objective: Molecular cytogenetic analyses are widely used in diagnosis of sarcomas. The detection of fusion genes, amplifications, deletions and mutations have been included in the diagnostic criterions of the World Health Organization's classification of tumors of soft tissues and bones since 2013. Notably, the presence of *SS18-SSX1* or *SS18-SSX2* fusion gene is pathognomonic of synovial sarcoma. Although *MDM2* amplification can be observed in a variety of tumors, it is strongly correlated to well-differentiated or dedifferentiated liposarcoma in the particular context of sarcomas. In the prospective multicentric study GENSARC (NCT00847691), we demonstrated that molecular analyses (FISH, RT-PCR or CGH-array) were crucial for an appropriate clinical management of six types of sarcoma [1]. Among the cohort of 384 sarcomas, one case of poorly differentiated sarcoma was shown to harbor both *SS18-SSX2* fusion and *MDM2* amplification. Review of the literature showed high discrepancies concerning the incidence of this association *SS18-SSX* fusion and *MDM2* in synovial sarcoma: from 2%[2-4] up to 40% [5]. Our goals were: -i) to better determine the frequency and characteristics of association of *SS18-SSX* fusion with *MDM2* amplification in sarcomas; -ii) to evaluate the impact of the simultaneous presence of both anomalies in diagnosis.

Methods: We performed a retrospective and prospective study of 71 cases of sarcomas. Firstly, using FISH and/or array-CGH, we performed the detection of *MDM2* amplification in 40 cases of synovial sarcomas with *SS18-SSX* fusion gene. Secondly, using FISH, we performed the detection of *SS18* rearrangement in a series of 31 well-differentiated or dedifferentiated liposarcomas with *MDM2* amplification.

Results: None of the 71 cases of the cohort presented both *SS18* and *MDM2* alterations. We concluded that *MDM2* amplification in synovial sarcoma is a rare event (2% or less). Only the index case (1/72) presented both anomalies.

Conclusion: The simultaneous presence of two relevant genetic alterations –*i.e SS18-SSX* fusion and *MDM2* amplification- in a same tumor raised three main issues: -i) which one of the two genetic anomalies had to be considered as the prominent one? –ii) what should be the impact of this observation for diagnosis: is the tumor a synovial sarcoma or a dedifferentiated liposarcoma? -iii) what is the frequency of such a double alteration ? *SS18-SSX* fusion has been described only in synovial sarcomas so far. Therefore the index case was eventually diagnosed as a synovial sarcoma that had *MDM2* amplification as a secondary alteration. However, it is not possible to formally exclude a genuine sarcoma with double differentiation. Our results are consitent with some of the some previous studies [2-4] that estimated a low frequency of *MDM2* amplification in synovial sarcoma.

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Poster 341 3041738

DESMOID FIBROMATOSIS THROUGH THE PATIENTS' EYES: TIMES TO CHANGE THE FOCUS AND ORGANISATION OF CARE?

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Objective: Desmoid Fibromatosis (DF) is a rare, unpredictable disease with no established, evidence-based treatments. Individual management is based on consensus algorithms. This study aimed to examine the specific health-related quality of life challenges faced by DF patients, current experiences and expectations of care.

Methods: Twenty-seven DF patients were purposively sampled from The Royal Marsden Hospital London, United Kindgdom. Two focus groups and thirteen interviews (males 12, females 15; mean age at study 39.5 years) explored health-related quality of life issues and experiences of healthcare. Thematic content was analysed.

Results: Discussions revealed 4 key themes (diagnostic pathway; treatment pathway; living with DF; supportive care). Diagnostic delay resulted from lack of recognition by patients and healthcare professionals. Some patients received an initial diagnosis of cancer, causing significant distress. Treatment decisions were challenging and patients experienced uncertainty among clinicians about optimal therapies. Side-effects of treatment were severe, including fatigue, nausea, anorexia, low libido and depression. Pain was the most debilitating symptom and dependency on painkillers was a significant concern. Functional limitation and restricted mobility frequently affected daily activities. Patients experienced difficulty accomplishing their role in society; relationship problems, caring for children, employment and financial difficulties. Social isolation and lack of understanding were common. The psychological impact of this "life-changing and life-long" condition was profound. All patients requested knowledgeable healthcare professionals, more information, continuity of care and peer support.

Conclusion: DF patients face complex physical, psychological and practical challenges. Comprehensive care services are needed. Increasing awareness may help to improve diagnostic pathways and overall patient experience.

Poster 342 3041928

IS ANYBODY LISTENING? CLINICIAN UNDER-RECOGNITION OF SYMPTOM SEVERITY IN RETROPERITONEAL SARCOMA PATIENTS: A COMPARISON OF PHYSICIAN ASSESSMENTS AND PATIENT SELF-REPORTED OUTCOMES

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Objective: Patients with retroperitoneal sarcomas (RPS) experience significant physical and psychosocial symptoms related to this diagnosis and its treatment, with attendant impact on their quality of life. As part of a rising global recognition of the heavy symptom burden that patients with cancer may face, patient-reported outcome measures have been developed

and implemented. In our center, at each clinic visit, patients complete the Edmonton Symptom Assessment System (ESAS) questionnaire that scores symptoms in 9 domains on a Likert scale from 0 to 10. Such standardized measures are purported to identify symptom-related patient needs that would not otherwise be addressed. It is unclear whether the symptoms thusly reported by RPS patients are recognized and attended to by their health-care team.
We investigated the correlation between symptoms as self-reported by RPS patients via ESAS, and symptoms as recorded in the chart by the health-care team.

Methods: A mixed-methods retrospective chart review was performed for all patients with primary non-metastatic RPS who were treated with curative resection at our centre between 01/14 and 12/16. ESAS scores for pain, tiredness, depression (categorized by severity: 0 (none), 1-3 (mild), 4-6 (moderate), 7-10 (severe)), and self-reported ECOG scores entered at preoperative and one-year postoperative visits were collected and analyzed. Patients were excluded if they did not undergo resection, died prior to the planned one-year postoperative visit, or did not complete ESAS questionnaires. Two researchers independently coded patients' symptoms and severity as documented in clinician notes.

Results: Fifty-three primary RPS patients met the inclusion criteria. In this study cohort, median age was sixty-one (range 23-83), and 25 patients were female. Median tumour size was 17.6cm (3.2 -61.4cm). Histologic subtype was predominantly liposarcoma (28 dedifferentiated, 6 well-differentiated) and leiomyosarcoma (12). 100% of patients had completed ESAS scores across all domains at their one-year postoperative visit, while 94% completed scores across all domains at their preoperative visit. Inter-rater reliability for independent coding of clinician notes was 98%. There was high correlation (93-100%) between clinician documentation of symptoms of pain, tiredness and depression with 0 or mild (1-3) ESAS scores, both pre- and post- operatively. As symptom severity increased, correlation between ESAS scores and clinician documentation decreased, with moderate symptoms correlating 0-50% and severe symptoms 0-33% of the time. Correlation of moderate and severe symptoms was highest for pain (20-50%) and lowest for depression (0-17%). There was only moderate correlation between patient-reported and clinician identified ECOG scores (30% pre-operatively, and 49% post-operatively). Alarmingly, for patients with moderate or severe symptoms recorded via ESAS, 42% of the time there was no mention of any such symptoms in the clinician notes.

Conclusion: A goal of ESAS is to facilitate recognition of symptom-related needs, and improve patient care by improving symptom management. The impact of RPS and its treatment on quality of life may be under-recognized and under-treated by practicing clinicians, resulting in greater morbidity that is costly to patients and the health system.

Poster 343 3042701

EXPERIENCES OF PATIENTS WITH BONE CANCER: THE ROLE OF ILLNESS AND DEVELOPMENT TRAJECTORIES, HEALTHCARE PROFESSIONALS, SOCIAL SUPPORT AND COPING STRATEGIES

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Objective: Treatment of bone cancer often involves long-term hospitalisation, extensive surgery, loss of mobility, complex rehabilitation programmes, and in many cases accompanied by low expectations of survival. Subsequently, poorer patient-reported outcomes (Kwong et al. 2014; Ginsberg et al. 2007) are recorded in comparison to patients with other cancer types (Hinds et al. 2009). To improve quality of life of patients with bone sarcoma, it is necessary to clarify the status of and the problems regarding their quality of life. Studies that have examined the psychosocial functioning in bone cancer are rare and results remain inconclusive (e.g., Teall et al. 2013). The aim of this study is to explore the experiences of patients with primary bone cancer.

Methods: Qualitative study design using semi-structured interviews and focus groups. We will report on the findings from 26 participants (23 individual interviews and 3 focus group participants) with primary bone cancer [69% male; aged between 13 to 77 years old (M=40.5; SD=17.9); 38.5% had an amputation]. All interviews and focus groups were recorded and transcribed verbatim. Framework analysis was used to analyse the data.

Results: The health-related quality of life domains of physical, emotional and social wellbeing were the overarching themes of analysis. Exploration of the data considering age, gender, treatment type (amputation/limb salvage) revealed the common and different themes across the interviews. Overall, the experience of patients was influenced by where they were in their trajectory (e.g. diagnosis, treatment, end of treatment, recurrence), and developmental stage.

Mobility loss/constraints, pain, fatigue were aspects of physical wellbeing mentioned by patients throughout their illness. Others such as constipation, nausea, mouth ulcers were mainly described during the treatment phase. Patients described an 'identity loss' linked with physical changes (e.g., amputation) and the impact that diagnosis and treatment had on employment (e.g. having to change roles or carer) and leisure activities (e.g. having to stop practising a certain activity/ sport). End of treatment was highlighted as a transition point where some patients 'struggled' to return to the 'normal' life; having time to process what they had gone through was overwhelming with some describing feeling depressed. Although some patients reported no impact on their financial wellbeing, others reported loss of income, need to access benefits, and having to take loans from family and friends. Parking and travelling costs were also mentioned.
Three influencing factors hindered/improved patient experience: healthcare professionals' role, social support and coping strategies. Healthcare professionals played a key role in patients' experience. Patients described experiences of being reassured and receiving information at the right level. The Clinical Nurse Specialist expertise and accessibility was valued by patients. Patients who accessed therapy/counselling reported positive effects on their wellbeing. Therapy was one of the ways patients dealt with their thoughts and feelings after diagnosis. Family and friends was the main source of support for others. Adaptation after diagnosis, treatment and/or surgery was influenced by the way patients dealt with stress and adversity, with some finding a new outlook in life, and others struggling with finding their 'new normal'. Rehabilitation services had a considerable role in patient's physical and emotional welling, but access to these services was not equitable across the country.

Conclusion: This study uncovers protective and risk factors which help understand patients with bone cancer experiences. Healthcare professionals, social support and individual coping strategies were important resources in managing the biographical disruption caused by illness.

Poster 344 3022139

PERCEPTIONS OF CLINICAL TRIAL ENROLLMENT AND MOLECULAR PROFILING IN PATIENTS WITH BONE AND SOFT TISSUE SARCOMA

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Objective: Clinical trials represent a critical component in the evaluation of effective cancer therapies. Low rates of participation have negatively impacted progress in bone and soft tissue sarcoma clinical trials. The objective of this survey study was to evaluate patients' attitudes toward clinical trials, knowledge about clinical trials, self-efficacy for clinical trial decision-making, patient receptivity to clinical trial information, general willingness to participate in clinical trials, and thoughts and perceptions related to molecular profiling of tumors.

Methods: Institutional Review Board approval was obtained. Patients with sarcoma who were evaluated at an academic medical center between 2007 and 2017 were identified through the Enterprise Data Warehouse. A link to an online self-administered survey was emailed to patients. Attitudes were measured using 20 items, knowledge was measured using 13 items, and self-efficacy to carry out actions involved in making informed decisions about clinical trial participation was assessed using 8 items. Receptivity to learning more about clinical trials and willingness to participate in clinical trials were measured using one item. Perceptions of molecular profiling tumors for patients who heard of this were assessed with 9 items. Thoughts about molecular profiling in patients who had undergone molecular profiling of their tumors was assessed with 19 items. A $50 VISA gift card at completion of the survey was offered. Data were analyzed using Spearman correlations and the Mann-Whitney test.

Results: Surveys were emailed to 750 patients of which 309 opened, 283 started the survey, and 183 completed the survey (24.4% of total and 59.2% of opened). The median age was 56 years, 59.4% were female, and 26.8% reported metastatic disease. Most common histologies were liposarcoma (n=33; 16.5%) and leiomyosarcoma (n=32; 16.0%). 160 (84.2%) had never been enrolled in a clinical trial. Greater knowledge of clinical trials correlated with increased positive attitudes toward clinical trial participation ($p<0.001$) and positive attitudes correlated with greater clinical trial self-efficacy ($p<0.001$). Patients with metastatic disease had more positive attitudes compared with non-metastatic patients ($p=0.033$). Clinical trial enrollment was associated with greater knowledge ($p=0.002$) and positive attitudes ($p<0.001$). Among patients who reported knowledge of tumor molecular profiling (n=46), 30.4% credit molecular profiling with a >50% chance of isolating a targetable result, and 71.7% assume if an experimental treatment was found based on these results, there is a >50% likelihood of it being effective. Better attitudes and higher self-efficacy for clinical trial enrollment were associated with expectations of lower likelihood of developing side effects from an experimental therapy ($p=0.0096$; $p=0.0184$). Of patients who had molecular

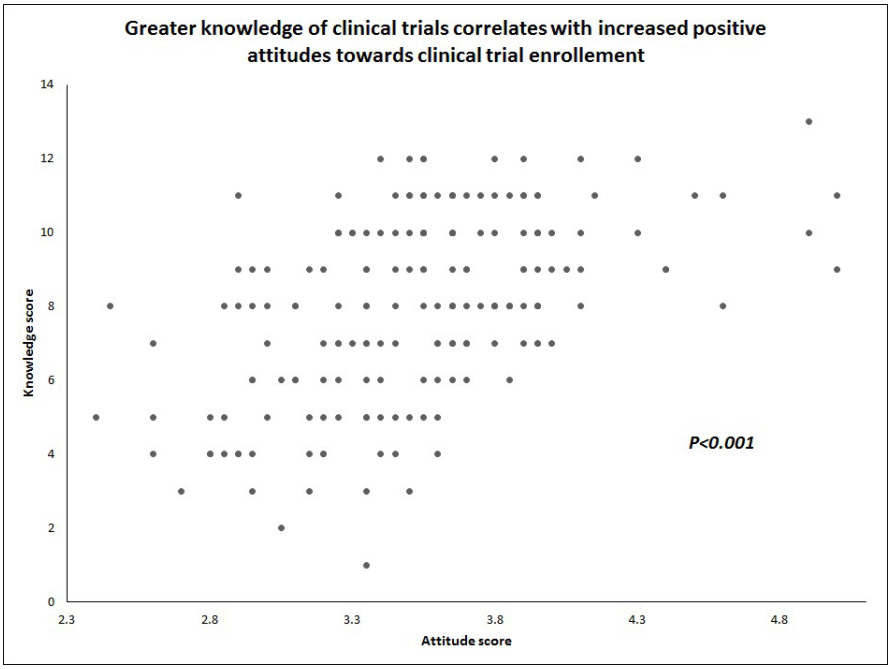
profiling performed (n=18), important considerations for this test was its ability to improve their survival and quality of life. Of patients eligible for a $50 VISA gift card, 38.6% donated the compensation to further bone and soft tissue sarcoma research.

Conclusion: Improving knowledge of clinical trials among sarcoma patients may lead to more positive attitudes and greater self-efficacy regarding trial enrollment. Sarcoma patients tend to overestimate the potential benefit of molecular profiling; thus, setting expectations with regards to potential benefit of molecular profiling is critically important. Patients with bone and soft tissue sarcoma remain committed to improving outcomes for both themselves and other patients.

Table 1: Participant demographics and patient characteristics.

Participant Demographics and Clinical Characteristics			
Characteristic	No.	Percent (%)	Total Count (N)
Age (years)			283
Median	56		
Min	20		
Max	88		
Gender			217
Male	88	40.6	
Female	129	59.4	
Marital status			220
Single, never married	45	20.5	
Married or domestic partner	141	64.1	
Other	34	15.5	
Race			220
White	194	88.2	
Nonwhite	21	9.5	
Prefer not to answer	5	2.3	
Ethnicity			216
Hispanic	13	6.0	
Non-hispanic	194	89.8	
Prefer not to answer	9	4.2	
Education			203
College or university graduate or higher	140	69.0	
No college degree	63	31.0	
Income			206
Greater than $100,000	80	38.8	
Less than $100,000	101	49.0	
Prefer not to answer	25	12.1	
Disease stage			190
Metastatic	51	26.8	
Nonmetastatic	124	65.3	
Not sure	15	7.9	
Clinical trial enrollment			190
Currently enrolled in clinical trial	7	3.7	
Previously enrolled in clinical trial	23	12.1	
Never been enrolled in clinical trial	160	84.2	
Sarcoma histology			200
Liposarcoma	33	16.5	
Leiomyosarcoma	32	16.0	
Synovial	19	9.5	
Osteosarcoma	14	7.0	
Rhabdomyosarcoma	13	6.5	
Ewing's sarcoma	10	5.0	
Angiosarcoma	10	5.0	
Pleomorphic sarcoma	10	5.0	
Other	59	29.5	
Previous treatmnets			190
Surgery	173	91.1	
Radiation	101	53.2	
Chemotherapy	98	51.6	

Table 2: Correllation of knowledge about clinical trials and positive attitudes towards clinical trial enrollment.



Poster 345 3031162

PATIENT-REPORTED FUNCTIONAL OUTCOMES IN A COHORT OF HAND AND FOOT SARCOMA SURVIVORS TREATED WITH LIMB SPARING SURGERY AND RADIATION THERAPY

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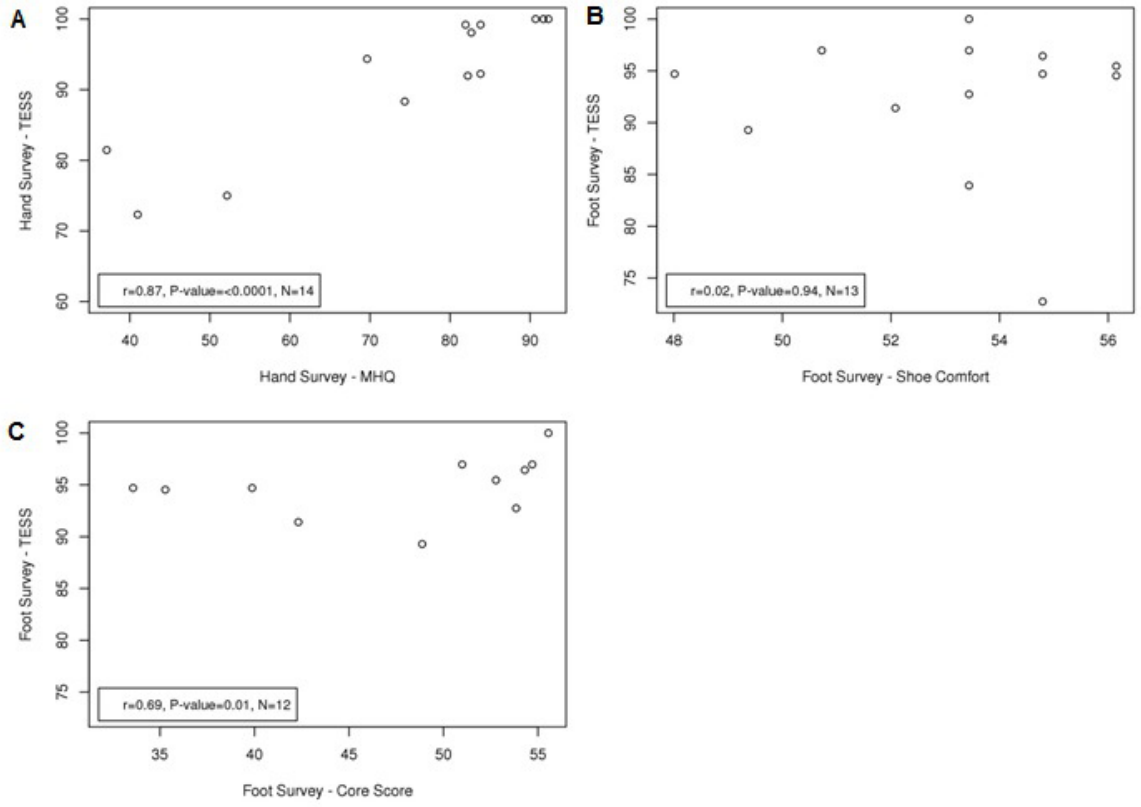
Objective: Limb sparing surgery (LSS) plus radiation therapy (RT) is associated with oncologic outcomes equivalent to amputation for extremity sarcomas. Data analyzing patient-reported functional outcomes for hand and foot sarcomas treated with a limb preserving approach are nonexistent. The purpose of this study is to describe patient-reported functional outcomes in hand and foot sarcomas treated with LSS and RT in the modern era.

Methods: Survivors of hand and foot sarcomas ≥18 years of age treated with LSS and RT from 1991-2015 completed

self-assessed functional surveys. Hand sarcoma survivors completed Michigan Hand Outcomes (MHQ) and Toronto Upper Extremity Salvage Score (TESS-UE) Questionnaires. Foot sarcoma survivors completed Foot and Ankle Outcomes (FAOS) and Toronto Lower Extremity Salvage Score (TESS-LE) Questionnaires. A 0-100 scale is used for MHQ and TESS questionnaires. Normative scales of -26-56 and 25-59 are used for FAOS core and shoe comfort surveys, respectively. A higher score for all questionnaires denotes superior function and performance. Pertinent clinical information was extracted from medical charts. Local failure and overall survival rates were calculated using the Kaplan-Meier method. The Kruskal-Wallis test was used to determine correlations between survey results and clinical factors.

Results: The cohort consisted of 30 hand sarcoma and 24 foot sarcoma patients. Median age at diagnosis was 40.2 years (range, 11.4-81 years). Histologies included synovial sarcoma (n=16, 29.6%), leiomyosarcoma (n=11, 20.4%), undifferentiated pleomorphic sarcoma (n=5, 9.3 %), and other (n=22, 40.7%). All patients underwent LSS (marginal excision, n=14 (25.9%); wide local excision, n=36 (66.7%); ray/metacarpal resection, n=3 (5.5%); incisional biopsy, n=1 (1.9%). Twenty-seven patients (50%) underwent >1 surgery, primarily for an oncologic resection following excisional biopsy (96%). Median RT dose was 50.4 Gray (Gy) (range, 45-70.4 Gy), with preoperative RT delivered in 29 patients (54%). Intraoperative RT or brachytherapy was utilized in 20 patients (37%), with a median dose of 10.5 Gy (range, 8–20 Gy). The 5 year local recurrence and overall survival was 88% (95% confidence interval (CI), 78-98%) and 93% (95% CI, 86-100%), respectively. Questionnaires were sent to 24 hand and 18 foot sarcoma survivors after excluding patients with local recurrence requiring amputation (n=4) and deceased patients (n=8). Fourteen hand (58%) and 14 foot (78%) sarcoma survivors returned the surveys. Median time from surgery to survey completion was 15.7 years (range, 3-26 years). For foot sarcoma survivors, the mean TESS-LE score was 92.4±6.9, mean core FAOS score was 46.19±8.98, and mean shoe comfort FAOS score was 53.1±2.5. For hand sarcoma survivors, the mean TESS-UE score was 89.4±12.6. The MHQ final score was 72.8±18.8, with subscale scores of 67.5±15.3 for function, 76.7±23.3 for activities of daily living, 85±18.2 for work, 80±21 for pain, 62±26.8 for aesthetics, and 65.2±26 for satisfaction. There was no correlation between survey outcomes and patient factors or surgical factors. TESS-UE and MHQ total scores strongly correlated with a Pearson correlation coefficient of 0.87, whereas TESS-LE and FAOS scores were associated with a poor correlation (r=0.02 and 0.69, Figure 1).

Conclusion: The first patient-reported functional outcomes analysis for hand and foot sarcoma survivors treated with LSS+RT demonstrates excellent local tumor control and acceptable functional outcomes per TESS, FAOS, and MHQ assessments. Given the small cohort size, evaluation in a larger cohort is warranted. Additionally, further exploration of optimal functional assessment tools for hand and foot sarcomas is needed given the potential scope differences of questionnaires.



Questionnaire response correlation with A) TESS-UE and MHQ, B) TESS-LE and FAOS Core Score, and C) TESS-LE and FAOS Shoe Comfort Score.

Poster 346 3043080

A SCANDINAVIAN POINT OF VIEW -CARING FOR PATIENTS WITH SARCOMA ACROSS BOUNDARIES

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Objective: Sarcoma affect more than 15,000 people per year in the United States, whereas in the countries of Denmark, Finland, Iceland, Norway and Sweden, with the combined population of 27 million people, about 800 patients are diagnosed with sarcomas evey year. Given the rarity of sarcomas in Scandinavia and relative small populations of those countries, it is important for healthcare providers to collaborate across boundaries.
Nurses play a pivotal role in supporting patients with sarcoma and their caregivers. Therefore, it is essential that nurses working in this complex clinical landscape have advanced knowledge to competently address and manage the psysical and psychosocial concerns of this patient population.
How can nurses working with this rare form of cancer achieve these important benefits?

Methods: To facilitate collaboration among Scandinavian sarcoma professionals, the Scandinavian sarcoma Group (SSG) was formed in 1979. The SSG is composed of subgroups of oncologists, surgeons, radiologists, pathologists, tumor biologists, nurses and psysiotherapists from Scandinavian countries. The aim of the SSG is to improve the diagnosis, treatment, and care of patients with sarcoma by sharing information and education, and coordinating basic and clinical research.
The SSG for Nurses and Physiotherapists initially began in 2005 as the Sarcoma Forum for Nurses and Physiotherapists for professionals working at the Norwegian Radium Hospital, which is part of Oslo University Hospital in Norway. One of the goals was to establish a forum in which nurses and physiotherapists could network and share knowledge and experiences with the rest of Norway and Scandinavia. This was realized in 2007 when the SSG for Nurses and Physiotherapists officially was established as a subcommittee of the SSG.
To achieve the goal of collaboratin among sarcoma healthcare providers in Scandinavia, the SSG for Nurses and Physiotherapists created different arenaes for cooperation.

Results: -The SSG Plenary Meeting
- **Raising sarcoma awareness in the community**; The Lump Day was first organized in Oslo, Norway, in 2010, and consists of two different sessions. The first session is a one-day conference organized for physicians and other healthcare providers who do not work with sarcoma patients on a daily basis. The goal is to teach participants about which lumps may need further investigation. The overall ambition of this session is to increase sarcoma awareness in the community of medical professionals who may serve as referrals to sarcoma specialists. The second session is for patients and their families, caregivers, and bereaved.
Since 2013, Lump Day also has been held in Sweden, and a similar day is planned for Denmark in 2019.

-**Scandinavian Preceptor Program;** An exchange of experiences among nurses working in hospitals in Scandinavia that treat patients with sarcoma. Examples of new procedures implemented as a result of the preceptorship are changed routines for drinking restrictions with high-dose methotrexate and the outpatient administration of trabectedin.

-**Development of iSNAP**; In 2015, a global project was launched on the initiative of the Scandinavian group, and an overseas collaboration among nurses working with patients with sarcoma was established. Two nurses from the SSG for Nurses and Physiotherapists and two nurses from the United States formed International Sarcoma Nurse and Allied Professionals (iSNAP), which is a network of nurses from Scandinavia, Europe, and the United States who are working with patients with sarcoma and treatment protocols.
The first iSNAP conference was held in 2015, in conjunction with CTOS.

Conclusion: No country has the knowledge and capacity to treat all rare and complex diseases. The purpose of the international cooperation is to enhance the knowledge, skills, and experiences among healthcare providers who work with sarcoma patients. In addition, the aim is to inspire nurses working with other uncommon cancer diagnoses to collaborate across countries

Poster 347 3042521

DEPRESSION AND ANXIETY AMONG NEWLY DIAGNOSED SARCOMA PATIENTS

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Objective: Depression and anxiety are common psychological comorbidities among cancer patients. The impact of

psychological comorbidity has been increasingly associated with poor adherence to therapy, poor quality and life and poor cancer prognosis. There is limited information regarding psychological comorbidity status among sarcoma patients assessed soon after diagnosis.

Methods: All sarcoma patients who attended BC Cancer from April 2011-2016 and prospectively completed the validated Psychosocial Screen for Cancer (PSSCAN-R) questionnaire at the time of their first visit were evaluated. The PSSCAN-R identifies at risk individuals who require timely psychosocial intervention. First consultation visits were undertaken within 6 months of pathological diagnosis. GIST were excluded. Baseline demographics including age, performance status (ECOG), location of disease, resectability of disease and histology were collected by retrospective chart review. Emotional status, such as depressive and anxiety symptoms, were collected via the PSSCAN-R. Positive responses on the PSSCAN-R were evaluated to determine evidence of depression or anxiety. Analysis was conducted using descriptive statistics and univariate analysis using Chi-squared test and Fisher's exact test to compare groups based on gender, age, performance status, resectability of disease and location of primary.

Results: 413 sarcoma patients were identified. The majority of patients were over the age of 40 (83.3%) with ECOG 0-1 (82.6%). Location of sarcoma were identified as: 55.4% lower extremity, 26.4% trunk, 14.8% upper extremity, 3.4% head and neck. The most common diagnoses were liposarcoma 21.3%, undifferentiated pleomorphic sarcoma 12.1% and myxofibrosarcoma 11.1%. At initial consultation 42.6% of patients were deemed resectable, 8.5% unresectable/metastatic and 48.9% of patients required further staging investigations. In the two weeks prior to consultation, the top four patient reported psychological symptoms were: feeling tense and unable to relax (50%), feeling nervous and shaky (48%), experiencing repetitive and scary thoughts (42%), and feeling restless and unable to sit still (37%). 38% of patients had subclinical, or clinical anxiety and 21% of patients had subclinical or clinical depression. Suicidal ideation was present in 5% of patients. Female patients reported more anxiety (50.5% vs 28.6%, $p<0.01$) and depression (25.8% vs 17%, $p=0.03$) compared to males. Patients with poorer performance status (ECOG 2 or greater) reported more anxiety (32% vs 16%, $p=0.01$) and depression (18% vs 7%, $p<0.01$) than fitter patients. No difference in anxiety or depression scores were identified for patients less than 40 years of age versus older, resectable versus unresectable disease or location of primary.

Conclusion: Up to one half of all sarcoma patients experience some form of psychological distress at disease presentation, with higher distress scores identified in female patients and those with poor performance status. Targeted support interventions can be tailored to these individuals to treat psychological comorbidity.

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RELAX: AN IMMERSION VIRTUAL REALITY RELAXATION INTERVENTION FOR QUALITY OF LIFE IMPROVEMENT IN CANCER PATIENTS

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Background and Significance: Interventions that reduce symptom distress and enhance positive feelings are crucial for improving quality of life and, conceivably, overall survival of cancer patients. One remedy is the immersive Let's Relax!™ virtual reality relaxation (VR-R) environment/s designed by IFGCURE, to inspire an emotion-focused coping mechanism in cancer patients. Let's Relax!™ environments are part of the IFG Virtual Wellness Center™.

Objective: Herein, we report on our initial experience with the use of this VR-R intervention in normal volunteers and cancer patient volunteers.

Methods: Patients and Methods: Twelve normal volunteers and 50 cancer patient volunteers underwent VR-R training and used the Let's Relax!™ VR-R environment/s for 5-30 minutes. VR-R is a software-based simulation, which allows an individual to be placed inside an experience, hearing and interacting with stimuli that correspond with visual images of an artificial world. The VR equipment consists of the Oculus Rift Head Mounted Display (HMD) that enables play of an interactive scenario or game that patients can experience from a first-person perspective (i.e., upon entering the interactive scenario, participants are transported into a virtual, 3D world). After the immersion VR-R intervention, patients reported on their experience during the VR-R intervention by answering a QoL questionnaire created by IFGCURE/Cancer Center of Southern California/Sarcoma Oncology Center.

Results: Safety analysis: Two normal volunteers experienced mild motion sickness. One volunteer is known to have motion sickness (sea sickness). Ten of 12 normal volunteers had no adverse reactions. Eight of 50 (16%) patients experienced mild motion sickness as the only adverse event associated with its use. Forty-one of 50 (82%) patients had no adverse reactions. **Efficacy analysis:** Table 1 shows the emotions that patients reportedly experienced during VR-R intervention. Table 2

shows a point scoring system using yes/no questionnaire or a modified EORTC QLQ C-30 v3 questionnaire.

Conclusion: Taken together, the data support the premise that Let's Relax!™ VR-R intervention is safe and may be efficacious in improving symptom distress and quality of life of cancer patients. A Phase 1/2 study is planned to evaluate the safety and efficacy of the Let's Relax!™ VR-R intervention in improving quality of life in a larger number of cancer patients. A prospective study is planned to confirm that VR-R intervention is safe and effective in reducing symptom distress and improving quality of life in cancer patients undergoing cancer treatment.

Patient Reported Experience during VR-R Intervention	# Patients/Total #	% Patients
Felt relaxed	46/50	92
Reduction in anxiety	45/50	90
Reduction in fear	44/50	88
Reduction in depression	46/50	92
Had positive feelings	40/50	80
Reduction in tension*	39/40	98
Reduction in fatigue*	39/40	98
Will use VR-R again	44/50	88
Will use VR-R at home*	30/40	75
Would use as adjunct to chemotherapy	39/50	78

*Queries were added to second group of 40 patient volunteers

Y/N Score	# patients	%
Excellent	30	75.0%
Good	6	15.0%
Satisfactory	2	5.0%
Poor	2	5.0%
EORTC QLQ Score		
Excellent	37	92.5%
Good	3	7.5%
Satisfactory	0	0.0%
Poor	0	0.0%

Poster 349 3012461

CAREER AND FINANCIAL SITUATION OF PATIENTS DIAGNOSED WITH SOFT TISSUE SARCOMAS

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Objective: Progress in therapeutic intervention allows many cancer patients a social reintegration into their careers. About one third of cancer patients are younger than 65 years old, and with the constant increase in work life periods, a cancer diagnosis also presents a financial burden for those affected.

Methods: We analysed the data of 30 patients diagnosed with soft tissue sarcomas using self-outcome questionnaires in combination with retirement insurance data from the date of first diagnosis up to three years after. Out of 280 sent questionnaires we received 86 completed forms of which 56 had to be excluded. The remaining completed questionnaires of 30 patients were analysed according to self-determined outcomes and included a calculation of the financial changes caused by the disease.

Results: 30 patients (median age at first diagnosis 42.2 years, range 31-61; 24 female) were included with an average unemployment period of eight months. For 67% (20) the employment situation changed after the period of unemployment. 27% (8) requested pension payments (reduced income insurance). Thirteen percent (4) reduced their weekly working time, and two patients lost their employment due to the disease. One patient had an increase in income of about 24%; another patient received a regular old-age pension. In four patients the income reduction was due to other reasons. Altogether, the average income was reduced by about 25%. Analysing only the eight patients requesting pension payments, partial or full unemployment benefits led to an average loss of income of as high as 62%.

Conclusion: Reduced ability to work may cause severe financial problems for those affected by the diagnosis of a soft tissue sarcoma. We found an average income reduction of 25%, for those requesting pension payments of 62%. This eventually relates to a higher risk of reduced wealth and may lower the patients' social standing.

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PREFERENCES FOR END-OF-LIFE DISCUSSIONS AND CARE AMONG PATIENTS WITH ADVANCED OR RECURRENT SARCOMA

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Objective: End-of-life discussions (EOLds), which center on topics such as incurability, prognosis, site of death, and do not attempt resuscitation (DNAR) status, are indispensable for planning treatment programs for patients with advanced malignancies. However, the preferences for EOLds by Japanese sarcoma patients have not yet been elucidated as well as they have been for cancer patients. To clarify the preferences for EOLds and end-of-life care among Japanese patients with newly diagnosed advanced or recurrent sarcoma. An additional aim is to reveal whether actual situations are consistent with their hopes, especially concerning where they would like to spend their time after the termination of aggressive treatments.

Methods: A single-centered questionnaire survey was administered to adult Japanese patients with sarcoma who had been diagnosed as incurable within the three months prior to the study. We asked patients whether they would like to have an EOLd with their physician at the time of the survey as well as about various patient characteristics. We followed up their treatment courses and outcomes.

Results: Starting from August 2015, we distributed the questionnaire to 31 patients at National Cancer Center Hospital for 1 year. Responses were obtained from 23 patients (10 males, 13 females; response rate: 74%), some of whom died by the end of the survey. The median age was 61 years (range: 34-79). A total of 60 percent of the patients (n=14) answered they would like to have an EOLd, whereas nine patients reported that they would not at all. When we asked them where they would like to stay during their final moment, eight patients hoped to go back their home whereas seven patients selected PCU. A total of 17 patients had already died by December 2017; the median duration from this questionnaire survey to their death was 8 months (range: 1-30). Seven patients actually spent their final moment at PCU, an additional seven died in the general hospital, and only three patients received home hospice care. The rate of agreement between the participants' wishes and realities was limited to about 40%.

Conclusion: Even just after being diagnosed with an incurable disease, more than half of the sarcoma patients were willing to have an EOLd with their treating physician. However, there were still some discrepancies between patients' wishes and the reality, especially concerning the site of death, partly because of the reality of their diseases. Therefore, we wish to share the results of our study to all nurses, medical practitioners, and social workers who are engaged with sarcoma patients in order to make their "last hope" come true.

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A NOVEL APPROACH FOR ASSESSING FUNCTIONAL BURDEN OF SOFT TISSUE SARCOMA SURGERY: DIGITAL PHENOTYPING AND RECOVERY AFTER RESECTION OF RETROPERITONEAL AND ABDOMINAL SOFT TISSUE TUMORS

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Objective: The combination of smartphone sensor and usage data (passive data) along with smartphone-based surveys (active data) gives rise to *digital phenotyping*, the "moment-by-moment quantification of individual-level human phenotype *in situ* using data from personal digital devices." This approach offers insight into changes in behavioral patterns, physical mobility, and social interactions that can inform surgical recovery. Digital phenotyping has the potential to improve shared decision-making, the setting of treatment expectations, and postoperative monitoring. We have developed the open-source Beiwe research platform for smartphone-based digital phenotyping. This study assesses the feasibility of digital phenotyping methods in patients undergoing procedures to remove intraabdominal and retroperitoneal soft tissue tumors.

Methods: Patients downloaded the Beiwe smartphone app, which continuously collected pre- / post-op passive data: GPS (1 minute of every 11), accelerometer (10 seconds of every 20), and phone call log (number of incoming/outgoing calls). Patients also received daily 5-item surveys taken from the RAND-36, which taps eight health domains. Data quality for GPS and accelerometer sensors was assessed by calculating data coverage proportion, the number of time periods of data collected (cycles) divided by the total number of data collection periods, and average number of samples per cycle, the

number of sensor observations divided by the number of cycles. A related issue to feasibility is whether the smartphone is on-person because it determines our ability to infer activity and geographic location from passive data. Thus, we calculated a GPS-based measure of away-from-home time to provide an estimate of phone on-person time. Daily GPS and phone call log data summaries were plotted perioperatively to identify trends. The proportion of surveys completed when notified of having a survey to complete was calculated.

Results: Six surgical patients (2 myxoid chondrosarcomas, 1 leiomyosarcoma, 1 liposarcoma, 1 GIST, and 1 lipoma) were followed for a mean of 155 days. The mean coverage proportion of GPS and accelerometer data was 0.56 (range: 0.15, 0.83). The mean accelerometer and GPS sampling rates were respectively 43.9 and 5.1 samples per cycle; these rates have been found to be adequate for gaining insight into patient behavior in prior studies. GPS-based assessments of away-from-home time could be made for five patients: the mean proportion of days in which patients carried their phones away from home was 0.43 (range: 0.13, 0.82), visiting 2-5 significant locations on such days, and the mean proportion of hours away from home was 0.26 (range: 0.06, 0.55). Although not perfect proxies for on-person time, these measures do capture aspects of phone-use habits and support the argument that GPS data can offer meaningful insight into patient mobility. GPS data summaries—such as daily distance traveled and significant locations visited—plotted perioperatively capture reduced mobility postoperatively (Figure 1). Similar declines seen in phone call data postoperatively suggest that surgery may also impact patients' social functioning (Figure 2). The mean proportion of surveys completed by patients when notified was 0.62 (range: 0.06-1).

Conclusion: Digital phenotyping is a powerful approach that can provide nuanced behavioral insights. The proportions of passive and active data collected in this cohort are satisfactory to gain some insight into surgical recovery, but these rates are lower than in other surgical cohorts we have studied (e.g., breast cancer). This underscores that it may be necessary to tailor methods for data collection to different types of surgical patients to maximize the potential to collect high quality digital phenotyping data. These findings provide proof-of-concept that smartphone data may be a powerful window into the physical and social functioning of soft tissue sarcoma surgery patients.

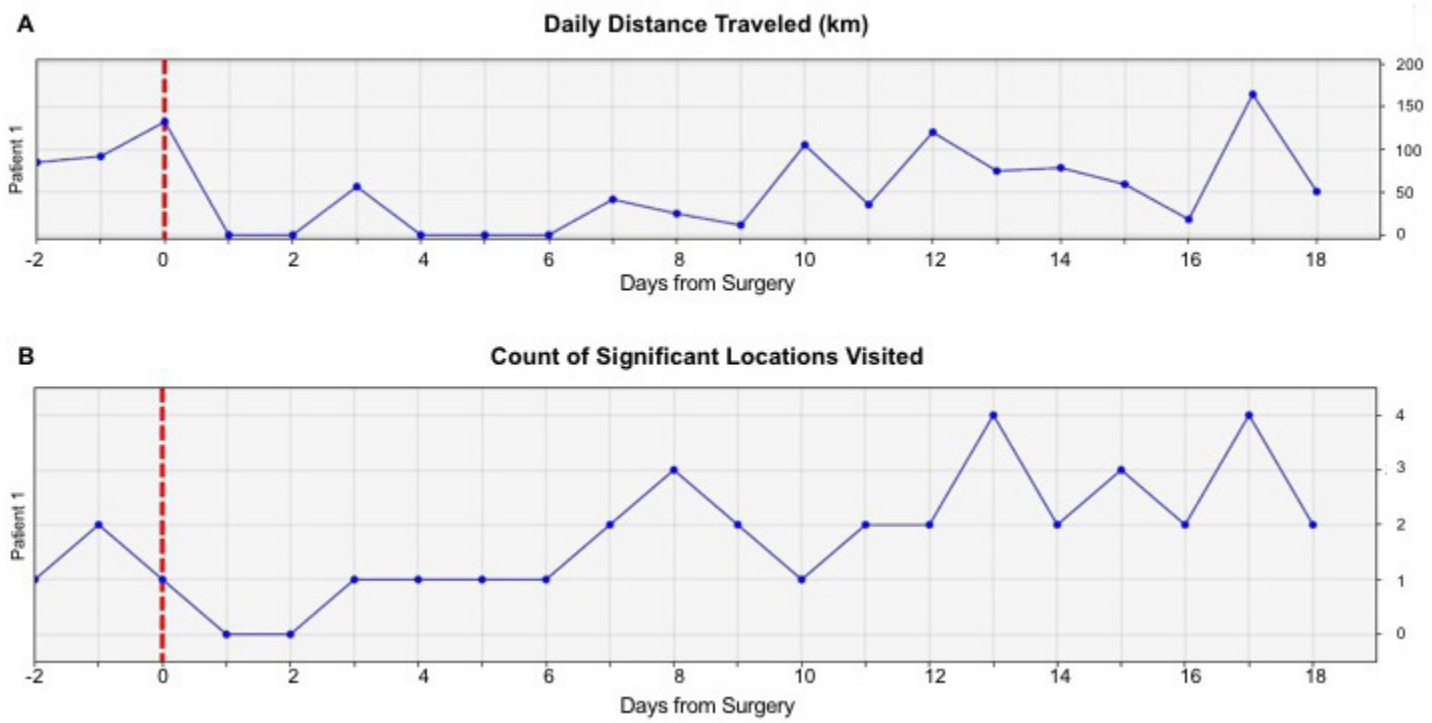

Figure 1: Plots of GPS data summaries for a patient undergoing resection of a soft tissue tumor found to be a lipomatous tumor with fat necrosis via an abdominoperineal approach. Each plot presents daily summaries for approximately 3 weeks (2 days before surgery and 18 days after). The red line indicates the date of surgery and the x-axis indicates the days before and after surgery. Plot A shows the daily distance traveled in kilometers. Plot B shows a count of significant locations visited.

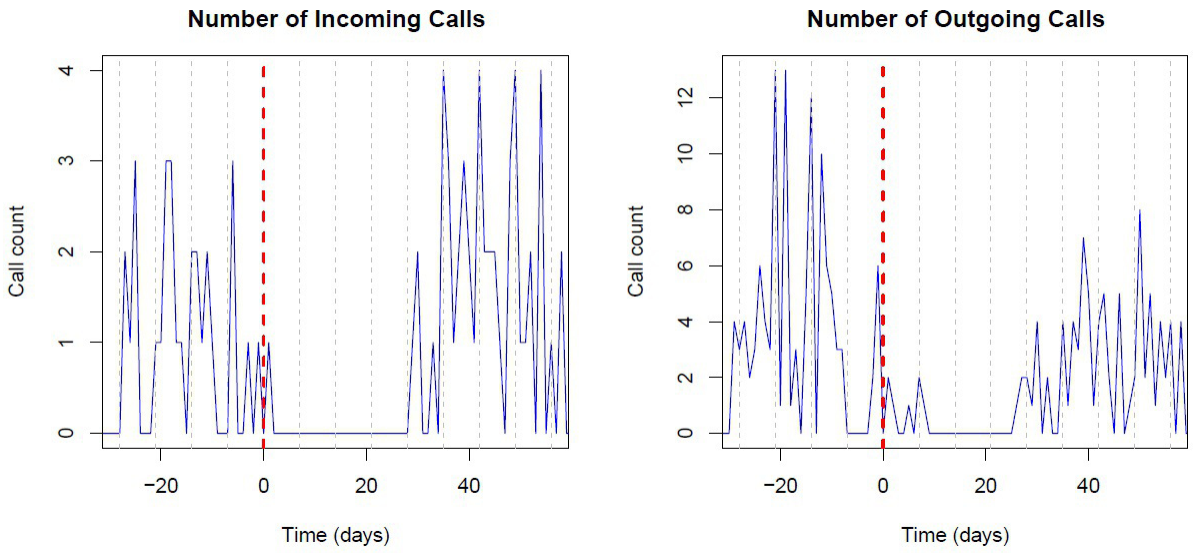

Figure 2: Call data for a patient with a retroperitoneal leiomyosarcoma undergoing a radical resection 4 weeks before surgery (vertical red lines) to 8 weeks after. The left panel shows daily incoming calls; the right panel outgoing calls. An obvious decline in phone call activity for this patient is noted after surgery, which only starts to increase towards baseline levels several weeks later.

Poster 352 3042895

DEFINITIVE HIGH DOSE PROTON THERAPY FOR UNRESECTED OSTEOSARCOMAS OF THE SPINE AND PELVIS: A VIABLE ALTERNATIVE?

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Objective: Osteosarcoma in the spine and pelvis are rare and challenging tumors to treat and resection is associated with significant complications. We report a cohort of patients who received definitive chemoradiation without surgery as local treatment and compared to outcomes of patients treated with multimodality therapy.

Methods: Patients with osteosarcoma in the spine and pelvis were identified from a large institutional sarcoma database. We retrospectively reviewed the clinical presentation, treatment, outcome, and patterns of failure. Kaplan-Meier analysis and Cox Proportion Hazards were used to analyze survival outcomes.

Results: A total of 160 patients with spine and pelvic osteosarcomas were identified on an IRB approved retrospective protocol. 140 patients underwent resection (R0 44,3%, R1 2.9%, R2 45.0%). 80 patients received adjuvant radiotherapy (RT) preoperatively (60%) or postoperatively (40%). Ten patients met the criteria for having localized disease treated with a definitive dose of RT alone (> 60Gy total) without surgical resection. Median age was 46 years (range 16 – 80). Locations were sacrum (6), pelvis (2), lumbar (1), and cervical (1). Seven had conventional osteosarcoma, two chondroblastic sarcoma and one fibroblastic sarcoma. Seven patients had tumor size >= 8cm and 3 were < 8cm. All received chemotherapy and RT dose minimally 60 Gy to a median dose of 70.2Gy; 70% had > 70Gy given with proton therapy. Median follow up time was 83 months (range 3-180). One patient died 3 months after diagnosis and did not complete therapy and one patient developed metastatic disease shortly after completing chemoRT. Six patients were still alive by the end of the follow up without evidence of disease. The 3 and 5 year overall survival was 86% and 69% respectively; local control rate was 57% at 3 and 5 years. Comparison between patients who had definitive chemoRT alone with a cohort of 60 patients who did not receive RT (surgery only) and 80 patients with no difference in tumor size, grade, histology, age, or locations, treated with a combination of surgery and RT showed no difference in overall survival (p=0.3) or local control (p=0.34). There were no spinal myelopathy, new lumbosacral neuropathy, fractures, or wound healing complications with chemoRT alone, in contrast to 27% wound healing complication, 8.5% hardware failure, 1.6% fractures in patients having both RT and surgery +/-chemotherapy. One patient with a cervical spine osteosarcoma treated definitively to 72 Gy developed secondary sarcoma 8.5 years after chemoRT. Three patients receiving trimodality treatment developed ALL or MDS. Preoperative RT was most predictive of wound complication (p<0.001). Among all spine and pelvic osteosarcoma patients without metastatic disease (M0, n=129), older age (HR = 1.01 per year, P = 0.02), radiation associated osteosarcoma (HR = 2.28, P = 0.01),

chondroblastic osteosarcoma (HR = 2.14, p = 0.01), positive margin (HR = 3.70, p < 0.001) were negative independent prognostic factors whereas chemotherapy (HR = 0.29, p = 0.001), high dose RT (HR = 0.48, p = 0.04) were positive independent factors affecting OS. Majority of the initially M0 patients deveolped distant metastasis (57%).

Conclusion: Definitive chemoradiation treatment for osteosarcoma in the spine and pelvis shows comparable survival results compared to surgery only or combined surgery and radiation treatment for spine and pelvic osteosarcomas (where only slightly over 1/3 of patients achieve R0 resection) without significant wound healing, hardware, or fracture as complications. Given the high metastatic risk of these large osteosarcomas, durable long term local control and survival with chemoRT alone is possible and a viable option, though more experience using defintive chemoRT only for unresected spine and pelvic osteosracoma is needed to determine whether this is a viable alternative to aggressive trimodality therapy in patients not able to achieve R0 resection.

Poster 353 3027641

RADIOTHERAPY FOR EXTREMITY SOFT TISSUE SARCOMA: THE ROLE OF A NORMAL SOFT TISSUE STRIP IN VMAT PLANNING

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Objective: Most guidelines for extremity soft tissue sarcoma (STS) lack details for contouring and planning, largely due to lack of evidence. Many institutional protocols for extremity STS include a longitudinal strip of healthy soft tissue as an avoidance structure (hsOAR: healthy strip as an organ at risk), although its dosimetric significance has not been established.

Methods: We aimed to determine spatially variant normal tissue objectives (NTOs) that may confer an equivalent healthy strip sparing and to dosimetrically compare with plans that use hsOARs. 17 patients previously treated for extremity STS between 2015 and 2018 at the BC Cancer Vancouver Clinic were identified and anonymized. Optimization PTVs were derived from the original contours and used to contour hsOARs. Two separate plan optimizations via standard protocol (using hsOAR) and the NTO protocol (without hsOAR) were done for each patient. The 17 sets of plans were compared for PTV coverage, hotspots, and hsOAR V20Gy and analyzed using the Wilcoxon rank sum test. Various parameters of the hsOAR and PTV were calculated using the relative volumes (hsOARs:PTV).

Results: Average hsOAR volume in proportion of the corresponding limb segment was 43.6%. Overall, there was one plan that showed exactly equivalent V20Gy, 3 plans with better V20Gy for NTO protocols, and the remaining 14 plans achieved better V20Gy using the standard protocol, 5 of which with less than 10% difference between the two protocols. Mean Dmax for the two protocols were statistically different: 108.2% for the NTO protocol and 106.5% for the standard protocol ($p<0.01$). V20Gy values were not statistically different between the NTO and the standard protocol ($p=0.06$). Review of individual plans did not reveal any pattern among the plans that achieved significantly different V20Gy between the two protocols.

Conclusion: V20Gys achieved by NTO protocol were not statistically different from the ones with standard hsOARs although there appears a trend to favour the standard protocol. There was a small difference in Dmax favouring the standard protocol although still meeting the commonly used constraint. Given statistically uncertain dosimetric advantage, eliminating hsOARs in contouring and planning of extremity STS may be appropriate once an NTO protocol is optimized to allow more efficient workflow of RT planning.

Poster 354 3041869

FEMUR FRACTURE IN PRIMARY SOFT-TISSUE SARCOMA OF THE THIGH AND GROIN TREATED WITH INTENSITY-MODULATED RADIATION THERAPY: OBSERVED VS EXPECTED RISK

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Objective: Patients with soft-tissue thigh sarcoma are at increased risk of femur fracture from radiation therapy. Intensity-modulated radiation therapy (IMRT) can reduce the dose delivered to bone. We assessed the observed risk of femoral fracture in primary soft-tissue sarcoma (STS) of the thigh treated with IMRT compared to the expected risk using the Princess Margaret Hospital (PMH) nomogram.

Methods: Patients treated with IMRT for STS of the thigh/groin were included (92); those receiving prophylactic internal fixation were excluded (2). Expected femoral fracture risk was calculated using the PMH nomogram. Cumulative risk of fracture was estimated using Kaplan-Meier statistics. Prognostic factors were assessed with univariate and multivariate (MVA) analysis using Cox's stepwise regression.

Results: Between 2/2002 and 12/2010, 92 consecutive eligible patients were assessed. Median follow-up was 73 months (106 months in surviving patients). Preoperative IMRT (50 Gy) was delivered in 13 (14%) patients, and postoperative IMRT was delivered in 79 (86%) patients (median dose of 63 Gy, range 59.4-66.6 Gy). The observed crude risk of fractures was 6.5% compared to 26.4% expected risk from the nomogram; the cumulative risk of fracture using IMRT at 5 years was 6.7% (95% CI 2.8-16.0%). The median time to fracture was 23 months (range 6.9-88.6). Significant predictors of fracture on univariate analysis were age (P=0.03), compartment of thigh (P=0.008), and extent of periosteal stripping (P<0.0001). On MVA, age and extent of periosteal stripping retained significance (P=0.04 and P=0.009, respectively).

Conclusion: In this study, the cumulative risk of femur fracture in patients treated with IMRT (6.7%) is less than the expected risk using the PMH nomogram (26.4%). Established predictors of femur fracture such as gender, tumor size, and dose of RT seem to exert less influence when using IMRT.

Poster 355 3042909

HISTOPATHOLOGIC RESPONSE TO NEOADJUVANT RADIATION THERAPY DOES NOT PREDICT ONCOLOGIC OUTCOME IN PATIENTS WITH SOFT TISSUE SARCOMA OF THE TRUNK AND EXTREMITY

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Objective: Soft tissue sarcoma (STS) is an uncommon but heterogeneous group of neoplasms of mesenchymal origin. Current standard of care for intermediate to high grade STS includes neoadjuvant radiation therapy (NRT) followed by limb preserving surgical resection. There are few studies that correlate histopathologic response to NRT with oncologic outcome in patients with STS. Studies in rectal cancer patients confirm that complete pathologic response to neoadjuvant chemoradiation therapy had improved oncologic outcomes. However, the correlation between histopathologic response and outcomes in STS is less clear. In this study, we attempted to correlate histopathologic response to NRT with overall survival (OS) and disease-free survival (DFS) in patients with STS of the trunk and extremity.

Methods: All patients over the age of 18 undergoing surgical resection for STS of the limb and trunk between 2006-2015 at Duke University were identified using DEDUCE. We identified 65 patients who received NRT followed by surgical resection for primary intermediate or high-grade STS. Patients with either percent tumor necrosis (TN) or treatment effect (TE) in the pathology report at the time of surgical resection were stratified into four quartiles for each factor, no TE/TN, minimal TE/TN, intermediate TE/TN, or high TE/TN with the following values, 0-25%, 25-50%, 50-75%, and 75-100%, respectively. Overall (OS) and disease-free survival (DFS) were calculated from the date of surgical resection to date of last follow-up and date of disease relapse, respectively. Unadjusted OS and DFS was calculated using the Kaplan-Meier method. In addition to TN and TE identified from the surgical pathology records, we performed additional histopathologic characterizations of 23 patient tumor samples by quantitative analysis of percent tumor infarction, fibrosis/hyalinization, coagulative necrosis, and remaining viable tumor.

Results: Of the 65 patients who were treated with NRT, 39 patients had either percent TN or TE identified in the surgical pathology report. In this cohort of patients, the average age was 62, average tumor size was 11 cm, most common STS subtype was undifferentiated pleomorphic sarcoma (UPS) (30%) and the majority of tumors were high grade (61%). Mean OS was 5.9 years and in that time 48% of patients had either local or metastatic recurrence with average time to recurrence of 1.3 years. Based on chi-square analysis, tumor grade (intermediate or high), patient gender, and tumor size prior to radiation therapy (<5cm, 5-10cm, and >10 cm) were correlated with levels of tumor necrosis (P<0.05). There was no significant correlation between patient demographics or clinical characteristics among the treatment effect groups. Kaplan-Meier analysis of the OS and DFS curves were not significantly different between the TE groups or the TN groups. Preliminary analysis of 23 patients with additional histopathologic factors beyond TN and TE including percent infarction, fibrosis/hyalinization, coagulative necrosis, and viable tumor remaining did not show any significant difference in OS or DFS in the various groups.

Conclusion: These results are similar to our prior institutional data using retroperitoneal sarcoma demonstrating no statistically significant association between percent TN or TE and overall survival or disease-free survival. Preliminary data from analysis of additional histopathologic tumor characteristics not included in the FNCLCC grading system also show no difference in oncologic outcomes between groups. Tumor percent necrosis, a factor commonly used in both tumor grade determination and in characterizing pathologic response to radiation, does not predict overall survival or development of local recurrence or metastatic disease. Further studies in identifying radiographic changes from pre-and-post NRT could elucidate specific imaging findings that are predictive of treatment response.

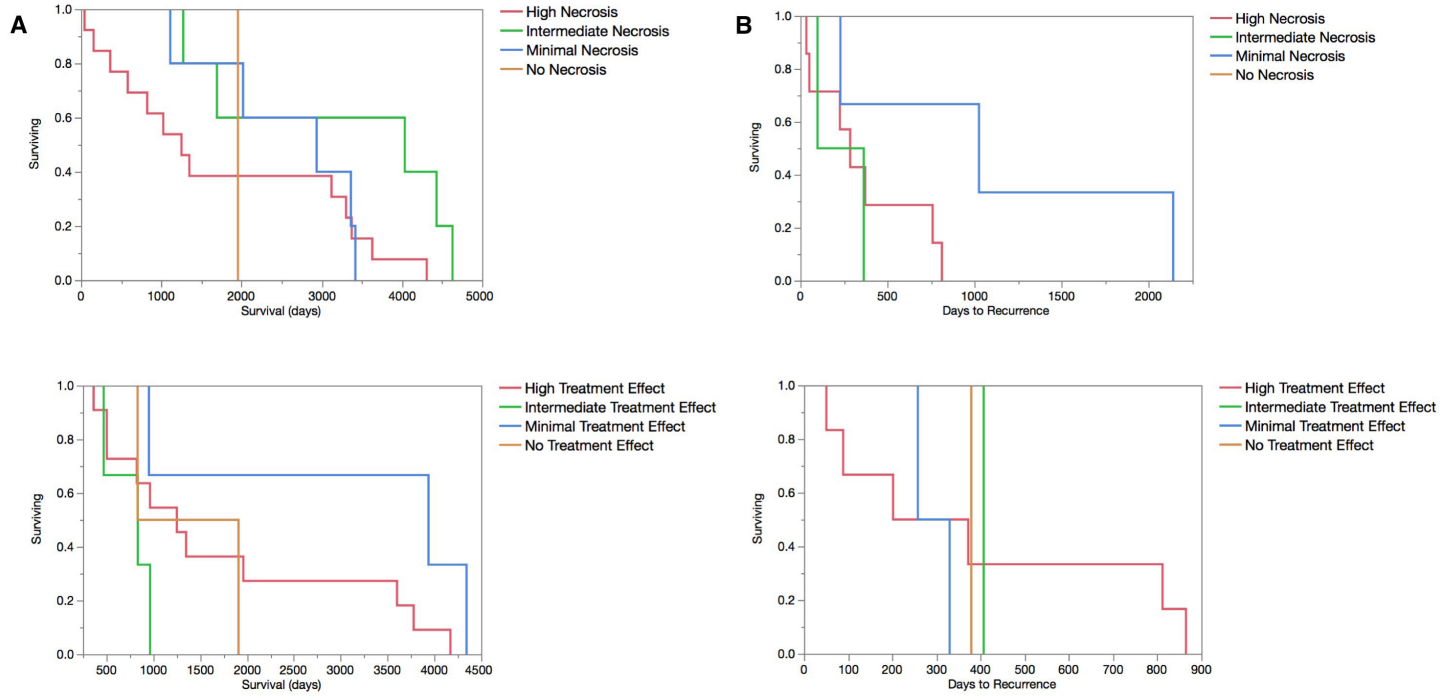

Figure 1. For patients with soft tissue sarcoma of the extremity, neither treatment effect nor tumor necrosis predicts overall survival or disease free survival. A. Kaplan-meier curves of overall survival based on percent necrosis (n=24) or treatment effect (n=19) showed no statistically significant trend between groups. B. Kaplan-meier curves of disease free survival based on percent necrosis (n=12) and treatment effect (n=10) also showed no trend between groups.

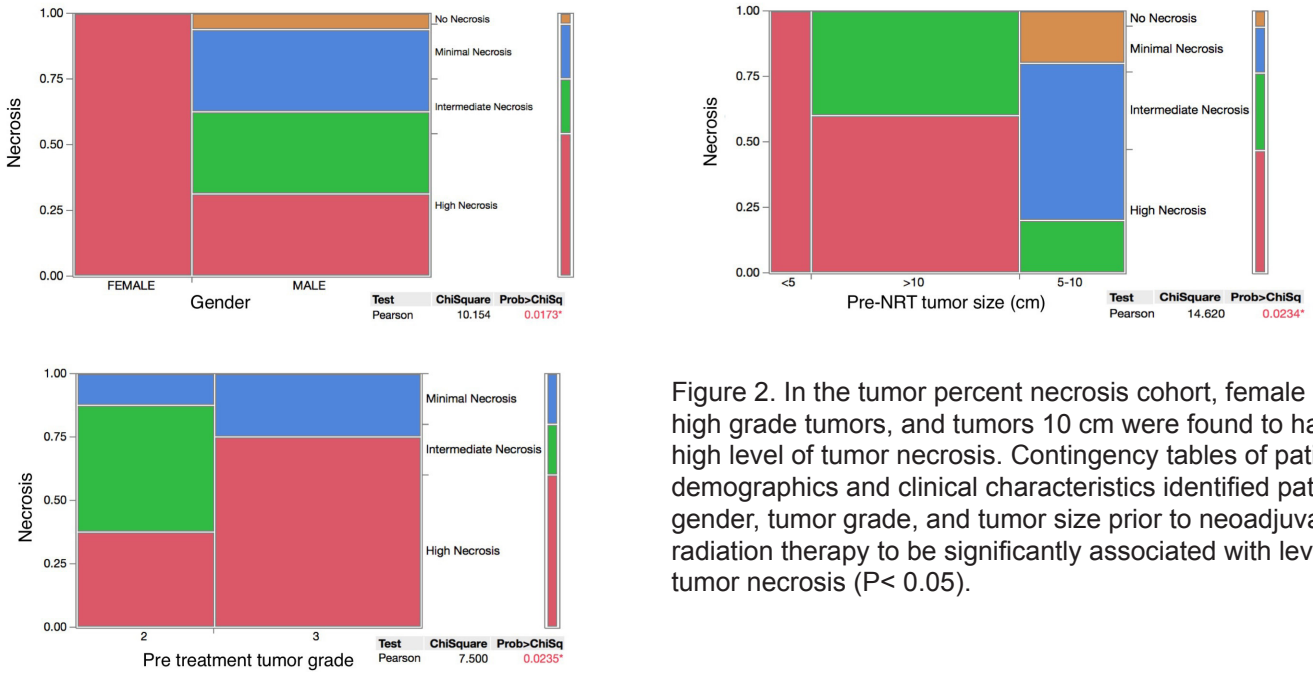

Figure 2. In the tumor percent necrosis cohort, female patients, high grade tumors, and tumors 10 cm were found to have a high level of tumor necrosis. Contingency tables of patient demographics and clinical characteristics identified patient gender, tumor grade, and tumor size prior to neoadjuvant radiation therapy to be significantly associated with levels of tumor necrosis (P< 0.05).

Poster 356 3042911

ACUTE POST-OPERATIVE WOUND COMPLICATIONS FOLLOWING PRE-OPERATIVE PROTON BEAM IRRADIATION FOR SOFT TISSUE SARCOMAS

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Objective: Proton beam therapy (PBT) is being increasingly utilized for patients with soft tissue sarcoma of the extremity/trunk and retroperitoneum. Theoretically, PBT may allow for treatment of previously irradiated fields or for tumors adjacent to vital structures where volumes may exceed normal tolerances using photon-based RT. The effect of preoperative PBT on postoperative complications in this patient population is unknown. This study describes a single institution experience with preoperative PBT for soft tissue extremity/trunk and retroperitoneal sarcoma and quantifies the acute postoperative wound complications.

Methods: Patients who received PBT for soft tissue sarcoma of the extremity/trunk or retroperitoneum and subsequently underwent surgical resection were retrospectively identified from a large single institution database. Patient demographics, tumor type and location and indication for PBT were recorded. Acute postoperative wound complications were identified and described.

Results: Eleven patients were treated with neoadjuvant PBT during the time period 2012-2018; 6 (54%) were female and 5 (46%) were male. The median age of the cohort was 61.5 years. Six patients (54%) were being treated for recurrent disease. Tumor type was varied and included: dedifferentiated liposarcoma (n=4), leiomyosarcoma (n=2), fibromyxoid sarcoma (n=2), pleomorphic sarcoma (n=1), Ewing sarcoma (n=1) and sarcomatoid carcinoma (n=1). Tumor location was retroperitoneum (n=6), chest wall (n=2), mediastinum (n=2) and thigh (n=1). The most common reason PBT was utilized in place of photon beam irradiation was tumor proximity to vital structures (n=9, 82%). Two patients (18%) had previously received photon beam to the same field. The rate of acute postoperative wound complication in this series was 27% (n=3). These included a postoperative wound infection requiring percutaneous drainage, a postoperative hematoma that required no intervention and a wound dehiscence requiring return to the operating room for wound debridement.

Conclusion: In this current series evaluating the safety of our initial experience with PBT in patients with soft tissue sarcoma of the extremity/trunk or retroperitoneum, there appears to be a similar acute postoperative complication rate and profile to previously reported complication rates of patients receiving preoperative photon beam irradiation. PBT may potentially allow for treatment of tumors that would otherwise not be candidates for RT due to location, volume of normal tissue irradiated, or previous radiation treatments. Important follow up studies are required to better define the late toxicities, particularly for patients getting repeat treatment. Additionally, future studies comparing the efficacy of the two modalities in the neoadjuvant setting are warranted.

Poster 357 3042914

PROTON-BASED HIGH-DOSE PRE-OPERATIVE RADIATION IS ASSOCIATED WITH HIGHER LOCAL CONTROL THAN LOW-DOSE PRE-OPERATIVE RADIATION WITH EQUIVALENT RATE OF WOUND COMPLICATION IN SACROCOCCYGEAL CHORDOMAS

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Objective: Proton-based pre-operative radiation (pre-op RT) to 19.8 – 50.4 GyRBE, complete resection, then post-operative radiation (post-op RT) to ≥70 GyRBE total results in high local control rates for spine chordomas. However, the ideal pre-op RT dose is not known. We investigated the impact of high- vs. low-dose proton-based pre-op RT on local control and wound complication rates in patients with sacrococcygeal chordomas.

Methods: We retrospectively reviewed 103 patients; 39 patients received ≤30 GyRBE (“low dose,” median: 19.8 GyRBE) and 64 patients received >30 GyRBE (“high dose,” median: 50.4 GyRBE). Major wound complication was defined as wound dehiscence and/or infection within a 3-month post-operative period.

Results: Mean age at diagnosis was 55 years, mean tumor size was 8.1 cm, and 35.9% of patients were female. At median follow up of 76.2 and 47.6 months, respectively, 5-year local control rates for the low and high dose groups were 67% and 92% (p=0.03) (Figure 1). Factors related to better local control: high pre-op RT dose, addition of post-op RT. Factors associated with worse local control: dedifferentiated histology, lymph node positive disease, R2 resection. Higher pre-op RT doses were associated with higher rates of R0 resection (81.3% vs. 56.4%, p=0.03). There was no difference in wound complication rates (low vs. high: 43.7% vs. 42.2%, p=0.84).

Conclusion: Proton-based high-dose pre-op RT is associated with higher rates of R0 resection and local control and equivalent wound complication rates when compared to low-dose pre-op RT. Based on these results, we recommend use of higher dose pre-op RT for sacrococcygeal chordomas, followed by resection and post-op RT.

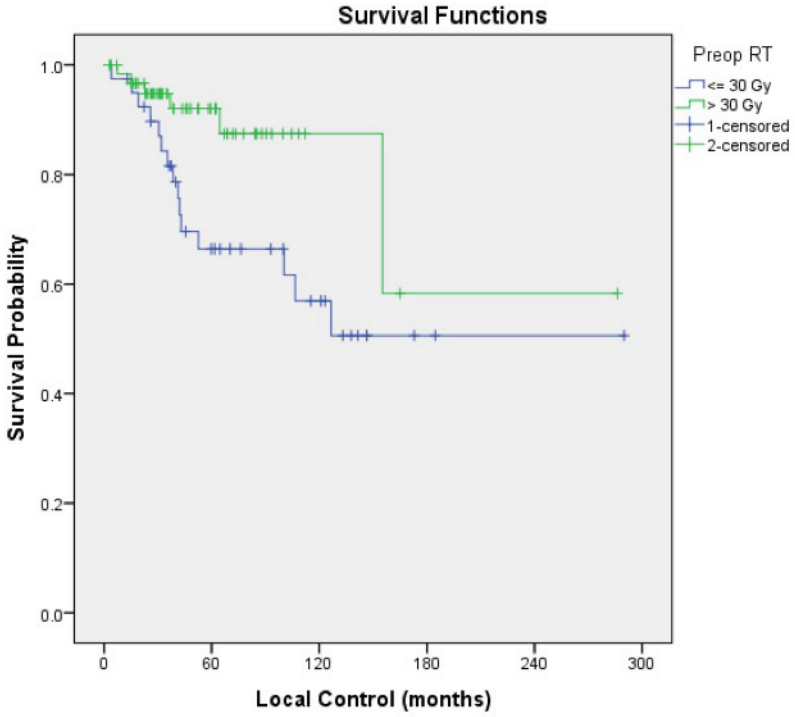

Figure 1. Local control for the low- (blue) and high-dose (green) groups.

Poster 358 3042987

URETERAL STRICTURE AND RADIATION DOSE CONSTRAINT IN THE TREATMENT OF RETROPERITONEAL SARCOMA

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Objective: Incidence of ureteral stricture following radiation therapy (RT) is low and dose tolerance of the ureter is not well described in the literature. Ureters are often closely associated with retroperitoneal sarcomas (RPS) and are at risk for receiving high radiation doses during treatment. We assessed risk factors for ureteral stricture (US) after treatment of RPS and aimed to identify an evidence-based dose constraint for the ureters.

Methods: We analyzed 75 RPS patients treated with RT from 2006-2016 at our institution and reviewed clinicopathologic variables, treatment details, and adverse events. We used 61 available RT treatment plans to contour all retained ureters as a total ureter or separated into upper, middle, and lower third segments based on anatomical landmarks. Dose-volume histograms were extracted from RT plans. Primary event was development of ureteral stricture. Multivariate analysis was performed to identify predictors of US.

Results: Of the 61 patients analyzed, median age was 60 years, median follow up was 43.3 months (1.4-137.4 mo) and median total external beam radiation therapy (EBRT) dose was 54.8 Gy (19.8-70.2 Gy). Most common histologies were dedifferentiated liposarcoma (44.3%), leiomyosarcoma (26.2%) and well-differentiated liposarcoma (16.4%). 50 (81.9%) received preop RT, 6 (9.8%) received postop RT only, 5 (8.2%) received RT only, and 11 (18%) received intraoperative RT

(IOERT). 65 (42.6%) had R0 resection and 28 (45.9%) had R1+ resection. 87 ureters were retained across all patients after resection. Five (8.3%) patients developed ureteral stenosis after treatment (two grade 1, one grade 2, two grade 3 requiring stenting) with median latency period of 5.1 months (2.9-44.5 mo) post-RT and 5.8 months (3.1-44.5 mo) post-surgery. None went on to require dialysis. There is no difference in clinical characteristics between those who developed US vs no US. All patients with US had pre-op RT with both IMRT and protons, 4 had manipulation of ureter during surgery, 2 had IOERT, and 1 had ureteral stent placed prior to treatment. On MVA, V50.4 (volume of ureter receiving 50.4 Gy or greater) to the middle third of the ureter was identified as a risk factor for development of ureteral stenosis (HR 1.074, p-0.0495).

Conclusion: Ureteral stricture is a potential complication after RT treated RPS. Volume of middle third of ureter receiving 50.4 Gy or greater appears to be more predictive than mean or max point dose. Prior stenting, IOERT and surgical manipulation may also influence US. Current RPS protocols at our institution constrains ureters to maximum dose of 50.4 Gy. More events are needed to develop a full Normal Tissue Complication Probability (NTCP) model. Protocols evaluatging preoperative RT in retroperitoneal sarcoma, particularly those involving dose painting, might considering incorporating these constraints to reduce risk of ureteral stenosis. Preoperative multidisciplinary considerations of potential manipulation, necessity for stenting, planned ureter/kidney resection, residual ureter function, as well as external beam and intraoperative radiation dose to the ureter are important to reduce this complication.

Table 1. Clinical and DVH comparison between patients with ureteral stenosis and those without

	Stricture (n=5)	No Stricture (n=82)	P
Tumor size (median, cm)	12 (9 to 19)	15.2 (2.3-30)	
Total EBRT dose (median)	61.6 (48-63)	54.7 (19.8-70.2)	NS
IOERT use	40%	16.1%	0.22
R0/R1	80%	67.9%	0.90
Total ureter (mean values)			
Mean Dose (Gy)	22.84	15.47	0.213
Max Dose (Gy)	44.56	30.18	0.099
V45 (%)	25.75	15.12	0.092
V50.4 (%)	16.49	5.39	0.078
Middle 3rd			
Mean Dose (Gy)	33.79	19.61	0.119
Max Dose (Gy)	44.46	27.34	0.068
V45 (%)	48.14	22.58	0.095
V50.4 (%)	32.43	9.89	0.035

Poster 359 3042212

LONG TERM OUTCOMES AND TOXICITIES FROM A PHASE II TRIAL OF FOCAL CONFORMAL RADIATION THERAPY (RT) FOR CHILDREN WITH RHABDOMYOSARCOMA (RMS)

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Objective: To assess risk of local failure (LF), disease free survival (DFS), and late toxicities of a conformal photon radiotherapy approach in children with RMS.

Methods: 68 patients (median age at diagnosis 6.9 y, range1.2 – 23.8) were treated with conformal photon RT (either 3D Conformal or Intensity Modulated RT) to the primary site. Target volumes included imaging-defined soft tissue tumor post-chemotherapy and areas of normal tissue initially infiltrated with tumor (gross tumor volume, GTV), expanded with a 1-cm margin for microscopic diseases to form the clinical target volume (CTV) and an additional 0.5-1cm margin for positioning uncertainty. Prescribed RT doses were 36Gy to the CTV and 50.4Gy to the GTV. Systemic therapy consisted of vincristine and dactinomycin (VA) (6 patients), vincristine, dactinomycin, cyclophosphamide (VAC) (37 patients), or VAC-based combinations (25 patients). Patients were followed using MRI of primary site, whole body 18F-FDG-PET, and CT chest scans, out to 5 years. Pre-RT PET was assessed for its predictive value for local failure after induction chemotherapy (typically prior to week 12).

Results: 5 year DFS differed across the risk groups as follows: low risk 88% (n=8), intermediate risk 76%

(n=37), and high risk 36% (n=23); (p≤0.01 for LR/IR compared to HR). The cumulative incidence (CI) of LF at 5 years of the entire cohort was 10.4%. Tumor size at diagnosis as a continuous variable was a significant predictor of LF (p<0.01) and dichotomized tumor size of ≤5cm vs >5cm approached significance (CI LF 0% vs 14.8%, p=0.067). In 28 patients with tumor imagable by PET prior to local control, the CI of local failure for patients with positive PET activity after induction chemo was 18.2% vs. 0% for PET negative, though not significant (p=0.075).

Patients with head and neck (H&N) primary tumors (n=31) had a CI of cataracts of 35%. All patients with orbital primaries developed cataracts, and the risk was correlated with RT dose to the lens (p=0.0025). No cataracts we identified when the dose to the lens was below 15 Gy. Jaw dysfunction was more severe (3.4cm vs 4.4cm opening) when the pterygoid and masseter muscles received a mean dose of >20 Gy (p=0.013). Orbital hypoplasia, assessed by the extent of posterior recession of the globe, developed more frequently in patients with mean bony orbit dose >30 Gy (p=0.041) and higher RT dose to the lens (p=0.049). Of those patients with genitourinary (GU) primary tumors, GU toxicity following RT consisted of measurable hematuria in 9/14 patients and bladder wall thickening in 10/14 patients, neither of which correlated with bladder RT dose. Two of five patients with gynecologic primaries experienced significant vaginal stenosis. Extremity toxicities included one fracture in 14 patients, yet without evidence that RT dose to the physes promoted early closure (p=0.46).

Conclusion: Long-term local control outcomes with limited margin photon-based RT are favorable, with larger primary tumor sites having higher rates of local failure. Treatment-related toxicities, particularly H&N toxicities, were still prevalent and resulted in measurable functional deficits despite the conformal RT targeting approach.

Poster 360 3042856

ACHIEVING HIGH RATES OF LOCAL CONTROL AND FAVORABLE TOXICITY USING STEREOTACTIC BODY RADIOTHERAPY FOR SARCOMA PULMONARY METASTASES: A MULTI-INSTITUTIONAL EXPERIENCE

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Objective: Oligometastatic pulmonary metastases from sarcoma have traditionally been treated with resection and/or systemic therapy. We hypothesize that stereotactic body radiotherapy (SBRT) can be an alternative treatment to surgery that can achieve high rates of local control with limited toxicity.

Methods: All consecutive patients treated with SBRT for pulmonary sarcoma metastasis from 2011-2016 at two high-volume academic sarcoma centers were analyzed. Patients underwent CT or PET/CT scans every 3 months after SBRT. Local failure (LF) was defined as >20% increase in longest tumor diameter. Toxicities were scored using CTCAE v4.0.

Results: 44 patients with 56 separate lung metastasis were treated with SBRT. Median age was 59 (range 19 – 82) and median pre-SBRT ECOG status was 1 (range 0-2). The most common histologies were leiomyosarcoma (30%), pleomorphic sarcoma (18%), synovial sarcoma (9%), and fibrosarcoma (9%). Most patients (82%) had received prior chemotherapy, 66% had prior pulmonary resections (range 1-5 resections), and 32% had received prior thoracic radiotherapy. Median lesion size was 2.0 cm (range 0.5-8.1 cm). SBRT was most commonly delivered to 50 Gy in 4 or 5 fractions (80%). Median follow-up was 16 months for all patients and 21 months for patients alive at last follow-up. Overall survival at 12 and 24 months was 74% (95%CI 67-81%) and 46% (95%CI 39-55%). Local control at 12 and 24 months was 96% (95%CI 93-98%) and 90% (95%CI 84-96%), respectively. There were 3 LFs. Two lesions (1.6 and 2.0 cm) failed at 5 months, and one lesion (3.9 cm) recurred 21 months after SBRT. Two of the 3 patients with LF received SBRT as salvage after failing metastatectomy at the same site. In the entire cohort, local control and OS did not differ based on age, gender, histology, fractionation regimen, lesion location, or size (all p>0.05). Three patients developed grade 2 chest wall toxicities; one patient had grade 2 pneumonitis. No other acute or late grade ≥2 toxicities were observed.

Conclusion: To our knowledge, this is the first multi-institutional series reporting on SBRT for pulmonary sarcoma metastases and demonstrates that SBRT is well-tolerated with excellent local control. SBRT should be considered in these patients as an alternative to surgical resection. Prospective trials of SBRT vs. surgery are warranted.

Poster 361 3011135

TIME DEPENDENT DYNAMICS OF WOUND COMPLICATIONS AFTER PREOPERATIVE RADIOTHERAPY IN EXTREMITY SOFT TISSUE SARCOMAS

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Objective: The purpose of the study was to investigate the time dependent dynamics of wound complications and local control after preoperative radiotherapy (RT) in Extremity Soft Tissue Sarcomas (ESTS).

Methods: In this retrospective cohort study, all patients treated for an extremity sarcoma with pre-operative radiotherapy followed by surgery were identified from a prospectively maintained database. A wound complication (WC) was defined as any local complication of the surgical area requiring intervention, hospital readmission or significant extension of the initial admission period.

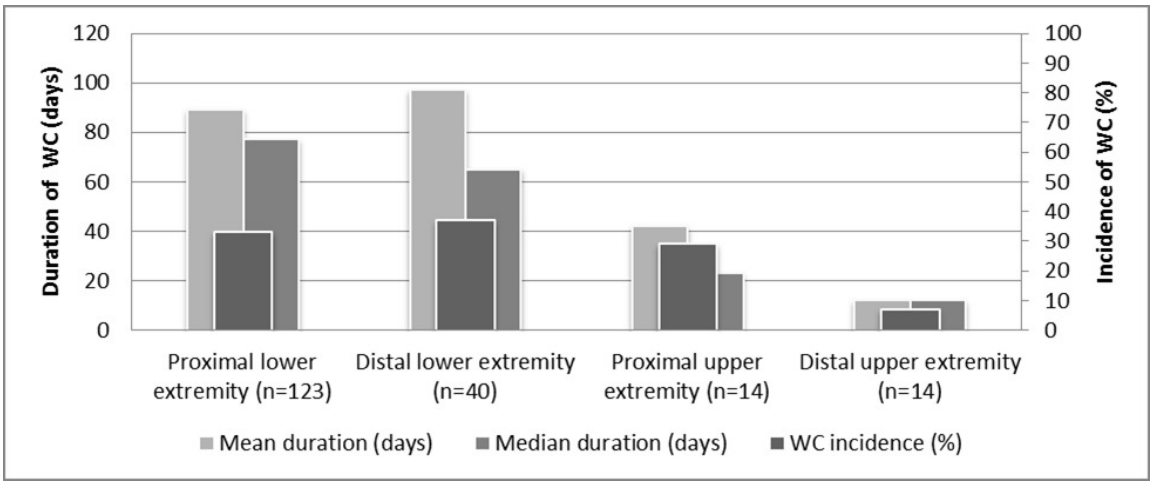
Results: A total of 191 preoperatively irradiated ESTS patients were included in this study. WC was seen in 31% of the patients (n=60). WC started after a median time of 25 days from surgery, with a median duration of 76 days. Adiposity, smoking and a lower extremity or superficial tumor localization were significantly correlated with an increased WC rate. Risk factors for a duration of WC ≥ 120 days are early development of WC (≤ 21 days after surgery) and smoking. Local control rates after 1, 3 and 5 years were 99%, 93% and 93%, respectively.

Conclusion: Approximately one-third of patients selected for preoperative RT develops a WC, typically in smoking, adipose patients with superficial tumor localizations in the lower extremity. Based upon the well-established superior long-term functional outcome, maintained excellent local control rates and the temporary nature of the WC issue, preoperative RT remains our preferred treatment. Although, in patients at high risk of WC, post-operative RT might be considered.

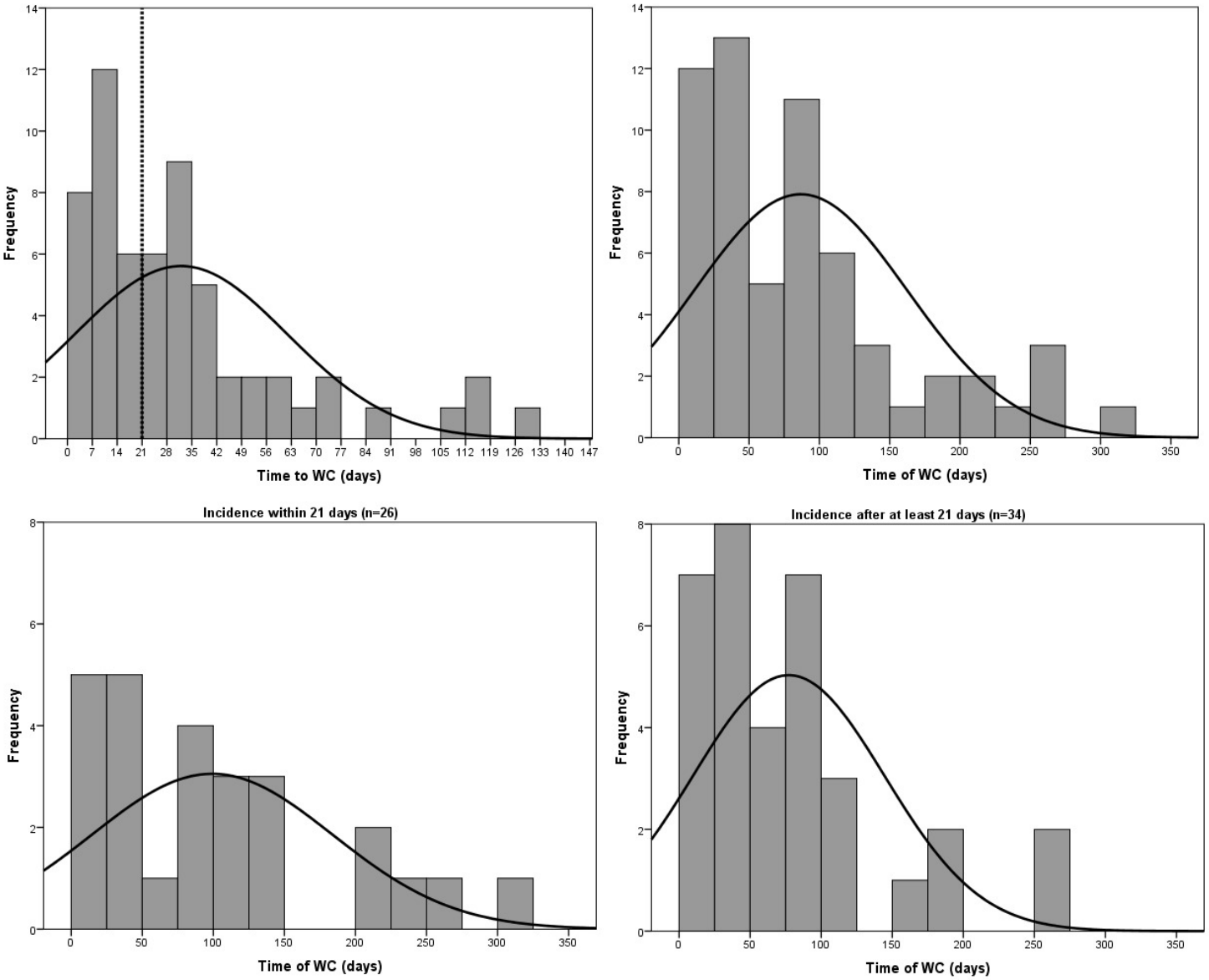
Prognostic factors wound complication

Prognostic factor	OR Univariate	p	OR Multivariate	p
Superficial tumor	2.813	0.002	4.064	0.000
Age ©	0.989	0.227		
Lower extremity	2.364	0.098	4.978	0.008
High grade	0.839	0.592		
Adiposity	3.589	0.002	4.048	0.002
Hypertension	1.149	0.667		
Diabetes	1.602	0.311		
Smoking	3.967	0.001	4.588	0.001
TD > 10cm	0.678	0.228		

OR= odds ratio, TD= Tumor Diameter, ©= continuous variable



Duration and incidence of WC by tumor localization



Above: distribution of the time to incidence (left) and duration of wound complications (right). Below: distribution of the duration of wound complications when it occurs within (left) or after21 days (right). Note that the x-axis is different in the figure left above, representing the time to occurrence of a wound complication instead of the duration of it.

Poster 362 3014815

EFFICACY OF ADJUVANT RADIOTHERAPY IN NON-EXTREMITY SOFT TISSUE SARCOMA WITH MODERATE CHEMOSENSITIVITY

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Objective: Soft tissue sarcoma (STS) is a rare and heterogeneous type of cancer known to have over 50 subtypes. It is difficult to understand how adjuvant treatment plays a role in STS. We aimed to reveal the benefits of adjuvant treatment for a rare subset of STS, non-extremity STS with moderate chemosensitivity.

Methods: We reviewed medical records from Pusan National University Hospital and Kosin University Gospel hospital that having detailed pathological reports on patients diagnosed between 2006 and 2016. The most important criterion of inclusion was resection with curative intent. We grouped STS by chemosensitivity based on reported data and analyzed non-extremity STS with moderate chemosensitivity. The analyses of survivals were performed by SPSS Statistics 22 (IBM, Chicago, IL, USA).

Results: We investigated 142 patients with 20 pathological subtypes of STS. Eighty-six patients had extremity STS and 56 had non-extremity STS. Thirty-eight of 56 patients were categorized as having moderate chemosensitivity. Seventeen of 38 patients (44.7%) received adjuvant radiotherapy and 14 patients (36.8%) received adjuvant chemotherapy. A log rank test showed longer disease-free survival (DFS) in the adjuvant radiotherapy group compared to a group treated without adjuvant radiotherapy (not reached vs. 1.468 years, P = 0.037). A Cox proportional hazard model with covariates including age, stage, resection margin, and adjuvant chemotherapy showed that adjuvant radiotherapy was associated with longer DFS (Odds ratio = 0.369, P = 0.045). The overall survival did not show correlation with adjuvant radiotherapy.

Conclusion: Adjuvant radiotherapy might be associated with longer DFS in patients with non-extremity STS with moderate chemosensitivity.

Table1. STS pathologies in this study.

Pathology	n
Epithelioid sarcoma	1
Intimal sarcoma	1
Angiosarcoma	2
Well differentiated lilposarcoma	2
Malignant peripheral nerve sheath tumor	4
Myxofibrosarcoma	5
Dedifferentiated liposarcoma	6
Leiomyosarcoma	8
Undifferentiated pleomorphic sarcoma	9

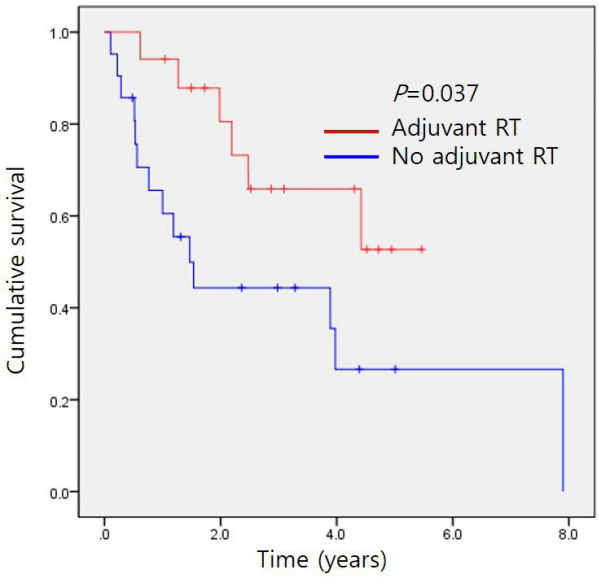

Fig1. Disease-free survival difference between patients treated with adjuvant radiation therapy (RT) and without RT.

Poster 363 3019507

IMPACT OF RADIATION DOSE AND METHOD OF DELIVERY ON SURVIVAL IN CHORDOMAS

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Objective: We investigated the largest registry of primary bone tumors, the national cancer database (NCDB), to determine (1) does increasing radiation dose improve survival and (2) does the modality of radiation delivery improve survival.

Methods: We retrospectively reviewed 1456 patients in the NCDB from 2004-2015 with a histologic diagnosis of chordoma. Inclusion criteria into the radiotherapy subset of patients required documented dose of radiation therapy and the modality of radiation delivery. The radiotherapy cohort consisted of 652 patients. 5-year survival rates were compared between stereotactic therapy (SRS), intensity modulated radiation therapy (IMRT), proton beam therapy (PBT), and conventional radiotherapy utilizing univariate and multivariate statistics. The cohort was subsequently divided into low dose (<40Gy), intermediate dose (40-60Gy), and high dose (>60Gy) groups, and 5-year survival rates between these groups were compared utilizing both univariate and multivariate statistics. Multivariate analysis adjusted for dose and treatment modality. The Kaplan-Meier (KM) method with statistical comparisons based on the log-rank test was used to identify univariate factors associated with LOS.

Results: The entire cohort included 1456 patients; including chordomas of the sacrum (n=563), the mobile spine (n=362), and the skull base (n=531). The overall 5-year survival rate was 75.7%. The radiotherapy cohort included 652 patients who received external beam radiotherapy (EBRT); conventional therapy (n=213), SRS (n=98), IMRT (n=170), and PBT (n=171). The dose of treatment was low dose (n=148), moderate dose (n=212), and high dose (n=218). The 5-year survival in the high dose group (84.9%) was significantly improved over moderate dose (67.1%, p<0.001) and low dose (69.6%, p<0.001) in both univariate and multivariate analysis. PBT had significantly improved survival over conventional EBRT (83.8% v. 69.1%, p=0.001); however, when controlling for dose in the multivariate analysis PBT was equivocal to conventional EBRT (hazard ratio [HR] 0.75 (0.46-1.23), p=0.26). In the multivariable analysis, SRS was an independently associated improved

survival over conventional EBRT ([HR] 0.53, (0.31-0.93), p=0.03).

Conclusion: This study provides the largest powered study investigating patient survival following radiotherapy in patients with axial chordomas. High dose radiotherapy (>60Gy) was associated with improved survival over intermediate (40-60Gy) and low dose (<40Gy) radiotherapy. PBT was associated with improved survival in univariate analysis; however, when adjusting for dose in the multivariate analysis survival between PBT and conventional EBRT were equivocal. SRS was associated with improved 5-year survival irrespective of the dose.

Figure 1: Dose of Radiotherapy versus Survival

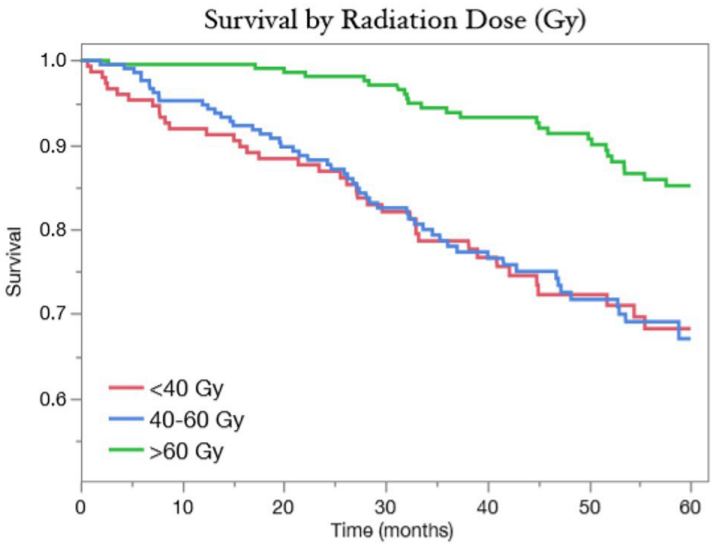
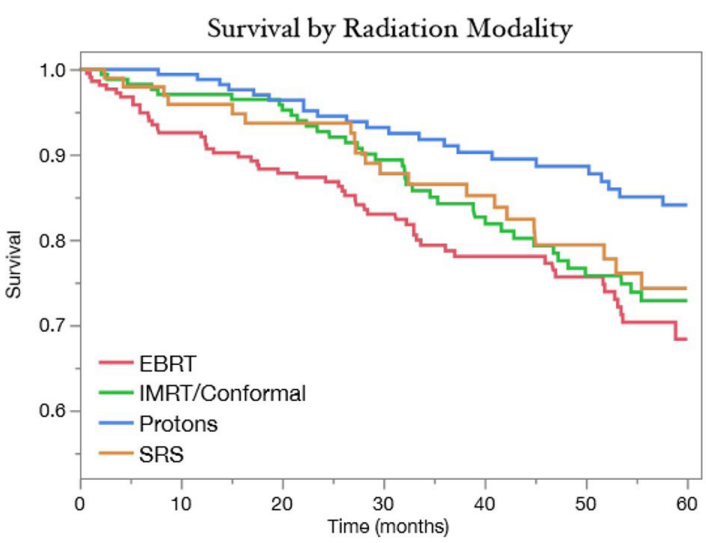


Figure 2: Radiotherapy Modality versus Survival



Poster 364 3026070

EARLY ANALYSIS OF PROSPECTIVE PHASE II CLINICAL TRIAL ON PREOPERATIVE HYPOFRACTIONATED RADIOTHERAPY (RT) COMBINED WITH CHEMOTHERAPY IN PRIMARY MARGINALLY RESECTABLE HIGH GRADE SOFT TISSUE SARCOMAS (STS) OF EXTREMITIES OR TRUNK WALL

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Objective: The management of marginally resectable high grade STS is challenging. The aim of the study was to assess the efficacy and safety of preoperative hypofractionated RT combined with chemotherapy in primary locally advanced STS.

Methods: In this single-arm clinical trial treatment consisted of one cycle of doxorubicin and ifosfamide(AI), followed by immediate 5x5 Gy RT, and 2 cycles of AI every 3 weeks in 7-8 weeks gap between RT end and surgery. Tumor response was assessed in DWI-MR imaging and pathologically by EORTC STBSG criteria. The primary endpoint is rate of limb-sparing surgeries and R0 resections.

Results: Since the opening of the study in February 2017 26 patients met eligibility criteria, 21 received the whole planned protocol treatment. 3 patients underwent extremity amputation, two after 1st AI cycle due to poor tolerance, one due to extensive tumor invasion without possibility of vessels reconstruction, two patients are still on preoperative treatment. One toxic death occurred outside our center related to severe bone marrow suppression with septic shock after 2nd AI cycle. Early tolerance of chemotherapy was acceptable. Grade 3+ CTCAE4.03 toxicity occurred in 11 patients. AI dose reduction occurred in 8 patients who completed therapy (4 patients in 2 cycles; 4 patients in 1 cycle). Early RT tolerance was satisfactory. EORTC grade 1 radiation dermatitis occurred in 13 and grade 2 in two patients. Postoperative wound complications occurred in 6 patients, in two were severe (wound dehiscence with hospitalization). Very good pathological response (<1% of stainable tumor cells; grade A/B) was observed in 5 patients. Good pathological response (<50% tumor cells; grade C/D) was found in 12 patients. Confirmed R0 resection with microscopic free margin > 1 mm was achieved in

14/21 patients (67%) with limb-sparing surgery, no R2 resection was performed. None of the patient had local recurrence, five patients developed distant metastases, two patients died due to disease progression.

Conclusion: Preoperative AI chemotherapy combined with hypofractionated RT is a feasible method of the management of marginally resectable high grade STS. It provides good pathological responses, high local control with acceptable treatment toxicity.

Poster 365 3038606

PATTERNS OF PRACTICE SURVEY: RADIOTHERAPY FOR EXTREMITY SOFT TISSUE SARCOMA

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Objective: Neoadjuvant or adjuvant radiotherapy (RT) for extremity soft tissue sarcoma (STS) confers significant local control benefit. To determine patterns of practice, a survey of RT planning practices was undertaken.

Methods: Members of the Connective Tissue Oncology Society and Canadian Association of Radiation Oncology participated in this survey pertaining general practice patterns of RT for extremity STS, patterns of contouring and planning, and use of quality control measures such as guidelines, tumor boards, and quality assurance rounds.

Results: 58 radiation oncologists treating extremity STS from 12 countries responded. 89.7% worked in academically affiliated centres, and 55.2% saw at least 20 cases of extremity STS per year. Most (96.7%) held multidisciplinary sarcoma boards, 85.5% of which discussed every sarcoma case. 78.6% held quality assurance rounds. Most (92.9%) used planning guidelines. Preoperative RT was used nearly twice as much as postoperative RT. CT simulation with MR fusion was used by 94.6%. Patterns of CTV contouring for both superficial and deep STS were variable. 69.8% contoured a normal soft tissue strip, 13.5% without routine constraints and the remainder with various constraints. Most (91.1%) used 50 Gy in 25 fractions pre-operatively and 39.6% reported using post-operative RT boost for positive margins. Post-operative dose was more variable, ranging from 59.4 Gy to 70 Gy.

Conclusion: Major aspects of RT planning for extremity STS were similar among the responders, and most were academically affiliated. Over twice as many employed pre-operative vs post-operative RT. There was considerable heterogeneity in use of: margins for contouring, normal healthy strip as an avoidance structure, and boost for positive margins. This survey shows variable patterns of practice and identifies areas that may require further research.

Poster 366 3041914

EFFECT OF RADIOTHERAPY ON MRI MEASURES OF TUMOR INVASIVENESS AND OUTCOMES IN PATIENTS WITH SOFT TISSUE SARCOMA TREATED WITH PREOPERATIVE RADIOTHERAPY AND SURGICAL EXCISION

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Objective: Soft Tissue Sarcoma (STS) describes a heterogeneous and rare, but deadly, group of soft tissue malignancies. Despite advances in management there has been little recent innovation in predicting prognosis, which has historically been based on histological factors alone. Recent studies suggest radiographic factors could be helpful in prognostication, but these studies were focused largely on patients treated with excision followed by postoperative radiotherapy (RT). No reported study has yet evaluated radiographic-based prognosis in STS treated specifically with preoperative RT, nor has anyone delineated the effect of preoperative RT on post-treatment radiographic measures of tumor invasiveness as compared to the pre-treatment images. We hypothesize that these radiographic parameters (size, extra-compartmental extension, peritumoral edema, central hemorrhage/necrosis, peripheral growth pattern, and apparent vascular invasion) on pre-operative MRI (1) will display little radiographic improvement after RT and (2) will correlate with worse prognosis in our population as compared to those patients who do not present with tumors that display such parameters, or display them to a lesser extent.

Methods: We retrospectively examined STS patients (from 2007-2017) with histologically confirmed soft-tissue sarcoma who were treated with preoperative radiation therapy followed by tumor excision, and who had both pre- and post-RT MR imaging (N = 38). Pre-RT and post-RT MRIs were reviewed for measures of tumor invasiveness: size, extra-compartmental extension, peritumoral edema, central hemorrhage/necrosis, peripheral growth pattern, and apparent vascular invasion.

Outcome measures including overall survival (OAS), disease free survival (DFS), local and distant failure rates, and time to local and/or distant failure were collected. Statistical analysis was performed with a paired student t-test for pre- and post-RT MRI comparisons and one-way ANOVA for effect of the categorical and ordinal MRI measures (in the initial pre-treatment tumor images) on outcomes.

Results: In assessing the effect of RT, post-radiation images were found to have significantly more peritumoral edema and central non-enhancement than the corresponding pre-RT images (p=0.001). However, no significant difference was found in average tumor size (p = 0.90), extra-compartmental extension (p = 0.08), peripheral growth pattern (p = 0.10) or vascular invasion (p = 0.08). Radiological vascular invasion on pre-RT MRI was the only significant predictor of a poorer outcome in our population, with a 53% reduction in quantitative OAS (p = 0.03) and an 83% reduction in quantitative DFS (p = 0.02). None of the other MRI measurements were found to be significantly predictive of decreased survival.

Conclusion: In conclusion, edema and central non-enhancement are the only factors which increased significantly following pre-operative radiotherapy in STS patients, in agreement with well-known radiotherapeutic treatment effect. Radiological evidence of vascular invasion on pre-RT MR imaging portends decreased overall and disease-free survivals, though the other MRI parameters studied do not demonstrate an effect on clinical outcomes in our population. Larger study cohorts and studies evaluating integrative scoring indices of MRI invasiveness may be more helpful in clarifying the role of these measures in the prognosis of soft tissue sarcoma.

Table 1

	Pre-RT Average	Post-RT Average	P-value
Tumor Size (cm)	11.26	11.19	0.90
Extracompartmental Extension	55.26%	63.16%	0.08
Peritumoral Edema (3-pt scale)	1.53	2.21	<0.0001
Central Non-Enhancement (3-pt scale)	2.16	2.63	<0.0012
R-inf	86.84%	84.21%	0.32
Peripheral Growth Pattern (3-pt scale)	1.97	1.87	0.10
Vascular Invasion	18.42%	10.53%	0.08

Radiological measures of tumor invasiveness and their average measurements on both pre-radiotherapy and post-radiotherapy MR imaging, accompanied by p-values (paired t-test). These parameters largely remained insignificantly different after radiotherapy, excepting the significant increased in peritumoral edema and central non-enhancement.

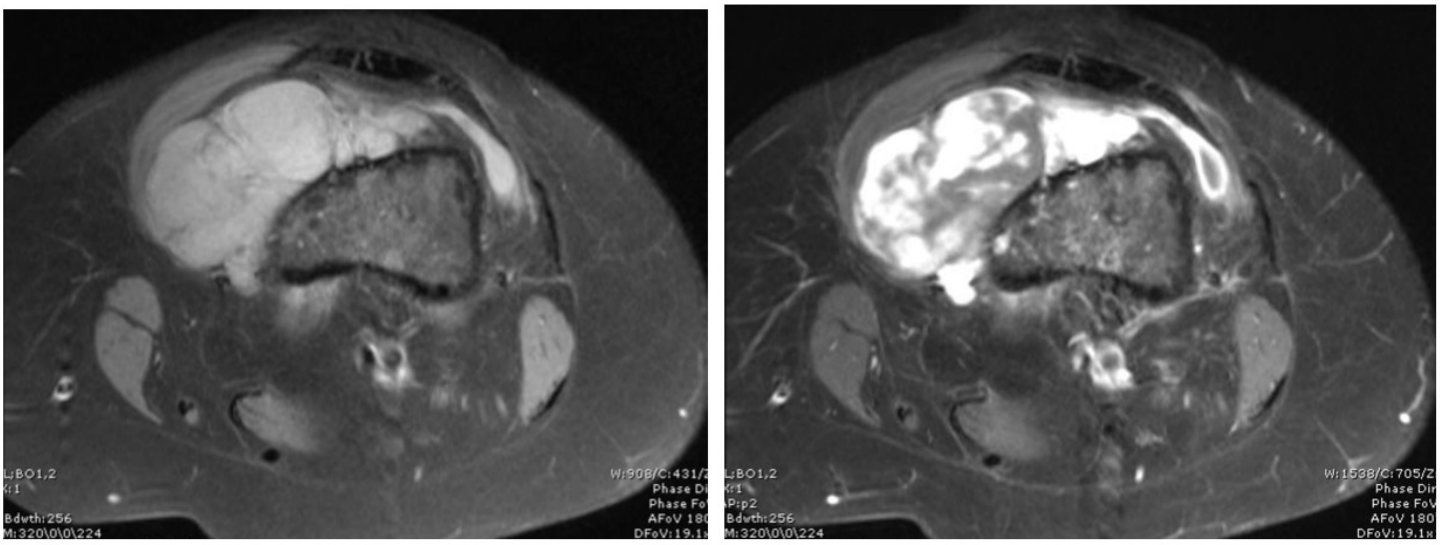

Figure 1. Representative axial slice on pre- and post-contrast T1 imaging sequence revealing a heterogeneously enhancing tumor of the left lower extremity anterior and medial to the distal left femur. Radiological infiltration (“r-inf”), which is equivalent to a “2” on our peripheral growth pattern scale, is exhibited by a peripherally enhancing lateral extension of the tumor from an otherwise largely circumferential tumor border.

Poster 367 3042496

PHASE 1 TRIAL OF PREOPERATIVE IMAGE GUIDED INTENSITY MODULATED PHOTON RADIATION THERAPY (IMRT) WITH SIMULTANEOUSLY INTEGRATED BOOST TO THE HIGH-RISK MARGIN FOR RETROPERITONEAL SARCOMAS

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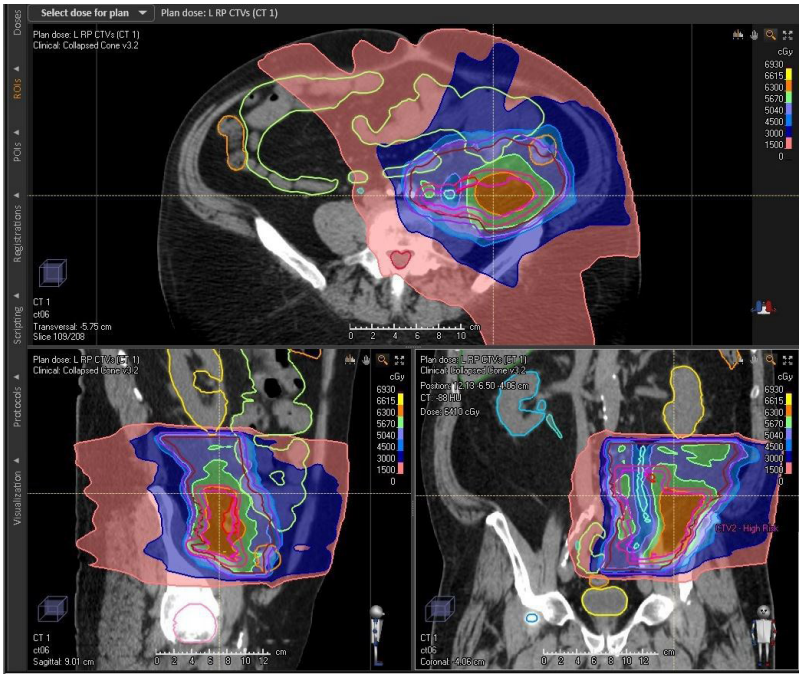
[1]Radiation Oncology, Massachusetts General Hospital, Boston, MA, USA; [2]Radiation Oncology, University of Utah, Huntsman Cancer Institute, Salt Lake City, UT, USA; [3]Radiation Oncology, Roswell Park Memorial Cancer institute, Buffalo, NY, USA; [4]Cancer Center, Massachusetts General Hospital, Boston, MA, USA; [5]Surgical Oncology, Roswell Park Memorial Cancer institute, Buffalo, NY, USA; [6]Radiation Oncology, Duke University Medical Center, Durham, NC, USA; [7]Radiation Oncology, Washington University Medical Center, St. Louis, MO, USA; [8]Radiation Oncology, Brigham and Women's Hospital/Dana Farber Cancer Institute, Boston, MA, USA; 9. Radiation Oncology, Rush University Medical Center, Chicago, IL, USA; [10]Surgical Oncology, Massachusetts General Hospital, Boston, MA, USA; 1[1]Surgical Oncology, Duke University Medical Center, Durham, NC, USA

Objective: To conduct a phase I/II trial with photon IMRT and proton IMPT arms to selectively escalate retroperitoneal sarcoma (RPS) preoperative radiation dose to a clinical target volume (CTV2) judged by the treating surgeon and radiation oncologist to be at high risk for positive margins, aiming to reduce the risk of LR. We have previously reported the proton IMPT phase I study arm and here present the photon IMRT phase I study arm.

Methods: Patients > 18 years with primary or locally recurrent RPS were entered on study and treated with preoperative IMRT. 50.4 Gy in 28 fractions of 1.8 Gy was delivered to the average risk clinical target volume (CTV1) encompassing the GTV and adjacent tissues at risk of subclinical disease. A simultaneous integrated boost was delivered to CTV2 to doses that were sequentially escalated from 60.2 Gy to 61.6 Gy and 63.0 Gy in 28 daily fractions of 2.15, 2.20, and 2.25 Gy respectively. Normal tissue constraints employed are those estimated to be tolerable. Phase I study primary objective was to reach the target dose of 63.0 Gy to CTV2 or, if not achievable with acceptable toxicity, to determine the maximum tolerated dose (MTD) of IMRT radiation to CTV2, which would then be further tested in the follow-on phase II study.

Results: Ten patients were accrued to increasing protocol IMRT dose levels. Dose was successfullly escalated to the target dose of 63 Gy to CTV2 without acute dose limiting toxicities (DLTs). Acute toxicity was generally mild with no radiation interruptions. One patient at dose level 1 developed peritoneal dissemination of tumor, noted on restaging scans after preop RT, and did not undergo surgery. Nine patients, three at each dose level, underwent resection. No unexpected perioperative morbidity was noted.

Conclusion: IMRT dose escalation to CTV2 to 63 Gy was achieved without acute DLT; phase II IMRT study will accrue to that dose. The parallel IMPT phase II arm has been accruing at that dose of 63 GyRBE to CTV2 since January 2016.



IMRT treatment plan delivering 50.4 Gy to average risk CTV1 and 63.0 Gy to the high-risk CTV2 in a protocol patient receiving preoperative radiation for a locally recurrent dedifferentiated left retroperitoneal liposarcoma.

Poster 368 3042574

NOVEL THERAPY WITH 103PD-DIRECTIONAL BRACHYTHERAPY DEVICE FOR RECURRENT SOFT TISSUE SARCOMAS: SAFETY AND EARLY POSTOPERATIVE OUTCOMES

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Objective: Recurrent soft tissue sarcomas (STS) are frequently associated with poor regional control and high relapse rates despite aggressive treatment. Conventional external beam radiation (EBRT) and boost dosing remain controversial due to concerns regarding toxicity to the surrounding structures. The CivaSheet® (CivaTech Oncology Inc., Durham, NC) is a novel alternative radiotherapy device that may facilitate highly localized radiation delivery while limiting toxicity to organs at risk. However, evidence reporting its safety and postoperative outcomes are lacking. Herein, we also describe intraoperative details, dosimetric analysis and postoperative radiological aspects after device implantation.

Methods: From March to June 2018, three patients with recurrent STS underwent resection with intraoperative brachytherapy and were prospectively reviewed at our Institution. CivaSheet®, an implantable unidirectional palladium-103 (^{103}Pd) planar low-dose brachytherapy device, was used. Following tumor resection, the device was sewn into the tumor cavity with 3-0 Prolene sutures. Postoperative imaging of the implanted membrane were obtained for dosimetric analysis and surveillance.

Results: Mean age was 42 years (19-63 years) and there were 2 females. Mean tumor size was 7.6 cm (4.5-13.5 cm). All patients underwent preoperative radiation with mean dosimetry of 56.1 Gy (30-72.4 Gy). Pathology included recurrent high-grade pleomorphic liposarcoma involving the vertebral body, recurrent dedifferentiated liposarcoma involving the left psoas muscle and recurrent phyllodes tumor of the right breast and chest wall. Surgical resection included right posterolateral thoracotomy with right lower pneumonectomy, laparotomy with left colectomy, and radical mastectomy with partial chest wall resection. Mean intraoperative brachytherapy dose was 40.7 Gy (38.6-43.4 Gy) at 5 mm from the surface of the device. The surgical margins were negative in all cases. There were no intra- or postoperative complications. Mean hospital stay was 7.3 (4-12) days. Mean follow-up was 65 (34-108) days and there is no evidence of recurrence to date.

Conclusion: The device was well tolerated in all patients and allowed irradiation of potential microscopic disease within the tissue immediately overlying the tumor cavity. The device may be of value especially in cases in which local control is suboptimal after resection and wherein existing techniques for the delivery of radiation therapy are inadequate. Advantages of the CivaSheet® included its ease of visualization with imaging, potential for intraoperative customization, ease of implantation with minimal training and radiation delivery in patients with prior history of EBRT. Despite relatively small number of patients, this is the largest series assessing the clinical utilization of ^{103}Pd device in patients with recurrent STS to date. Further experience with larger series and longer follow-up is warranted for widespread use.

Poster 369 3042878

TOMOTHERAPY IMRT IN MANAGEMENT OF EXTREMITY SOFT TISSUE SARCOMAS - 8 YEARS' EXPERIENCE, NORTHERN CENTRE FOR CANCER CARE, FREEMAN HOSPITAL

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Objective: Radiotherapy plays an important role in the treatment of soft tissue sarcomas (STS). IMRT is an advanced radiotherapy technique which enables delivery of a highly conformal dose to the target whilst sparing surrounding normal tissue. In the UK, a phase II clinical trial (IMRiS) is currently assessing the feasibility, efficacy and toxicity of IMRT in patients with bone and soft tissue sarcomas.

The NCCC was one of the first NHS centres in the UK to commission a Tomotherapy planning and delivery unit. Since 2009, all soft tissue sarcomas identified at the North of England Bone and Soft Tissue Sarcoma MDT as requiring radiotherapy have been treated with Tomotherapy based IMRT, as this was considered a distinctive solution to treating long treatment fields with IMRT.

We have undergone a retrospective review of patients treated with Tomotherapy based IMRT between March 2009-October 2017. The primary aim of this study is to assess out 5-year local control rates compared to modern series. Secondary aim is to evaluate if planning target volumes and organs at risk doses from our series meet the IMRis trial requirements.

Methods: Retrospective review of patients with extremity soft tissue sarcomas treated with Tomotherapy based IMRT between March 2009-2017, identified from our departmental database. Treatment target volumes and organs at risk delineation was done as per local protocol – for extremity sarcomas, this matched the VORTEX trial protocol. Pre operative radiotherapy was delivered using 50GY in 25 fractions. Post operatively the dose consisted of 60Gy in 30 fractions, which was initially delivered in a 2phase shrinking field technique. In recent years, this has been delivered using a concurrently with an integrated boost. Kaplan Meier method was used to estimate 5 year local recurrence rates.

Results: 45 patients with extremity soft tissue sarcomas were identified, with a median age of 57. 60% of patients had a tumour size of >=10cm. 76% of patients had high grade STS. N=18 were treated with a concomitant integrated boost. Over a median follow up of 50 months, local recurrence was seen in 4 patients. Estimated 5 year local recurrence rates using Kaplan Meier method was 8%.

Summary of dosimetry data comparison to IMRiS:
Target/OAR Dose IMRis trial requirement % Achieved (NCCC)
PTV high dose volume D98>90% 98%
PTV high dose volume D95>95% 98%
PTV low dose volume D98>90% 98%
PTV low dose volume D95>95% 98%
Normal tissue limb V20Gy <50% 62%
corridor
Mean Femur Dose Mean Dose <40Gy 91%
Mean Femoral Head Dose Mean Dose <40Gy 91%

Conclusion: These results show that our 5 year local recurrence rates are very comparable to international published data. In comparison to IMRis phase II trial, PTV dose targets were achieved in most patients. Normal tissue limb corridor dose constraints (V20Gy<50%) was met in 62% of patients – outlining and positioning the normal tissue limb corridor using an IMRT technique has been a learning curve for our unit. Another reason why the corridor dose may be higher is the fact that we use a complete contralateral leg block for most patients in our centre.

Poster 370 3041714

COMPLETION RATE AND TOXICITY OF HYPO-FRACTIONATED RADIOTHERAPY FOR RETROPERITONEAL AND PELVIC SOFT TISSUE SARCOMAS

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Objective: Retroperitoneal and pelvic soft tissue sarcomas are difficult tumors to resect with wide margins, thus incurring a high risk of local recurrence. Treatment frequently includes neoadjuvant radiation (RT) to improve local control. Standard neoadjuvant RT typically takes 5-6 weeks to complete. Hypo-fractionated RT may be an appealing alternative in that it allows patients to complete their course of treatment in a shorter amount of time, with potentially fewer unintended interruptions. This study examines patients receiving standard or hypo-fractionated RT for local control of these sites. We report completion of treatment, toxicity and surgical margins.

Methods: An IRB approved review was undertaken of a prospectively collected database initiated 11/2017. Of the 199 patients with histologically confirmed sarcomas collected at our institution, patients who did not receive neoadjuvant RT, non-retroperitoneal or pelvic sites, or missing data were excluded from analysis. Thus, 26 patients remained who were treated with RT to a primary or recurrent tumor of the retroperitoneum/pelvis for local control with or without intended surgical resection. Patients with standard palliative radiotherapy courses not planned for surgical resection were excluded. Patients treated to standard doses of 44-57.5 Gy given in 22-28 fractions were defined as a standard RT cohort. Patients treated to hypo-fractionated course ranged from 20-39 Gy given in 5-13 fractions. The primary endpoint of the study was acute toxicity (CTCAE v 4.03, ≤ 90 days from RT). Treatment tolerability and surgical margins were evaluated as well. Toxicity records and surgical margins were obtained from patient notes and surgical pathology respectively.

Results: Overall median age was 58.3 years (range 42-80). Ten of the 26 patients had disease involving the pelvis, while the remaining 16 had retroperitoneum disease. The most common histology was leiomyosarcoma (35%), and median tumor size was 12.6 cm (range 2.2- 27). Seven (27%) patients received hypo-fractionated RT and 19 (73%) received standard RT. All standard RT patients successfully completed their course without any interruptions. One of the 7 hypo-fractionated RT

patients did not complete the course as the patient opted to go to hospice prior to RT completion. Twenty (77%) of the 26 patients had surgery after RT as intended; 2 in the hypo-fractionated RT group and 18 in the standard RT group. Surgical margins were positive in 1 of 2 patients in the hypo-fractionated RT group, while 22.2% (4 of 18) in the standard RT group had positive margins. No patients experienced ≥ grade 3 toxicity. Within the hypo-fractionated RT group, 14.29% of patients experienced grade 2 toxicity of any kind, while 31.58% of standard RT patients experienced grade 2 toxicity of any kind; p = 0.7261. Analysis of GI toxicities (upper and lower) showed 14.29% of hypo-fractionated patients experienced GI toxicity (grade ≥ 1), while 47.37% of standard RT patients experienced GI toxicity (grade ≥1); p = 0.1904.

Conclusion: Our institutional review shows that both hypo-fractionated and standard RT was well tolerated with no grade 3 or higher toxicities in either group. In our limited series, hypo-fractionated RT was well tolerated, additionally, those patients intended for curative surgical resection completed resection as originally intended. The hypo-fractionated cohort of patients incurred less toxicities compared to standard RT, however, this was not statistically significant. Study limitations include the small size and limited follow-up, further research is needed to clarify the potential equivalence of hypo-fractionated RT relative to standard RT in the setting of retroperitoneal/pelvic sarcomas.

Poster 371 3042784

EFFICACY AND SAFETY OF STEREOTACTIC BODY RADIATION THERAPY SBRT WITH CONCURRENT TRABECTEDIN IN METASTATIC SOFT-TISSUE SARCOMA PATIENTS. A SINGLE INSTITUTION EXPERIENCE

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Objective: This report is an observational study, to evaluate whether treatment with Trabectedin (T), administered in association with stereotactic body radiation therapy (SBRT) in patients with metastatic soft-tissue sarcomas (STS), is effective and safe.

Methods: We retrospectively analyzed data patients treated at our institution with SBRT to metastatic lesions and concomitant Trabectedin between 2009 and 2017. Trabectedin was administered at a dose of 1.5 mg/m2 in 24-hour infusion, every 21 days. SBRT was considered associated to radiotherapy when it was delivered in a time interval of no more than 5 weeks from last cycle of chemotherapy. Radiotherapy was delivered with Volumetric Modulated Arc Therapy (VMAT). Prescription dose and number of fractions varied according to tumor location and size. We evaluated overall response rate using Response Evaluation Criteria in Solid Tumors version 1.1. Pain response was assessed according to Numerical Rating Scale (NRS). Radiotherapy-related adverse events were scored according to Common Terminology Criteria for Adverse Events scale version 4.03 and RTOG Common Toxicity Criteria.

Results: Between March 2009 and April 2017 a total of 23 metastatic STS patients were treated with concurrent trabectedin and SBRT for distant metastases, of these only twelve patients had a follow up of at least 3 years. Median age was 47.5 years (range 19-68). Histopathologic subtypes were leiomyosarcoma (33.3%), spindle and pleomorphic sarcoma (25%), synovial sarcoma (8.3%), pleomorphic liposarcoma (8.3%), pleomorphic sarcoma (8.3%), spindle sarcoma (8.3%) and malignant peripheral nerve sheath tumor (8.3%). Four (33.3%) patients had metastases at diagnosis. Mean number of chemotherapy lines received prior to Trabectedin was 1 (range 0-2). Eight (66.7%) patients had undergone a prior neoadjuvant or adjuvant treatments. Sites of metastatic disease treated were: bone (50%), soft tissue (25%), lung (16.7%), lymph nodes (8.3%). Metastases-related pain was present in seven (58.3%) patients, with a mean NRS value before SBRT of 5.28 (range 2-8). Before SBRT patients received a median number of 2.5 (range 0-9) chemotherapy cycles. Most common Grade 3 or more adverse events were hematological; anemia, thrombocytopenia and transaminase elevation represented 25%, 8.3% and 8.3% of cases, respectively. Radiation therapy-related adverse events were represented by dermatitis of Grade 2 or less in 16.6% of cases and by one case of pathologic bone fracture. After a median follow up of 39.4 months, 9 (75%) patients had stable disease (SD) and 3 (25%) patients had disease progression (PD). The median time to progression (TTP) was 34 months. Three months after SBRT, patients were asked to evaluate their pain according to NRS and median score was 1.85 (range 0-4).

Conclusion: In this report the association of Trabectedin and local treatment of metastatic disease with SBRT in STS patients was safe and resulted in a good local control. The toxicity was similar to the toxicity profile of each treatment administered alone. Nowadays the association of trabectedin and radiotherapy is not the standard, prospective trials are needed to confirm our results.

Poster 372 3042873

OPTIMIZING TREATMENT DECISIONS FOR PATIENTS WITH EXTREMITY SOFT TISSUE SARCOMA (STS): INDIVIDUAL IDENTIFICATION OF RESPONDERS TO AJDUVANT RADIOTHERAPY (AXRT).

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Objective: When adequate margins cannot be achieved circumferentially in the surgical resection of an extremity STS, aXRT is used, either pre- or post-operatively, to sterilize tumor cells which are potentially left behind in-situ *[ESMO, 2014; NCCN, 2016]*. According to the national cancer data base, 50% of the patients with negative margins receive adjuvant radiotherapy.

Despite the potential benefits of aXRT in minimizing local tumor recurrence following excision of extremity STS, radiation is known to be associated with impaired wound healing, fibrosis, edema, joint stiffness, pain and potentially second malignancy. Therefore, it is generally recommended that aXRT be reserved for patients at high risk of local recurrence (LR). However, patients at high risk of LR are not necessarily those for whom aXRT will be effective.

The goal of our study was to develop a statistical model which allows identification of patients who are most likely to benefit from aXRT from a large cohort operated on for a localized extremity STS with negative margins.

Methods: In this single center cohort study using prospectively collected data, 1057 patients underwent surgical treatment for a primary, localized, STS of the extremity or trunk with negative resection margins. Atypical lipomatous tumors, DFSP and myxoid liposarcomas were excluded. 704 (67%) patients received aXRT and 353 (33%) did not. Patients were significantly more likely to receive aXRT if the tumor was large, deep and high grade. The cumulative 10-year LR rate was 9.6% (95% CI: 7.2% to 12.4%) for the entire group, 7.8% in the “aXRT” group and 14.1% in the “no aXRT” group.

According to our newly developed model (based on the principal stratification framework and propensity score analysis using inverse probability of treatment weighted analysis), patients are classified into one of three groups: **always healthy** are patients who will never recur locally whether or not they are given aXRT; **always recurrent** are patients who will always recur locally with or without aXRT; and **responders** are patients who will recur locally if they are not given aXRT but will not recur if they are given aXRT. The premise is that aXRT should ideally only be given to responders.

Results: Overall 8.3% (95% CI: 2.3 to 14.2) of patients were considered to be **responders**, 84.4% were classified as **always healthy**, and 7.3% as **always recurrent** (Table 1). In the present study, 8% of the patients chosen for aXRT were **responders** compared to 8.8% in the no aXRT group (Table 1). For each patient the probability to be “**responder**”, “**always healthy**”, or “**always recurrent**” was estimated; an example is provided for 10 patients ordered by quantiles of the probability being a responder (Table 2).

Overall 75% of the patients had 10% or less chance of being a **responder** (Figure 1). Patients considered to have high risk tumors for LR (high grade, deep and >5cm) demonstrated little chance of response to aXRT (Figure 2). Figure 3 shows the average treatment effect/difference (ATE, equivalent here as the proportion of responders). The ATE ranges from 8.4% when treating all patients to 26.3% when treating only the 4% patients with highest predicted probability of being a responder. If the 34% of patients the most lilkely to respond to aXRT according to our model were given aXRT, the anticipated 10 year LR would be 9.6%. This latter LR rate is the same as the one observed in the present cohort where 66% of the patients received aXRT.

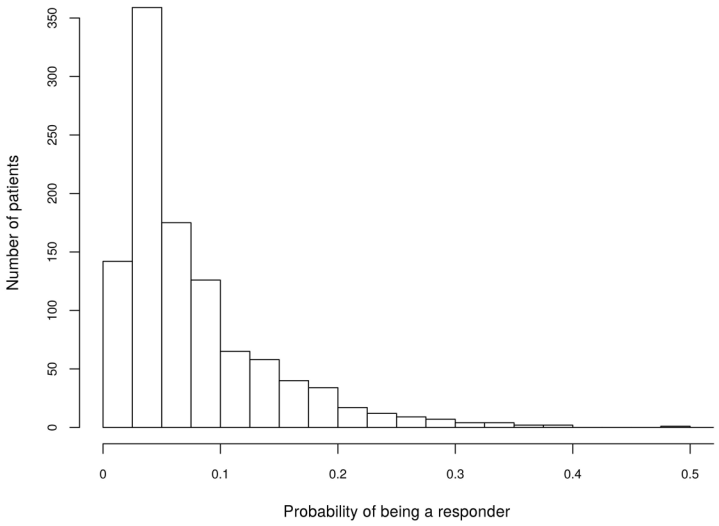
Conclusion: We developed a novel model to allow identification of individuals with extremity STS most likely to benefit from aXRT. However it appears that less than 10% of patients operated on for a localized STS with negative margins would be considered to be responders to aXRT. Using individualized predictors of patient response to assign the need for radiotherapy could help in decreasing the frequent use of this adjuvant therapy and its accompanying side effects without threatening the current high rates of local control.

Table 1. Probabilty of strata membership for all patients, patients receiving aXRT, and patients denied aXRT

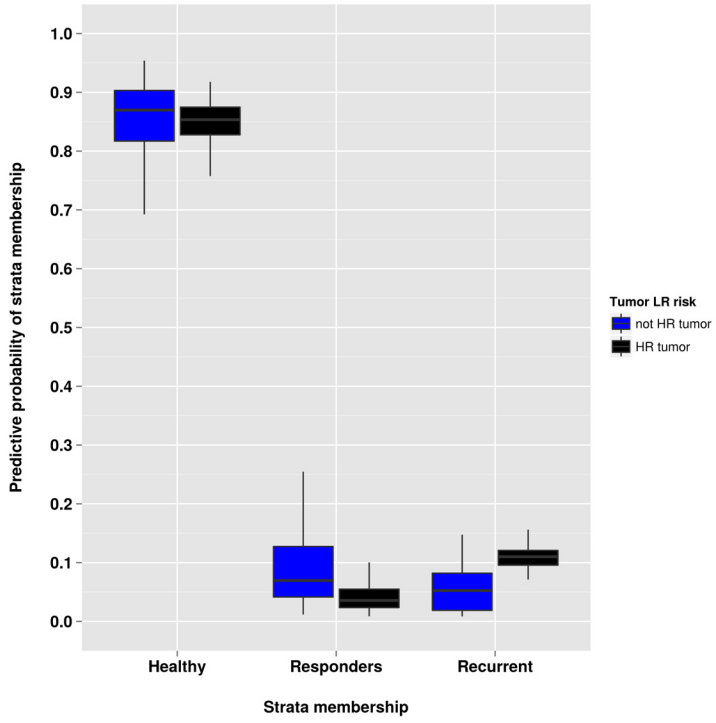
	All patients (n=1057)	aXRT (n=704)	no aXRT (n=353)
Responders	8.3% (2.3 to 14.2)	8.0% (0.9 to 15.1)	8.8% (3.4 to 14.2)
Always healthy	84.4% (78.9 to 89.9)	84% (77.3 to 90.8)	85.1% (80.6 to 89.6)
Always recurrent	7.3% (5.0 to 96)	7.9% (5.6 to 10.2)	6.1% (3.0 to 9.2)

Table 2: Probability of principal strata membership for 10 patients. Patients were chosen from quantile position along ordered responder probabilities.

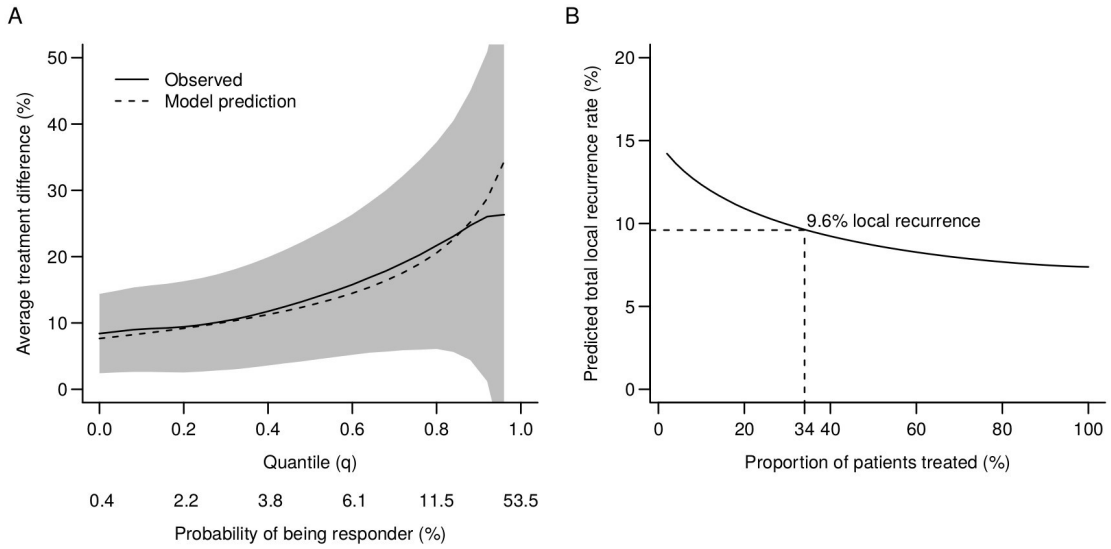
Quantile	Pr (always healthy)	Pr (responder)	Pr (recurrent)
0	90.5%	0.9%	8.7%
0.1	88.1%	2.2%	9.7%
0.2	88.9%	2.9%	8.2%
0.3	95.2%	3.6%	1.2%
0.4	86.8%	4.4%	8.8%
0.5	87.1%	5.2%	7.7%
0.6	82.8%	6.8%	10.4%
0.7	82.7%	8.6%	8.8%
0.8	78.2%	11.5%	10.3%
0.9	81.7%	16.7%	1.6%
1	50.4%	48%	1.6%



Histogram showing the probability of being a responder for all patients.



Predictive probabilities of being a responder according to the tumor risk profile (high risk being tumors larger than 5cm, of high grade, and deep seated).



A) The average treatment difference is plotted as a function of only treating patients with a probability of response superior to some level. The average treatment difference is 9.4% (95% CI: 2.5% to 16.3%) if patients with 2.2% chance or more of being responders (80% of the patients) are treated, 13.6% (95% CI: 4.4% to 22.8%) if patients with 4.8% chance or more of being responders (50% of the patients) are treated, and 21.6% (95% CI: 6.1% to 37.2%) if patients with 11.5% chance or more of being responders (20% of the patients) are treated. B) Corresponding estimated 10 year local recurrence rates as a function of only treating patients with a probability of response lower to some level. If only the 34% patients with the best probability of response are given adjuvant radiation, the estimated 10 year local recurrence rate is 9.6% as in the cohort where 66% of patients received adjuvant.

Poster 373 3042826

ANGIOSARCOMA OF THE SCALP AND FACE TREATED WITH HIGH-DOSE-RATE SURFACE APPLICATOR (HDR SA) BRACHYTHERAPY

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Objective: Angiosarcoma of the scalp and face is difficult to control locally due to its often multifocal presentation and propensity for regional recurrences. For this reason, surgery is frequently not performed. External beam radiation therapy fields cover large areas, which can deliver unintended doses to underlying brain or other nearby critical structures. High-dose-rate surface applicator (HDR SA) brachytherapy enables optimal dose conformality over complex surfaces with minimal dose to nearby organs at risk (Figure 1). The purpose of this study was to review outcomes for patients with angiosarcoma of the face or scalp treated with HDR SA brachytherapy during the course of their treatment.

Methods: We reviewed patients with both primary and recurrent angiosarcoma of the face or scalp diagnosed between 1/1/2000 and 12/31/2017 who received HDR SA brachytherapy as part of their local treatment. Prescription dose was 51 Gy in 17 fractions using Iridium-192 delivered to a depth of 3mm (or to the base of the lesion) and with at least a 5 cm clinical target margin radially, with a goal of treating to the point of moist desquamation by the end of treatment. Locoregional recurrence (LRR) after brachytherapy was defined as time from brachytherapy treatment to locoregional recurrence. Three types of LRR rates were recorded: in-field LRR, marginal LRR (within 2 cm of field edge), and discontiguous LRR (>2cm from field edge). Overall survival (OS) was defined as time from diagnosis until death. LRR and OS rates were calculated using the Kaplan Meier approach.

Results: Twenty patients comprised the cohort of which 75% were male, 50% had multifocal disease, and 40% had tumors 5cm or larger. Median age at diagnosis was 66 (range, 45 to 85 years). At diagnosis, two patients had lymph node involvement and one had metastatic disease. Table 1 shows initial treatment for the cohort. Thirteen patients (65%) received initial chemotherapy (all taxane-based). Of the remaining 7 patients, 5 received chemotherapy at disease progression later in their treatment course and two patients did not receive any chemotherapy. Fifteen patients (75%) received brachytherapy

as part of their initial treatment course and 5 (25%) received brachytherapy at the time of recurrence. Four patients stopped brachytherapy prior to the intended dose: two stopped after 14 and 16 fractions, respectively, due to moist desquamation and two stopped after 5 and 7 fractions, respectively, due to failure to thrive. Of the 18 patients treated for ≥ 14 fractions, 15 (83%) experienced CTCAE v5.0 grade 3 radiation dermatitis (confluent moist desquamation), which typically healed within 2-3 weeks with conservative management. The remaining 3 patients experienced grade 2 radiation dermatitis (patchy desquamation).

Median follow up from HDR SA brachytherapy was 31 months (range 3-113 months) and median follow up from diagnosis was 49.5 months (range 7-122 months). Three-year rate of in-field LRR was 23% [95% CI: 7.8-56.8%], of marginal LRR was 20.2% [95% CI: 5.0-62.8%], and of discontiguous LRR was 23% [95% CI: 7.8-56.8%]. One patient had distant metastases (DM) at diagnosis, 4 had DM at time of brachytherapy, and 3 developed DM after brachytherapy. Median overall survival was 71 months (IQR: 39-115 months). Overall survival rates at 3 and 5 years were 79.1% [95% CI 53.4-91.6%] and 61.6% [95% CI: 35.7-79.7%].

Conclusion: Although most patients develop confluent moist desquamation, HDR SA brachytherapy is an efficacious and well-tolerated local treatment alternative to external beam radiation for patients with angiosarcoma of the face and scalp. Improved systemic therapies are needed to further reduce marginal, regional and distant recurrences, all of which remain problematic.

Table 1. Initial treatment for 20 patients with angiosarcoma of the scalp or face.

Initial Treatment	N
Chemotherapy, Brachytherapy	7
Chemotherapy, Surgery, Brachytherapy	2
Chemotherapy	2
Chemotherapy, External beam RT	1
Surgery, Brachytherapy, Chemotherapy	1
Surgery, Brachytherapy	4
Brachytherapy	1
Surgery	1
Surgery, External beam RT	1

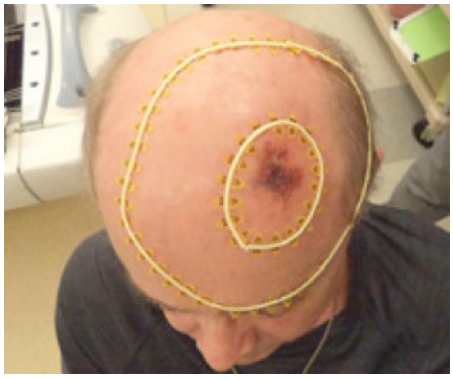

Figure 1. Example of high dose rate (HDR) surface applicator (SA) brachytherapy a) Angiosarcoma lesion of the scalp. Inner circle denotes extent of gross disease; outer circle denotes brachytherapy treatment field

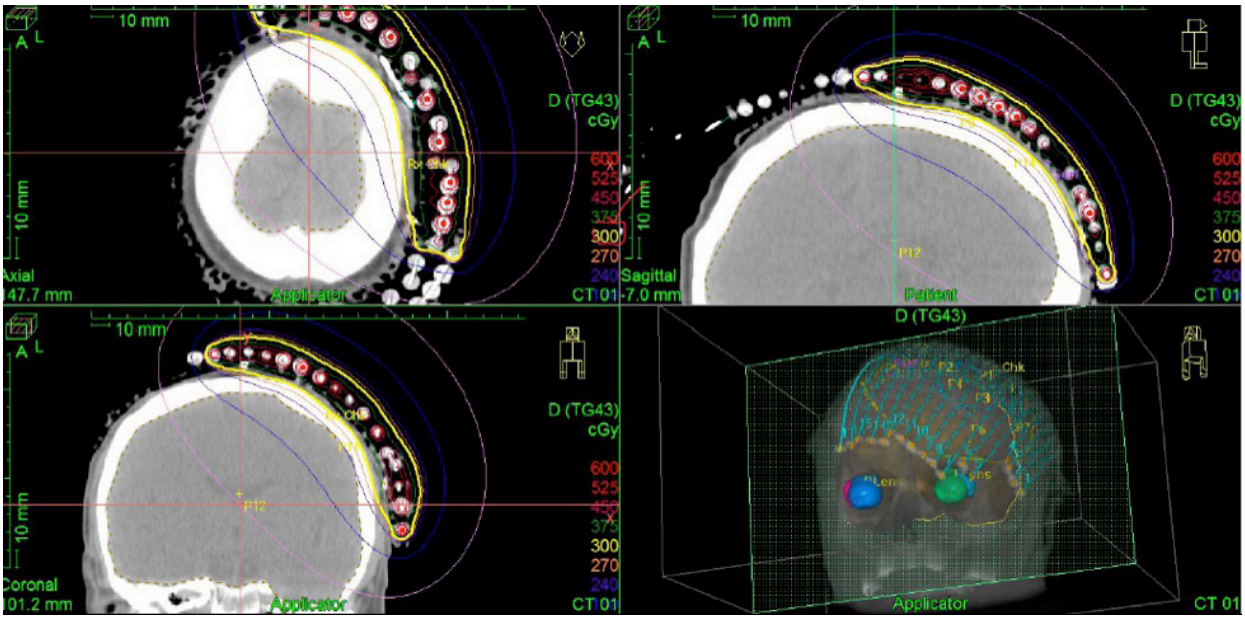

Figure 1. Example of high dose rate (HDR) surface applicator (SA) brachytherapy
b) HDR SA Brachytherapy plan showing multiple catheters covering the treatment field and dosimetry. The yellow line represents the prescription dose (100%); the cobalt blue line represents the 80% isodose line.

Poster 374 3042910

PREDICTORS OF LYMPH NODE INVOLVEMENT AND BENEFIT OF REGIONAL RADIOTHERAPY IN SOFT TISSUE SARCOMA

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Objective: While soft tissue sarcomas (STSs) commonly metastasize hematogenously, factors associated with higher lymphatic spread include certain histologic subtypes (e.g. rhabdomyosarcoma, epithelioid sarcoma, clear cell sarcoma, etc.). Due to the rarity of sarcomas, especially those with lymph node involvement, there is a scarcity of predictive data on this cohort of patients. We hypothesize that the use of a national database would yield sufficient power to identify predictors of lymphatic spread, and the potential overall survival (OS) benefit of regional radiotherapy.

Methods: The National Cancer Data Base (NCDB) was queried for adult patients between 2004-2014 with a diagnosis of soft tissue sarcoma, treated with radiotherapy with or without surgery. Radiotherapy (RT) targets were then subdivided to identify patients that also received regional RT. Clinicopathologic characteristics associated with lymph node positivity were compared via Pearson Chi-square and Mann-U-Whitney as appropriate. Overall survival was defined from date of diagnosis, estimated via Kaplan-Meier (KM) analysis with comparisons made via log-rank test. Histologies with a trending p-value (<0.2) were combined to improve predictive power in a cox regression multivariate analysis (MVA), which included variables: age, gender, grade, and Charlson-Deyo comorbidity score. All tests were two-sided and a significant value defined as $p<0.05$.

Results: A total of 26,256 patients were identified with a median follow-up of 40 months (0.4 – 155). Factors associated with LN positive disease includes: cT2 stage, male gender, non-low grade, and histology (e.g. epitheloid sarcoma, alveolar and embryonal rhabdomyosarcoma, clear cell sarcoma and primitive neuroendocrine tumor) (all $p<0.01$). The addition of regional RT was associated with a trending or significant benefit in the following histologies (giant cell sarcoma, undifferentiated sarcoma, mixed liposarcoma, dedifferentiated liposarcoma, myxoid leiomyosarcoma, pleomorphic rhabdomyosarcoma, and synovial sarcoma). The addition of regional RT to this primarily LN negative (96%) population (n=5156) was associated with an 8% absolute OS benefit at 5 years (57% to 65%, $p<0.01$), when compared to RT limited to the primary site, which continued its association on MVA (HR 0.80 95%CI 0.70-0.91, $p<0.01$) In patients with positive clinical or pathologic LNs, addition of regional RT had a trending improvement in OS for alveolar rhabdomyosarcoma (3-year OS: 58% vs. 30%, $p=0.051$) and malignant peripheral nerve sheath tumor (3 year OS 48% vs 28% $p=0.135$), when compared to primary site RT.

Conclusion: This large, population based study of patients with STS showed predictors of lymphadenopathy, and the potential overall survival benefit of regional RT in selected histologies. Further prospective studies are required to validate this hypothesis.

Poster 375 3018125

PENCIL BEAM SCANNING PROTON RADIOTHERAPY REDUCES DOSE TO THE PLANNED SURGICAL SKIN FLAP AND UNINVOLVED BONE IN PREOPERATIVE RADIOTHERAPY FOR SOFT TISSUE SARCOMAS OF THE LOWER EXTREMITY

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Objective: Over 40% of patients treated with pre-op radiotherapy for soft tissue sarcoma (STS) of the lower extremity develop severe wound complications. Reduced dose to the planned surgical skin flap and uninvolved tissues reduces the rate of severe wound complications. We compared photon and proton treatment planning for target coverage and dose avoidance to the planned surgical skin flap and uninvolved bone and soft tissues for STS of the lower extremity.

Methods: Plans were generated for 5 patients with deep, lower extremity STS treated with pre-operative radiotherapy. Plans consisted of volumetric arc radiation therapy (VMAT), passively scattered proton radiotherapy (PS) and pencil beam scanning proton radiotherapy (PBS). Target volumes were consistent with guidelines for RTOG 0630. Target volumes and OARs were contoured by a radiation oncologist specializing in sarcoma. Planned surgical flaps were contoured by an orthopedic oncologist. Planning goals were as follows: 1) ensure adequate target volume coverage, 2) achieve dose constraints to the planned surgical skin flap, and 3) avoid uninvolved bone. The prescription dose was 50 Gy in 25 fractions.

Results: The average mean dose to the planned surgical flaps was 38.3 Gy RBE (range, 28.1-45.6), 46.1 Gy RBE (range, 38.1-53.1), and 43.4 Gy RBE (range, 33.4-49.1) for the PBS, PS, and VMAT plans, respectively. The mean V30 of the surgical flap with PBS was 69.4% (range, 48.0-87.1%) compared to 86.8% (range, 72.7-98.9%) and 82.8% (range, 55.9-98.4%) with PS and VMAT, respectively. All patients had improved mean flap dose and flap V30 using PBS. Mean uninvolved bone V40 was 6.5% (range, 2.1-10.7%), 22.3% (range, 5.8-43.0%), and 14.6% (range, 2.1-37.8%) using PBS, PS, and VMAT, respectively. Mean bone dose was 17.2 Gy RBE (range 11.8-20.8), 14.4 Gy RBE (range, 4.4-26.1), and 21.7 Gy RBE (range, 13.7-33.3) with PBS, PS, and VMAT plans, respectively. The mean conformality index was 0.91, 0.67, and 0.87 for PBS, PS, and VMAT, respectively.

Conclusion: PBS achieved the lowest mean dose and V30 to the planned surgical flap, and the lowest bone V40 compared to PS and VMAT. It will be necessary to determine the clinical impact of if these dosimetric benefits.

Table 1. Individual patient dosimetry by radiotherapy technique.

	Mean dose to flap (Gy RBE)			Flap V30 (%)			Mean dose to bone (Gy RBE)			Bone V40 (%)		
Pt No.	PBS	PS	VMAT	PBS	PS	VMAT	PBS	PS	VMAT	PBS	PS	VMAT
1	28.1	38.1	33.4	48.0	72.7	55.9	20.8	9.1	17.8	5.2	14.2	7.7
2	45.6	53.1	49.1	87.1	98.9	92.6	11.8	4.4	14.1	2.1	5.8	2.1
3	42.1	48.3	47.1	74.1	90.3	90.5	19.9	26.1	33.3	10.7	43.0	37.8
4	38.3	46.1	47.7	69.7	84.1	98.4	14.5	20.4	29.7	5.4	29.9	17.9
5	37.1	44.8	39.6	68.3	87.9	76.6	18.8	12.1	13.7	9.3	18.7	7.4

Poster 376 3026104

PRELIMINARY DATA OF PROSPECTIVE PHASE II CLINICAL TRIAL WITH PREOPERATIVE HYPOFRACTIONATED RADIOTHERAPY (RT) IN PATIENTS WITH LOCALIZED MYXOID LIPOSARCOMAS

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Objective: Myxoid liposarcoma (MLPS) are considered to be more radiosensitive compared with other soft tissue sarcomas. The main objective of the study is to assess the efficacy of hypofractionated radiotherapy in neoadjuvant setting in patients with localized primary MLPS.

Methods: In this single-arm prospective clinical trial patients with locally advanced MLPS undergo preoperative 5x5 Gy RT with 6-8 weeks gap between RT end and surgery. The endpoints of the study are the rate of early wound healing complications and 5-year local control rate.

Results: Since the study start in May 2015 23 patients have been included: 20 finished the whole planned protocol treatment; 3 pts are awaiting surgery now. All but one of the patients had the tumors located on the lower limb. The median size of the tumor was 14.5 cm (range 5-20 cm), 40% of the patients had high grade tumors as assessed by FNCLCC and 40% of the patient had more than 5% od round cell component. Early RT tolerance was good. EORTC grade 1 radiation dermatitis developed in 10 pts and grade 3 in 1 patient. Postoperative wound complications occurred in 3 pts as wound dehiscence and prolonged wound healing. R0 margins were achieved in all but two patients, two patients had R1 resection margin. None of the patient had local recurrence, one patient developed distant metastases.

Conclusion: Preoperative hypofractionated RT with 6-8 weeks gap between the radiotherapy and surgery is a feasible method of the management of MLPS providing a good local control and low rates of treatment toxicity.

Poster 377 3042686

ADVANCED RADIATION TECHNIQUES TO PRESERVE FERTILITY IN FEMALE PATIENTS RECEIVING PELVIC RADIOTHERAPY FOR SOFT TISSUE TUMORS

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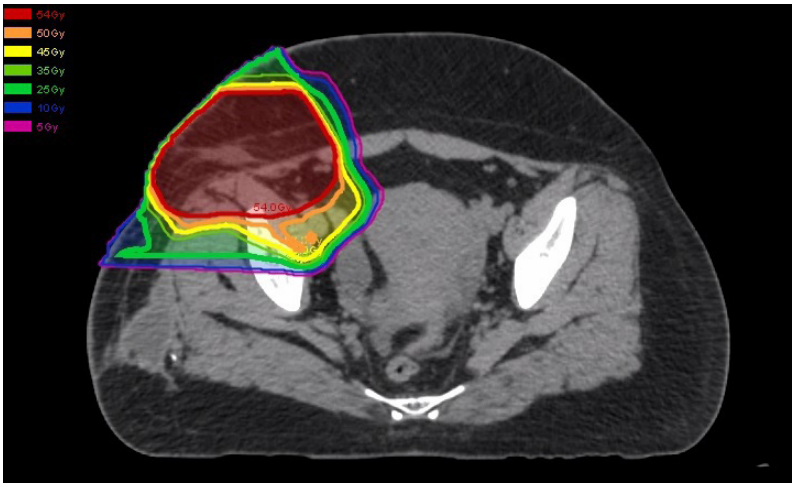
Objective: Female patients receiving abdominal/pelvic radiotherapy are at risk of permanent infertility due to adverse effects on ovarian and uterine function. Ovaries are particularly radiosensitive and can develop permanent dysfunction even after exposure to very low doses of radiation. Current fertility preservation strategies for female patients of childbearing age receiving pelvic radiotherapy involve egg harvest prior to treatment initiation, with possible subsequent need for surrogacy. Our study reports fertility outcomes in 4 patients who received radiotherapy to the pelvis in clinical situations in which the ovaries/uterus were adjacent to but not part of the tumor target volume.

Methods: This is a retrospective analysis of 4 female patients with pelvic soft tissue tumors (2 desmoid, 1 dedifferentiated liposarcoma, 1 undifferentiated high grade sarcoma) who were able to become pregnant after receiving radiotherapy to a portion of the pelvis for soft tissue tumors. Patients were treated from 2012 – 2016. Treatment planning was performed with the specific intention of limiting dose to the ovaries and uterus as much as possible without compromising target coverage. Patient ages at time of treatment were 25, 25, 27, and 34. Radiation doses from 50 – 64.35 Gy were delivered with conventional fractionation. Three patients were treated with protons and 1 patient was treated with Intensity-Modulated Radiation Therapy (IMRT).

Results: All 4 patients became pregnant after radiotherapy. Two patients delivered healthy babies and two are currently (as of 6/2018) in their third trimester without complications. One patient completed embryo preservation prior to treatment, but later became pregnant without medical assistance. No patients required medical intervention to become pregnant. Time from completion of radiotherapy to date of delivery (actual or estimated) was 10,24, 26, and 57 months (IMRT patient). Intrauterine growth restriction developed at 30 weeks in one patient; she delivered at 37 weeks without complication. All patients were followed in a high-risk obstetric clinic in coordination with their oncology care teams. Ovarian mean doses ranged from 1 – 320 cGy (maximum 11 – 970 cGy). Uterus mean doses ranged from 0 – 310 cGy, (maximum 0 – 4930 cGy). Patients treated with proton therapy did not experience alteration in menstrual cycles post-treatment. The patient treated with IMRT experienced ~ 1 year of irregular menses after treatment. No patients have developed tumor recurrences at 19, 26, 40, and 67 months after completion of radiotherapy.

Conclusion: Advanced pelvic radiation therapy techniques allow preservation of fertility without compromising oncologic treatment objectives. In patients with pelvic tumors that approximate but do not involve the uterus and ovaries, radiation dose to these critical reproductive organs may be limited by proton therapy or IMRT, allowing successful subsequent pregnancy. Mean and maximum radiation doses to these organs were lower among patients treated with protons compared to the patient treated with IMRT. While anecdotal, the more rapid conception by the three proton-treated patients suggests that the greater dose reduction to reproductive organs allowed by proton therapy may represent an additional benefit over IMRT in women of child-bearing age. This series demonstrates the feasibility of achieving fertility preservation with favorable oncologic outcomes by utilizing advanced radiation techniques that limit dose to the ovaries and uterus.



Example of a proton treatment plan covering a radiotherapy target volume that approximates the right ovary and uterus with minimal dose to these organs.

Poster 378 3042794

IS SURVEILLANCE IMAGING IN PAEDIATRIC PATIENTS TREATED FOR LOCALIZED RHABDOMYOSARCOMA USEFUL? THE EUROPEAN EXPERIENCE

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Objective: The event-free survival for patients with localized rhabdomyosarcoma (RMS) has increased over the last decades, however still up to one third of the patients experience a tumor relapse. Therefore patients with localized RMS are subject to intensive radiologic tumour surveillance after completion of therapy. During the first 5-years of follow-up patients undergo a total of 12 MRI's and 12 chest radiographs, however the clinical significance of surveillance is unclear. We aimed to analyze the value of this off-therapy surveillance, by retrospectively comparing survival of patients in whom relapse was detected by routine imaging to patients in whom relapse was first suspected by symptoms.

Methods: We included patients with relapsed RMS, after completion of treatment for localized RMS, treated in large paediatric oncology hospitals in France, the Netherlands, United Kingdom and Italy who were enrolled in either SIOP-MMT-95 (1995-2004), ICG-RMS96 (1996-2004) or E*p*SSG-RMS-2005 (2005-2013) studies. Survival time after relapse was compared by log-rank test between patients in whom relapse was detected by routine imaging (imaging group) and patients in whom relapse was first suspected by clinical symptoms (symptoms group).

Results: In total, 199 patients with relapsed RMS (treated in France, the Netherlands, United Kingdom and Italy) were included of which 78 patients (39.2%) had a relapse detected by routine imaging and 121 patients (60.8%) had a relapse detected because of clinical symptoms leading to additional imaging.
No significant differences in both groups were found concerning tumour characteristics previously shown to be associated with survival (see table). Median follow-up time after relapse was 7.4 years (IQR: 3.9-11.5 years) for survivors (n=86); 3-year post-relapse survival [95% CI] was 49.7% [38.3-61.1%] for patients detected by routine imaging and 45.9% [36.9-54.9%] for patients detected by clinical symptoms (p=0.65, see figure).

Conclusion: Although systematic routine imaging is standard of care after RMS treatment, the majority of relapsed patients were detected as a result of clinical symptoms. We found no survival advantage for patients with relapse detected by routine imaging, so before the emergence of clinical symptoms.

Based on the event-free survival rate in the E*p*SSG-RMS-2005 study and current follow-up recommendations (12 MRIs and 12 radiographs in the first 5 years of follow-up) we estimate that 112 scans of the primary site and 112 chest X-rays were needed to detect 1 asymptomatic patient with a relapse. Because patients with RMS are generally young, the majority of patients would also require general anesthesia, with subsequent risks, to generate good quality imaging. Furthermore, the repetitive surveillance imaging (and anesthesia) could induce stress and anxiety for patients and parents.

Therefore, based on the results of this study showing that the value of surveillance imaging is controversial, we believe that future studies should focus on risk-adapted follow-up strategies to improve the efficiency of follow-up.

Distribution of characteristics associated with survival based on the method of relapse detection.

	Routine imaging (n=78)		Clinical symptoms (n=121)		p-value
	No.	%	No.	%	
Histology					
Favourable	57	73.1	81	66.9	0.36
Unfavourable	21	26.9	40	33.1	
Tumour size					
≤5 cm	31	39.7	59	48.8	0.19
>5 cm	43	55.1	55	45.5	
Unknown	4	5.1	7	5.8	
Tumour site					
Orbit	9	11.5	25	20.7	0.16
Head & neck	6	7.7	12	9.9	
Parameningeal	19	24.4	28	23.1	
GU bladder-prostate	9	11.5	10	8.3	
GU nonbladder-prostate	11	14.1	6	5.0	
Limbs	12	15.4	14	11.6	
Other	12	15.4	26	21.5	
Type of recurrence					
Local	59	75.6	94	77.7	0.74
Metastatic with/without local	19	24.4	27	22.3	
Prior radiotherapy					
No	26	33.3	52	43.0	0.17
Yes	52	66.7	69	57.0	
Time to relapse					
	44	56.4	60	49.6	0.57
≥1.5 years	38	43.6	61	50.4	
Nodal status					
N0	63	80.8	99	81.8	0.94
N1	13	16.7	21	17.4	
Nx	2	2.6	1	0.8	
IRS group					
I	4	5.1	10	8.3	0.54
II	8	10.3	16	13.2	
III	66	84.6	95	78.5	

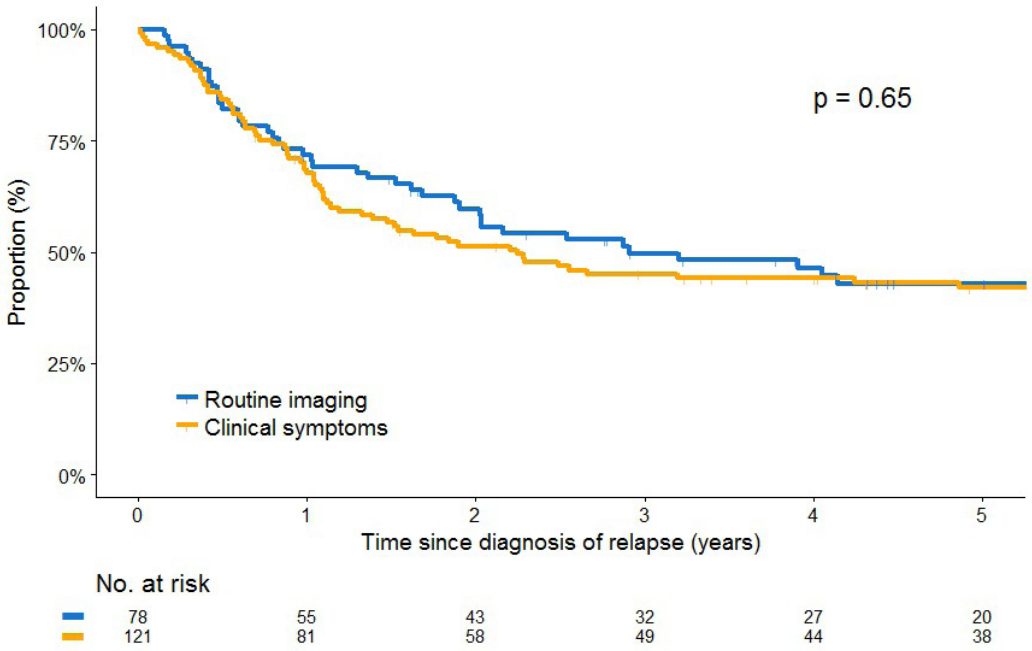

Figure showing post-relapse survival based on method of relapse detection.

Poster 379 3026152

MANAGEMENT OF PEDIATRIC PERITONEAL RHABDOMYOSARCOMATOSIS WITH CYTOREDUCTIVE SURGERY (CRS), HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY (HIPEC) AND WHOLE ABDOMINAL RADIOTHERAPY (WART)

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Objective: Peritoneal rhabdomyosarcomatosis represents a particularly pernicious form of high-risk rhabdomyosarcoma in children. In addition to chemotherapy and whole abdominal radiotherapy (WART), we employed cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) in its management. This case series documents the first 13 patients treated this way.

Methods: This was a retrospective analysis of a prospectively maintained database of patients who had undergone CRS/HIPEC for peritoneal rhabdomyosarcomatosis between January 2007 and January 2017. Demographic, disease and treatment-specific variables were analyzed in order to determine risk factors for disease development and outcome and specifically to determine if CRS/HIPEC, systemic chemotherapy and/or WART had any impact on recurrence free (RFS) and overall survival (OS). Survival times were calculated from the date of CRS/HIPEC. Survival outcomes were estimated using the Kapan-Meier method and compared using log rank test and the univariate Cox model.

Results: Thirteen patient were treated in the study period, totaling 14 CRS/HIPEC events. One patient was treated twice. Demographic and OS calculations were conducted on 13 patients however RFS calculations were on the 14 CRS/HIPEC events. Seven patients were male and 6 were female with a mean age of 7.5 years. Two had neurofibromatosis type I. Primary sites of disease included: genitourinary (GU) – 9, lower limb – 2, paraspinal – 1 and peritoneal – 1; all unfavorable sites. One lower limb and all GU primaries were of embryonal histology. Only the patient with the paraspinal tumor had a PAX3/FOXO1 fusion. At initial diagnosis, 4 had nodal and six distant metastases at diagnosis; six were IRS risk group 3 and the remainder risk group 4. All had VAC-based induction chemotherapy followed by delayed primary excision (DPE). All received adjuvant chemotherapy and all but two adjuvant radiotherapy. The median time from diagnosis to first disease recurrence and peritoneal recurrence was 15.1 months (range 0-40.9) and 15.1 months (range 0-90.9) respectively. Agents used for the 14 CRS/HIPEC events included cisplatin – 11, etoposide-2 and doxorubicin - 1. The median PCI was 22 (range 4-39). Cytoreduction was complete in 12/14 surgical events. All received post-operative systemic chemotherapy. Whole abdominal radiotherapy (WART) was given after four surgical events, five did not have WART and five had incomplete records. All but 1 of the post-WART recurrences were in the abdomen or pelvis. Log rank test and univariate Cox model suggest that WART was the only

Overall Survival

		N	Deaths	Median OS (95%CI)(months)	OS Rate at 1 year (95%CI)	p-value
GENDER	Female	6	4	5.12 (3.29 , NA)		0.206
	Male	7	5	7.8 (3.48 , NA)	0.333 (0.108 , 1)	
RESECTION STATUS	Completely Resected	2	2	4.96 (3.29 , NA)		0.348
	Positive Microscopic Margin	5	3	3.61 (3.48 , NA)	0.333 (0.067 , 1)	
	Positive Macroscopic Margin	6	4	7.49 (7.13 , NA)	0.2 (0.035 , 1)	
PRIMARY SITE	Lower Limb	2	2	5.09 (3.06 , NA)		0.454
	Bladder/Prostate	9	5	7.06 (3.48 , NA)	0.167 (0.028 , 0.997)	
	Paraspinal	1	1	3.61 (NA , NA)		
	Peritoneal	1	1	18.23 (NA , NA)	1 (1 , 1)	
HISTOLOGY	Alveolar	3	3	3.61 (3.06 , NA)	0.333 (0.067 , 1)	0.709
	Embryonal	10	6	7.13 (3.48 , NA)	0.143 (0.023 , 0.877)	
CCR AT HIPEC	No residual	11	7	5.12 (3.48 , NA)	0.25 (0.075 , 0.83)	0.981
	<0.25cm residual	1	1	7.13 (NA , NA)		
	0.25-2.5cm residual	1	1	7.49 (NA , NA)		
WART	No	5	4	5.06 (3.29 , NA)		0.018
	Yes	4	2	18.23 (7.49 , NA)	0.667 (0.3 , 1)	
TOTAL		**13**	**9**	**6.88 (3.48, NA)**	**0.2 (0.058, 0.691)**	

Table 1. Median overall survival of patients with peritoneal rhabdomyosarcomatosis following neoadjuvant chemotherapy, cytoreductive surgery, hyperthermic intraperitoneal chemotherapy, adjuvant chemotherapy and whole abdominal radiotherapy. Note that OS data is for 13 patients. (OS – overall survival; CI – confidence interval; CCR – completeness of cytoreduction; WART – whole abdominal radiotherapy)

variable associated with improved median overall survival (OS) (5.1 months (95% CI 3.29, NA) vs 18.23 months (95% CI 7.49, NA), p=0.018) and recurrence free survival (RFS) (1.6 months (95% CI 1.2, NA) vs 17.4 months (95% CI 7.49, NA), p=0.006).

Conclusion: Peritoneal rhabdomyosarcomatosis in children is most frequently of embryonal histology and GU in origin. Improvements in survival may be achieved with CRS-HIPEC but OS and RFS are significantly improved with post-operative WART.

Recurrence Free Survival

		N	Recurrences	Median RFS (95%CI)(months)	RFS Rate at 1 year (95%CI)	p-value
GENDER	Female	6	4	2.92 (1.61 , NA)		0.593
	Male	8	7	4.45 (1.54 , NA)	0.333 (0.116 , 0.961)	
RESECTION STATUS	Completely Resected	2	2	1.92 (1.61 , NA)		0.417
	Positive Microscopic Margin	5	3	3.61 (1.18 , NA)	0.375 (0.084 , 1)	
	Positive Macroscopic Margin	7	6	4.45 (1.54 , NA)	0.167 (0.028 , 0.997)	
PRIMARY SITE	Lower Limb	2	2	1.23 (0.92 , NA)		0.023
	Bladder/Prostate	10	7	4.45 (2.23 , NA)	0.167 (0.029 , 0.953)	
	Paraspinal	1	1	3.61 (NA , NA)		
	Peritoneal	1	1	17.44 (NA , NA)	1 (1 , 1)	
HISTOLOGY	Alveolar	3	3	3.61 (1.54 , NA)	0.333 (0.067 , 1)	0.975
	Embryonal	11	8	2.96 (1.61 , NA)	0.15 (0.026 , 0.868)	
CCR at HIPEC	No residual	12	9	3.29 (1.61 , NA)	0.25 (0.078 , 0.797)	0.002
	<0.25cm residual	1	1	0.92 (NA , NA)		
	0.25-2.5cm residual	1	1	7.49 (NA , NA)		
WART	No	6	6	1.61 (1.18 , NA)		0.006
	Yes	4	4	17.44 (7.49 , NA)	0.667 (0.3 , 1)	
TOTAL		**14**	**11**	**3.61 (1.61 , NA)**	**0.201 (0.06 , 0.676)**	

Table 2. Median recurrence free survival of patients with peritoneal rhabdomyosarcomatosis following neoadjuvant chemotherapy, cytoreductive surgery, hyperthermic intraperitoneal chemotherapy, adjuvant chemotherapy and whole abdominal radiotherapy. Note that RFS data is for 14 CRS-HIPEC events. (RFS – recurrence free survival; CI – confidence interval; CCR – completeness of cytoreduction; WART – whole abdominal radiotherapy)

Poster 380 3042806

EMBRYONAL AND ALVEOLAR RHABDOMYOSARCOMAS IN ADULTS: A SINGLE INSTITUTION RETROSPECTIVE ANALYSIS

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Objective: Embryonal and alveolar rhabdomyosarcoma (ERMS, ARMS) are subtypes of RMS that mainly occur in children with relatively good outcomes. Incidence in adults is extremely low and survival is significantly worse compared with children. Data on ERMS and ARMS solely in adults is scarce. Available literature mainly focusses on all RMS subtypes, including pleomorphic RMS, which primarily occurs in adults and behaves more like aggressive undifferentiated pleomorphic soft tissue sarcoma. The aim of this study was to evaluate patient and tumour characteristics, outcome and prognostic factors in adult patients with ERMS and ARMS.

Methods: All adult (18 years or older) ERMS and ARMS patients (presented 1990-2016) were identified from a prospectively maintained database and included in this analysis. Data collected from patient records included patient, tumour and treatment characteristics. In paediatric patients, favourable sites are considered head and neck (no parameningeal) and genitourinary (no bladder or prostate). Localized disease was considered a primary tumour with or without locoregional lymph node involvement.
Associations between RMS subtype and tumour, patient and treatment characteristics were determined. Median overall survival (OS) and recurrence-free survival (RFS) were calculated for patients with localized disease, median OS for patients with metastases at diagnosis. Univariate Cox proportional hazard regression analyses were performed to determine prognostic factors.

Results: Overall, 66 patients were included (42 male, 24 female). The median age at presentation was 28 years (range 18-71). Alveolar subtype was diagnosed in 42 patients and embryonal in 24 patients. Twenty-five patients (38%) had metastases at diagnosis. The most common site of origin was head and neck (36%). Treatment of the primary tumour involved surgery in 42%, chemotherapy in 92% and radiotherapy in 53% of all patients. Five patients did not receive chemotherapy in the early years of this cohort or because of poor performance status.
For several tumour and treatment characteristics, significant differences between ERMS and ARMS were found (Table 1).
The median OS for all patients was 18 months (95% CI 13-23) and the 5-year OS rate was 27%. Of all patients, 69% recurred or progressed with a median time to relapse of 11 months (95% CI 10-12). ARMS patients showed recurrence in 85%, whereas ERMS patients did in 50% of all cases (*p<.001*).
The 5-year OS in all ARMS patients was 11%, compared to 53% in ERMS patients (*p=.001*). Fusion-gene positive versus negative patients had a 5-year OS of 7% versus 69% (*p=.002*), respectively.
For patients presenting with localized disease (n=38, 58%), median OS was 30 months (95% CI 18-42). The 5-year OS rate was 36%. Over half of these patients developed local and/or distant recurrence (n=23, 61%). Among patients with localized disease who achieved a complete response (n=24, 63%), 14 remained disease-free (58%). Of all patients with localized disease, 13 developed local recurrence (34%). In these patients, recurrence within the radiotherapy field was present in 7 patients (6 with ARMS), absent in 4 and unknown in 2 patients.
Patients who presented with metastatic disease had a median survival of 11 months (95% CI 10-12) with a 5-year OS rate of 11%. All ERMS patients with metastases at diagnosis died within 5 years, of the 20 ARMS patients with primary metastases the 5-year OS rate was 14%.
With the restrictions of a univariate analysis, we found prognostic factors with a negative effect on survival (Table 2).

Conclusion: ERMS and ARMS are extremely rare in adults with only 66 cases over a 27-year period in a large tertiary referral centre. Survival is poor and local recurrence not uncommon. Protocols including both paediatric and adult patients will support better streamlining of therapies and give the opportunity to study biological and genetic factors in a prospective way. In addition, there is a need for novel active drugs.

Table 1. Tumour and treatment characteristics according to histological subtype.

	Embryonal RMS (n=24)	Alveolar RMS (n=42)	
	N (%)	N (%)	p-value (a)
Tumour site Favourable Head/neck Genitourinary Unfavourable Extremities Bladder/prostate Gynaecological Trunk Other	 9 (37.5) 2 (8.3) 7 (29.2) 15 (62.5) 5 (20.9) 1 (4.1) 6 (25.0) 1 (4.1) 2 (8.4)	 24 (57.1) 22 (52.4) 2 (4.7) 18 (42.9) 4 (9.5) 3 (7.1) 0 (0.0) 5 (11.9) 6 (14.4)	.125
Fusion gene Negative PAX3-FOXO1 Not available	 8 (33.3) 1 (4.2) 15 (62.5)	 5 (11.9) 16 (38.1) 21 (50.0)	.002 (b)
Infiltrative tumour T1 T2 Unknown	 15 (62.5) 6 (25) 3 (12.5)	 8 (19.0) 26 (62.0) 8 (19.0)	<.001
Nodal involvement (c) N0 N1 Unknown	 17 (70.8) 4 (16.7) 3 (12.5)	 12 (28.6) 25 (59.5) 5 (11.9)	<.001
Primary metastases M0 M1 Unknown	 18 (75.0) 5 (20.8) 1 (4.2)	 20 (47.6) 20 (47.6) 2 (4.8)	.027

Tumour size ≤5 cm >5 cm Unknown	 7 (29.2) 10 (41.6) 7 (29.2)	 5 (11.9) 21 (50.0) 16 (18.1)	.168 (b)
IRS Stage I II III IV Unknown	 5 (20.8) 2 (8.3) 10 (41.7) 4 (16.7) 3 (12.5)	 5 (11.9) 1 (2.4) 14 (33.3) 20 (47.6) 2 (4.8)	.074 (b)
Surgery Yes No Unknown	 16 (66.7) 8 (33.3) 0 (0.0)	 11 (26.2) 29 (69.0) 2 (4.8)	.002
Chemotherapy Yes No Unknown	 22 (91.7) 2 (8.3) 0 (0.0)	 37 (88.1) 3 (7.1) 2 (4.8)	.904
Radiotherapy Yes No Unknown	 8 (33.3) 15 (62.5) 1 (4.2)	 25 (59.5) 14 (33.3) 3 (7.2)	.025

(a) Chi-square tests were performed on complete data. (b) Fisher's exact. (c) Locoregional.

Table 2. Prognostic factors for ERMS and ARMS in a univariate Cox proportional hazard regression analysis.

Prognostic factor	Overall Survival		
	p-value	HR	95% CI
ARMS	.005	2.673	1.347-5.307
Fusion-gene positive	.008	4.556	1.474-14.085
Male gender	.060	1.838	.974-3.467
Age	.675	.995	.974-1.017
T2	<.001	3.950	1.867-8.354
N1	.054	1.884	.988-3.593
M1	<.001	3.067	1.644-5.720
Unfavourable site	.573	.845	.470-1.519
Size >5cm	.699	1.176	.517-2.673

Poster 381 3015934

DISEASE OUTCOME IN PATIENTS WITH INTERMEDIATE- AND HIGH- RISK RHABDOMYOSARCOMA BASED ON CHEMOTHERAPY REGIMEN: A SINGLE CENTER RETROSPECTIVE ANALYSIS

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Objective: Outcomes in intermediate-risk (IR) and high-risk (HR) rhabdomyosarcoma (RMS) remain suboptimal. Chemotherapy for IR RMS has historically been a backbone of vincristine, actinomycin, and cyclophosphamide (VAC). While cooperative group studies have not shown survival benefit over VAC for IR RMS, single institution data have demonstrated promising results with doxorubicin-containing regimens (vincristine, doxorubicin, cyclophosphamide alternating with ifosfamide, etoposide; VDC/IE). In HR RMS, dose-intensive regimens including doxorubicin (VDC/IE/VI/VAC) have improved outcomes vs. historical controls. We have treated patients with both approaches and evaluated the outcomes of patients treated with VAC vs. doxorubicin-containing regimens.

Methods: Retrospective chart review of pediatric patients diagnosed with IR or HR RMS from 2004-2015. Stage and group are based on ISRG criteria and risk classification is based on recent COG stratification. Data included demographics,

staging, treatment, and outcome. Patients treated with doxorubicin were compared with those who received VAC-based therapy. Patients were analyzed by risk group, stage, histology, and primary tumor site. Kaplan-Meier curves were generated to illustrate event-free (EFS) and overall survival (OS). Descriptive statistics were calculated, including counts, percentages, means and standard deviations, or medians and interquartile ranges. To compare outcomes between VAC and doxorubicin groups, chi-square tests were used for categorical variables, and 2-sample t-tests and Wilcoxon rank-sum tests were used for continuous variables. Statistical analyses were performed using SAS 9.4 (Cary, NC). Statistical significance will be assessed at the 0.05 level.

Results: Eighty-five patients were eligible for inclusion. The doxorubicin group was older and more likely of higher stage, group, and risk category. The groups were similar with regards to sex, primary tumor site, and local control modality (Table 1). 5-year EFS and OS were 50% (33-64%) and 71% (53-83%) for the VAC group (n=40) vs. 57% (41-70%) and 60% (43-74%) for those receiving doxorubicin (n=45; p=0.906 and p=0.198), respectively (Figure 1a and b). Hazard ratios were also calculated and were not significant, even when adjusted for age and HR. For IR patients (n=66), 5-year EFS was 51% (32-66%) in the VAC group (n=35) vs. 70% (50-83%) in the doxorubicin group (n=31; p=0.28), and 5-year OS was 79% (60-89%) in the VAC group vs. 72% (51-85%) for those receiving doxorubicin (p=0.573). In HR patients (n=19), 5-year EFS was 20% (1-58%) for the VAC group (n=5) vs. 29% (9-52%) for the doxorubicin group (n=14; p=0.697), and 5-year OS was 20% (1-58%) for the VAC group vs. 31% (9-57%) for those

	Doxorubicin (n=45)		VAC (n=40)		
	Median (IQR)		Median (IQR)		p-value
Age (yrs)	7.0 (3.0 - 15.0)		3.0 (2.0 - 9.0)		0.0031
	n	%	n	%	
Sex					0.6573
Male	26	57.8	25	62.5	
Female	19	42.2	15	37.5	
Histology					0.1833
Embryonal	24	53.3	27	67.5	
Alveolar	21	46.7	13	32.5	
Primary Site					0.3478
Orbit	1	2.2	0	0.0	
Head & Neck	4	8.9	3	7.5	
GU	4	8.9	2	5.0	
Biliary Tract/Liver	0	0.0	1	2.5	
Bladder/Prostate	3	6.7	10	25.0	
Extremity	7	15.6	9	22.5	
Parameningeal	16	35.6	9	22.5	
Other	10	22.2	6	15.0	
Stage					0.0117
1	2	4.4	4	10.0	
2	8	17.8	9	22.5	
3	12	26.7	20	50.0	
4	23	51.1	7	17.5	
Group					0.0044
II	1	2.2	3	7.5	
III	21	46.7	30	75.0	
IV	23	51.1	7	17.5	
Risk Category					0.0398
HR	14	31.1	5	12.5	
IR	31	68.9	35	87.5	
Surgery					0.4102
Yes	11	24.4	13	32.5	
No	34	75.6	27	67.5	
Radiation					0.5768
Yes	42	93.3	36	90.0	
No	3	6.7	4	10.0	
Stage (modified)					0.0019
2 + 3 combined	20	46.5	29	80.6	
4	23	53.5	7	19.4	
Group (modified)					0.0012
II + III combined	22	48.9	33	82.5	
IV	23	51.1	7	17.5	

Table 1: Patient characteristics for those treated with VAC-based therapy and those treated with regimens containing doxorubicin.

receiving doxorubicin (p=0.671). Similarly, there was no statistical difference in outcome by histology or stage (2+3 vs. 4), although there was a trend toward improved EFS for stage 4 RMS treated with doxorubicin (p=0.065; Figure 2a and b).

Conclusion: In this large single institution cohort of IR and HR RMS there was no difference in outcome between patients receiving VAC-based therapy and patients receiving regimens that included doxorubicin; however, the doxorubicin group is biased toward patients with poorer prognostic features (age and disease burden), and additional multivariate analyses are planned. When divided by risk category, EFS trended better for both IR and HR patients who received doxorubicin, but OS was split, with IR patients faring better with VAC, and HR patients faring better with doxorubicin-containing therapy. This difference is driven by stage 1 patients included in the IR group (stage 1, group III, non-orbit). When these patients are eliminated, those with stage 2+3 RMS also trend toward improved OS with doxorubicin. Notably, there was improvement in EFS and OS for stage 4 patients in the doxorubicin group that approached statistical significance. This, along with recent COG HR results, supports use of doxorubicin in future HR RMS trials.

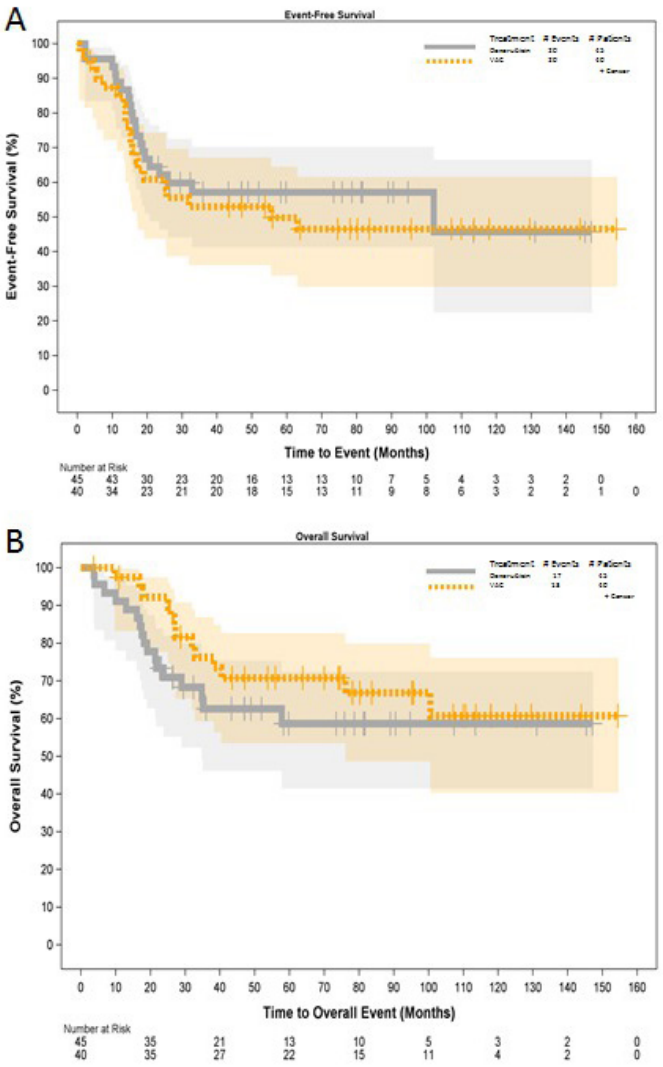

Figure 1: A) Event-free survival and B) overall survival by treatment regimen for intermediate- and high-risk rhabdomyosarcoma patients.

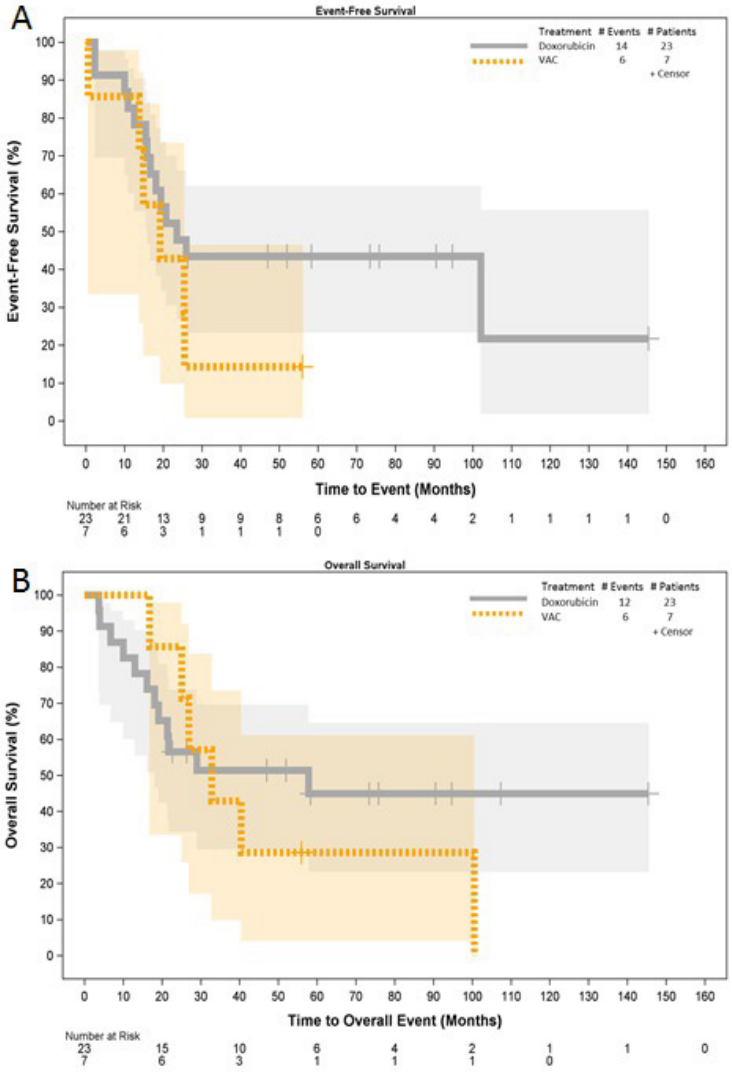

Figure 2: A) Event-free survival and B) overall survival by treatment regimen for stage 4 rhabdomyosarcoma patients.

Poster 382 3026150

RHABDOMYOSARCOMA IN ADULTS: A SEER POPULATION-BASED STUDY OF 1942 PATIENTS

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Objective: Rhabdomyosarcoma (RMS) in adults is a rare malignancy with poor prognosis. The pathophysiology, management and prognosis have yet been well established. Here we report the clinical characteristics and prognostic factors in adult patients with RMS by analyzing the data from the SEER database.

Methods: The data were retrieved from the SEER database (1973-2015). Patients with the International Classification of Diseases for Oncology, version 3 (ICD-O-3), morphology: 8900/3, 8901/3, 8902/3, 8910/3, 8912/3, 8920/3, and 8991/3, and were diagnosed at the age of 18 or older were included. Patients whose registration was in the form of autopsy or death certificate only and patients with no microscopic confirmation of diagnosis were excluded. The head and neck (nonparameningeal), genitourinary (nonbladder/prostate), and bile duct regions were classified as favorablesites, and all others were classified as unfavorable.
Survival estimates were calculated using the Kaplan-Meier method; the log-rank test was used to compare survival curves. Cox proportional hazards regression was used to conduct multivariate analysis. The statistics were performed with SPSS (version 20) and R (version 3.4.2).

Results: 1942 patients were included in the analysis. The median age was 51 years. RMS, NOS was the most common pathological type (37.2%), followed by embryonal (22.0%), pleomorphic (19.2%), and alveolar (17.8%), while other types are uncommon. Pleomorphic RMS are predominantly seen in older adults (Figure 1). Trunk and limbs, genitourinary (GU) were commonly involved, and most of the disease occurred in unpaired sites. Advanced stage was more common than localized and regional disease. 14% of the patients suffered from prior malignancy. 41% of the patients received surgery while 42% was treated with radiotherapy. Among patients underwent surgery, 34.0% received radiotherapy after operation, while 5.3% after surgery.

At the last follow-up, 1395 (71.8%) patients died. The median survival for the entire cohort was 17.0 month (95% CI 15.5-18.5) (Figure 2). Univariate survival analysis showed male, age > 51, histology other than embryonal RMS, unfavorable primary sites, unpaired primary site, regional or advanced SEER stage, former other malignancy, no surgery or no radiation are associated with poorer prognosis.
Multiple Cox-regression model revealed the following as the independent factors impacting overall survival: age, histology, primary site, SEER stage, surgery and radiation. (Table 1, Figure 3). The following factors has an adverse impact on overall survival: age >51 years, unfavorable primary site, regional or distant SEER stage. Embryonal RMS has a higher survival rate than other histology. Patients received surgery or radiotherapy had a better prognosis. Sex, record and lateral lost their significance in prognosis.

Conclusion: RMS in adults remained a rare disease with dismal prognosis. Pleomorphic RMS was more commonly seen in older adult patients. Patients with embryonal tumors, favorable tumor location, age < =51 years, localized disease, surgical resection and radiotherapy have longer survival. Radiation showed benefit for survival. And, preoperative radiotherapy should be further evaluated in future studies.

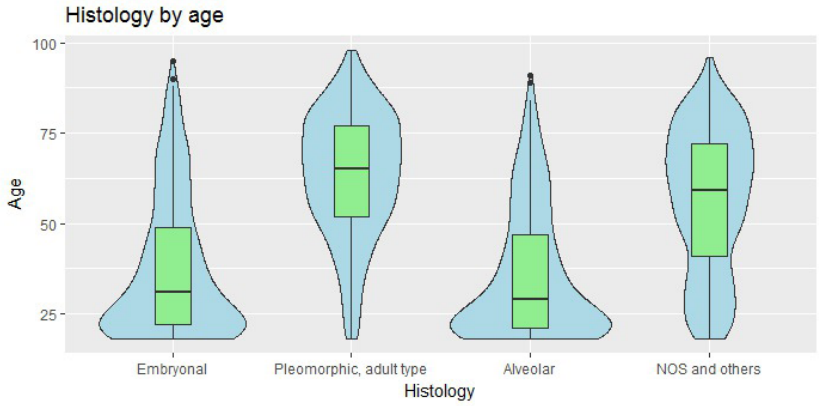

Figure 1. Histology by age

Table 1. Multivariate analysis in adult patients with RMS

Variable	HR	95% CI	P
Sex			
Male	1.0	ref	
Female	1.077	0.922-1.258	0.351
Age			
<=51	1.0	ref	
>51	2.347	1.996-2.759	0.000
Histology			
Embryonal	1.0	ref	
Others	1.279	1.035-1.581	0.023
Primary site			
Favorable	1.0	ref	
Unfavorable	1.307	1.092-1.563	0.003
Lateral			
Unpaired	1.0	ref	
Left/right	0.864	0.738-1.012	0.070
SEER stage			0.000
Localized	1.0	ref	
Regional	1.619	1.309-2.002	0.000
Distant	3.154	2.542-3.913	0.000
Record			
First cancer	1.0	ref	
Other	1.094	0.897-1.335	0.374
Surgery			
No	1.0	ref	
Yes	0.599	0.504-0.713	0.000
Radiotherapy			
No	1.0	ref	
Yes	0.557	0.477-0.652	0.000

Abbreviations: HR, hazard ratio; ref, reference.

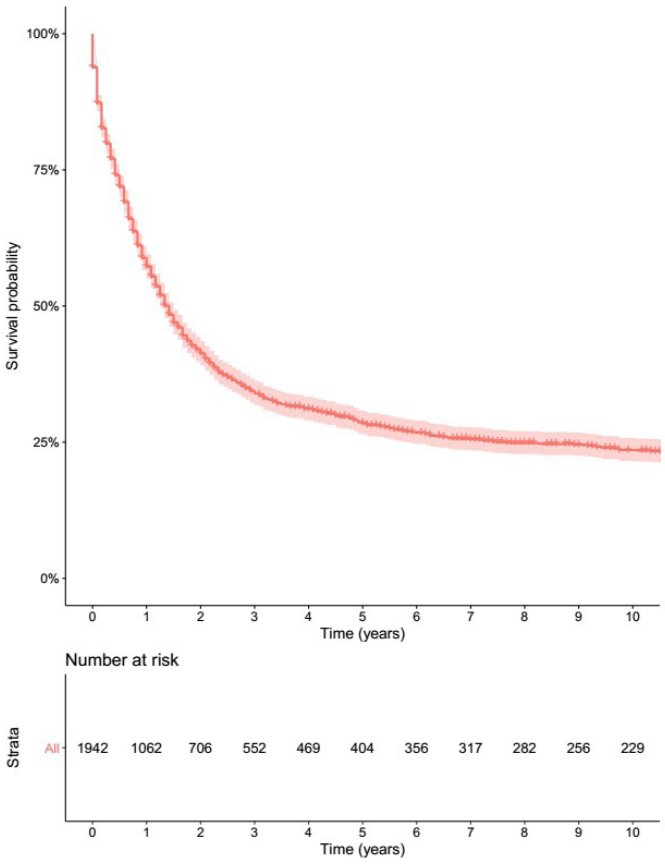

Figure 2. Survival curve of the whole cohort

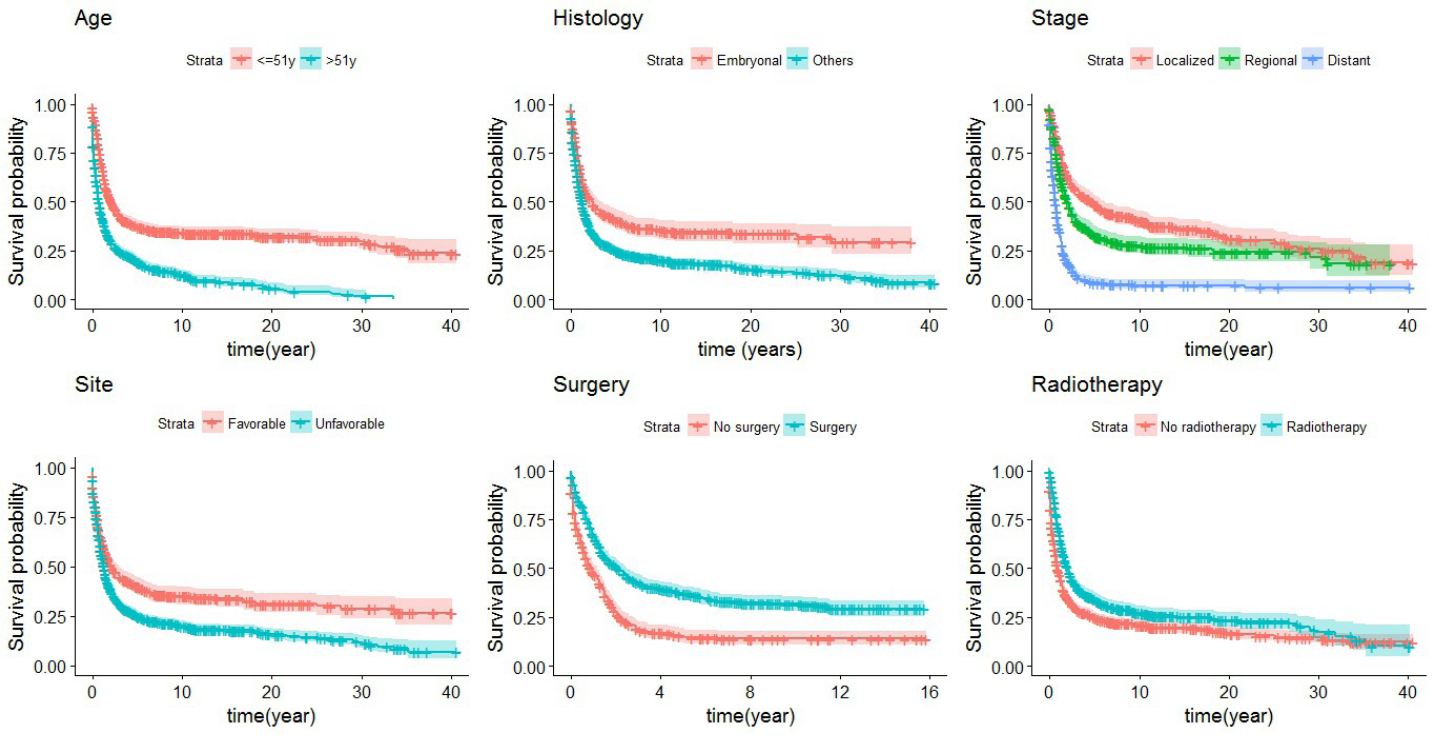

Figure 3. Survival curves by age, histology, stage, primary site, surgery and radiotherapy

Poster 383 3029847

VAC REGIMEN TO RHABDOMYOSARCOMA: THE DIFFERENCES OF RESPONSE ANS PROGNOSES IN PATIENTS OF AYA AND OLDER AGES

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Objective: It is known that adult rhabdomyosarcoma (RMS) patients have poor prognoses more than pediatric ones, but the differences of prognoses and treatment sensitivity between adolescent/young adult (AYA) and older patients have been not established yet. We tried to evaluate and compare the responses of vincristine/dactinomycin/cyclophosphamide (VAC), the standard combination chemotherapy regimen for pediatric RMS, of AYA and older patients.

Methods: We retrospectively reviewed clinical records of adolescent and adult RMS patients consulted to the department of medical oncology in Cancer Institute Hospital of Japanese Foundation for Cancer Research; of them, patients treated with VAC regimen with or without local definitive therapy (surgery or radiotherapy) were enrolled in the analysis. The differences of prognoses between patients with AYA and older ages (> 40 yo) were compared.

Results: Within total of 28 patients consulted to the department of medical oncology, 23 patients were treated by VAC regimen; median age was 36.4 years old (range 16-61), and 14 patients were AYA and 9 were older ages. Median follow-up time was 15.9 months (range 4.1~51.0), and the median progression-free survival (PFS) of VAC was 14.1 months (95% CI: 9.6~18.6) in total; there were not statistical significances between AYA (median 12.3 months, 95% CI: 8.6~16.9) and older patients (median 18.7 months, 95% CI: 7.0~30.5) (log rank p = 0.849). The median treatment cycles of VAC was 11 (range 3~14), and there were no differences of treatment cycles in AYA and older patients.

Conclusion: There were no significant differences of responses to VAC regimen and prognoses in RMS patients of AYA and older ages, and their prognoses remain to be poor than those of pediatric RMS. New treatment strategies for adult RMS are in need.

Poster 384 3042657

OPTIONAL PET SCAN UPSTAGING FOR CASES OF PEDIATRIC RHABDOMYOSARCOMA

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Objective: The standard staging imaging protocol for cases of pediatric rhabdomyosarcoma (RMS) includes CT, MRI, and bone marrow aspiration, but not PET, which is listed as optional. In addition, insurance does not reliably pay for PET scans. Standard imaging may not be sufficient for staging RMS due to the possibility of under-staging, subsequently following a protocol suited for a lower level diagnosis and leading to a less aggressive treatment plan and poorer prognosis. We report cases that highlight the value of incorporating PET scans into the standard imaging for evaluating/staging RMS.

Methods: We reviewed PubMed and Google Scholar using the following phrases/words: “rhabdomyosarcoma, staging, and PET scan”. The search was limited to cases of Rhabdomyosarcoma in the last 15 years and the English language.

Results: Three case reports of patients with RMS in addition to our case were found. The first case was a 38-year old woman had alveolar rhabdomyosarcoma from breast primary tumor. A PET/CT scan revealed hepatic and pancreatic metastases along with multifocal bone marrow involvement which a CT scan did not detect (Luporsi et. al). The second case was of a 26 year-old man with alveolar Rhabdomyosarcoma that had a 18F-FDG PET/CT scan that detected a significant level of bone metastases that were not detected in bone scintigraphy (Yang et, al, 2013). The third case was of a 9-year old male with paratesticular rhabdomyosarcoma. The PET/CT scan yielded positive findings of lymph node metastasis while the CT scan revealed negative results (Burnette et al., 2013). In each case, the PET scan upstaged the patient.

CASE REPORT:
We report a case of a 22-year old female originally evaluated as a stage II anterior mediastinal embryonal rhabdomyosarcoma. The standard imaging protocol of MRI, bone marrow, CT and bone scan showed no evidence of diffuse disease (Fig. 1a & 2a), but PET-CT revealed high risk metastatic disease with primary anterior mediastinal embryonal rhabdomyosarcoma with mets to the supraclavicular node, spine, and pelvis (Fig. 1b & 2b). This led to the patient being upstaged from II to IV and instead of a treatment protocol for non-metastatic RMS.

Conclusion: In the cases, aforementioned, without the optional PET scan imaging the patients would have been under-staged and treated with a different protocol that was not suited for metastatic RMS. These cases emphasize the importance of incorporating PET imaging into the standard protocol for evaluation and diagnosis of RMS as well as advocating for medical insurance to cover these scans(currently are not), rather than offering them as an optional supplement.

Case Reports of RMS upstaging by PET-Scan

Case #, age, sex	Subtype; primary location	Detected by PET missed by standard imaging	Original Stage pre-pet scan	Upstaged: YES/ NO
1) 38 F	ALV Breast	Hepatic and bone marrow	1	Yes; stage 4
2) 26 M	ALV Liver	Bone Mets	2	Yes; stage 4
3) 9 M	EMB Paratesticula	Lymph Node	1	Yes; stage 2
4) 22 F	EMB Mediastinum	Pelvic, vertebrae, and bone metastases	2	Yes; stage 4

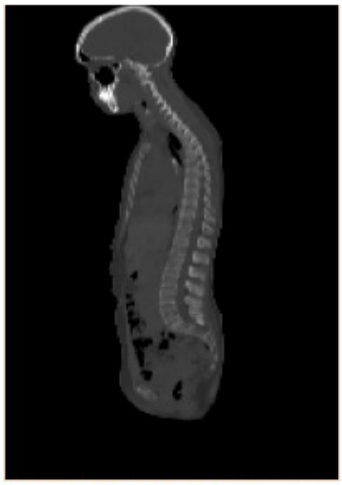

Figure 1a: Sagital (reformatted) CT image in spine

Figure 1a: CT of spine

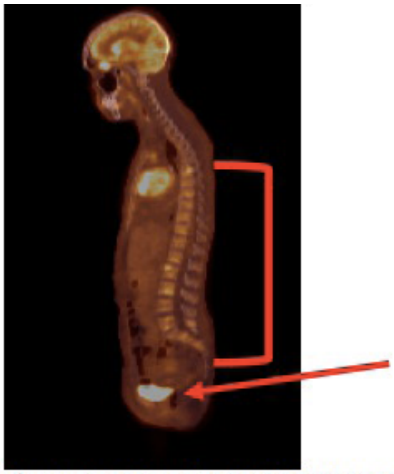

Figure 1b: Sagital fused FDG PET-CT image in spine

Figure 1b: PET scan of Spine

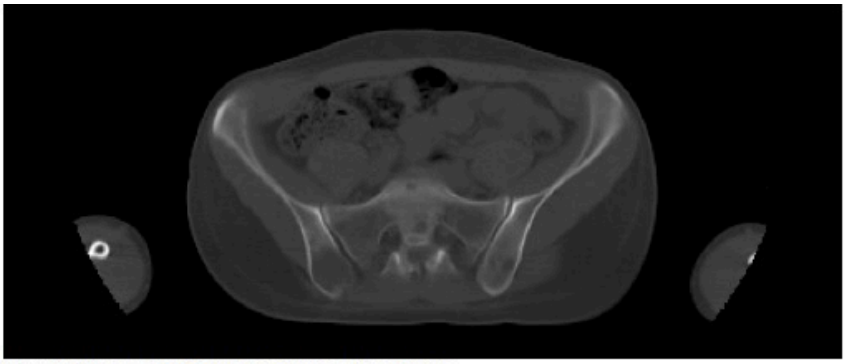

Figure 2a: Transaxial CT image in pelvic bones

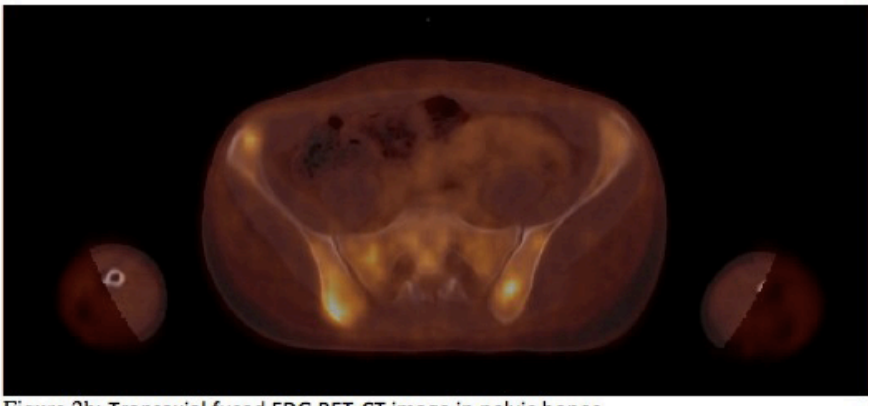

Figure 2b: Transaxial fused FDG PET-CT image in pelvic bones

Figure 2a and 2b. 2a demonstrates CT of pelvic bones and 2b shows PET scan of pelvic bones.

Poster 385 3027030

LIPOSARCOMA-SPECIFIC RADIATION THERAPY FOR RETROPERITONEAL SARCOMA - A REPORT FROM TARPSWG

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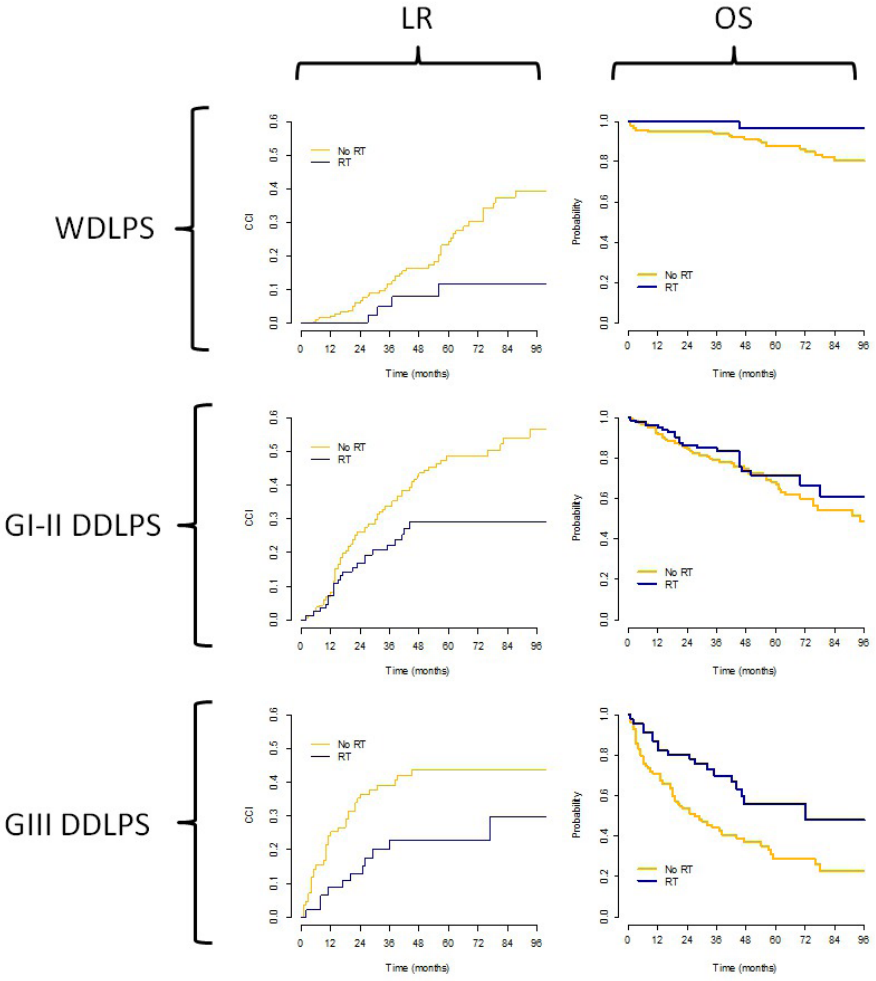
Objective: This study aims to investigate the role of radiotherapy (RT) in patients with primary non-metastatic retroperitoneal DDLPS and WDLPS, being subtypes where the local relapse rate is one of the leading causes of death.

Methods: 607 patients affected by localized retroperitoneal liposarcoma were resected with or without RT between January 2002 and December 2011 at 8 high-volume sarcoma centers: 234 WDLPS, 242 grade I-II DDLPS and 131 grade III DDLPS. RT was applied in 19.7%, 34.7% and 35.1% of these three cohorts respectively. Overall survival (OS) was estimated using the Kaplan-Meier method, and the incidences of local recurrence (LR) and distant metastasis (DM) were estimated in a competing-risk framework. To account for bias consistent with a non-random RT assignment a propensity score (PS) was estimated and Cox univariable analyses of association between RT and oncological endpoints was performed by applying an inverse-probability-of-treatment-weight (IPTW) using PS.

Results: Predominantly age, tumor size, and chemotherapy administration were significantly imbalanced between RT treated and untreated patients in all cohorts. IPTW removed all imbalances in key prognostic variables. The 8-year LR incidence in surgery + RT vs surgery only was 11.8% and 39.2% (p=0.011;WDLPS), 29.0% and 56.7% (p=0.008; grade I-II DDLPS), and 29.8% and 43.7% (p=0.025; grade III DDLPS), respectively, however this significant benefit was lost after IPTW analyses. There we no significant differences in DM and OS between patients treated with and without RT across all three cohorts.

Conclusion: Perioperative RT was associated with better LC on univariable unadjusted analyses in all three cohorts, but not after accounting for imbalances in prognostic variables. Use of RT did not impact on DM or OS. Appropriate selective prescription of RT in this disease remains a subject to further investigations and the results of the EORTC-STBSG 62092/22092 study are awaited.



Poster 386 3005908

MALNUTRITION AND PERIOPERATIVE NUTRITIONAL SUPPORT IN RETROPERITONEAL SARCOMA (RPS) PATIENTS. RESULTS FROM A PROSPECTIVE FEASIBILITY STUDY

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Objective: Perioperative protein energetic malnutrition (PEM) is known to affect post-operative recovery and surgical outcome. The prevalence of PEM and its impact in patients (pts) affected by RPS is unknown.

Methods: A prospective feasibility study enrolled patients affected by primary localized RPS and candidate to surgery. In the preoperative workout, pts were screened for PEM, classified as mild or serious (according to adapted SINPE criteria, reported in Table 1); disease-related risks were stratified as low, intermediate or high according to 7-yr OS estimates based on an externally validated multi-institutional nomogram (<35%, 36-70% and >70%). Preoperative high protein – beta-hydroxy-beta-methyl butyrate oral nutritional support (ONS) was provided according to degree of malnutrition, as detailed in Figure 1. After surgery, nutritional support was administered according to standard practice by either parenteral, enteral nutrition and/or oral feeding, targeting a 20 Kcal/Kg/die caloric intake within 3rd postoperative day (pod). Serial PEM evaluations were obtained the day before surgery, at 10th pod, at 4 and 12 months after surgery. Postoperative complications were recorded up to the 60th pod, according to Clavien-Dindo. Study outcomes were patient's compliance to preoperative ONS and physician's compliance to prescribed postoperative caloric target, defined as protocol adherence of 80% or higher.

Results: Between July 2016 and October 2017, 93 patients were surgically treated for primary RPS at our institution. Of them, 35 pts were enrolled in this study. Commonest histotypes were DDLPS (15, 43%) and WDLPS (8, 23%); median tumor size was 22 cm. Disease-related risk was low, intermediate and high in 12 (34%), 10 (29%) and 13 (37%) of cases, respectively. A median of 4 organs per operation were resected. PEM was documented in 16 patients (46%) at initial workout. Adherence to preoperative ONS was 91% (CI95% 0.7694-0.9820), without any significant adverse event. After ONS, PEM incidence before surgery was lowered to 38% (P=.45). The caloric target intake after surgery was reached on day 4,1 (SE ±2,7), with a protocol adherence of 51% (CI95% 0.3354-0.6920). On 10th pod the vast majority of patients still experienced PEM, as shown in Figure 2. Postoperative PEM worsening was greater in patients undergoing resection of 4 organs or more (P=.06). Conversely, at 4 and 12 months after surgery, almost all patients fully recovered from PEM. Clavien-Dindo complications grade ≥3 were recorded in 16 patients (46%); reoperations were performed in 7 (20%); postoperative mortality was nil. A significant correlation between PEM at surgery and Clavien-Dindo ≥3 complications was found (p = 0,035). No correlation between PEM and disease risk was found (p = 0,44).

Conclusion: A relevant incidence of PEM was documented in primary RPS patients. PEM correlates with greater morbidity, although patients recover to satisfactory nutritional status in the long term. Preoperative oral nutritional support was feasible and safe in this cohort of patients. Disease-related factors for PEM, as well as the ideal caloric target intake in the postoperative setting need to be further investigated. Nutritional support should be considered for future specific ERAS programs for RPS.

Table 1. PEM definition

	Mild PEM	Serious PEM
	If at least 3 criteria are encountered, including 2 biochemical criteria	If at least 2 criteria are encountered, including 1 biochemical criteria.
Circumference of the arm	22.8-15.2cm (M), 18.6-13.9cm (F)	< 15.2cm (M),
Oral intake (% of nutritional needs)	100-75	<75
Associated comorbidities	No SOFA score parameters ≥2	At least 1 among SOFA score parameters ≥2
Serum albumin (g/dl)	3,0-3,5	< 3
Lymphocitic count	1.500-800	< 800
Serum prealbumin (mg/dl)	20-10	< 10
Transferrin (mg/dl)	200-130	< 130

adapted from SINPE (Italian Society of Enteral Parenteral Nutrition) Guidelines, 2002

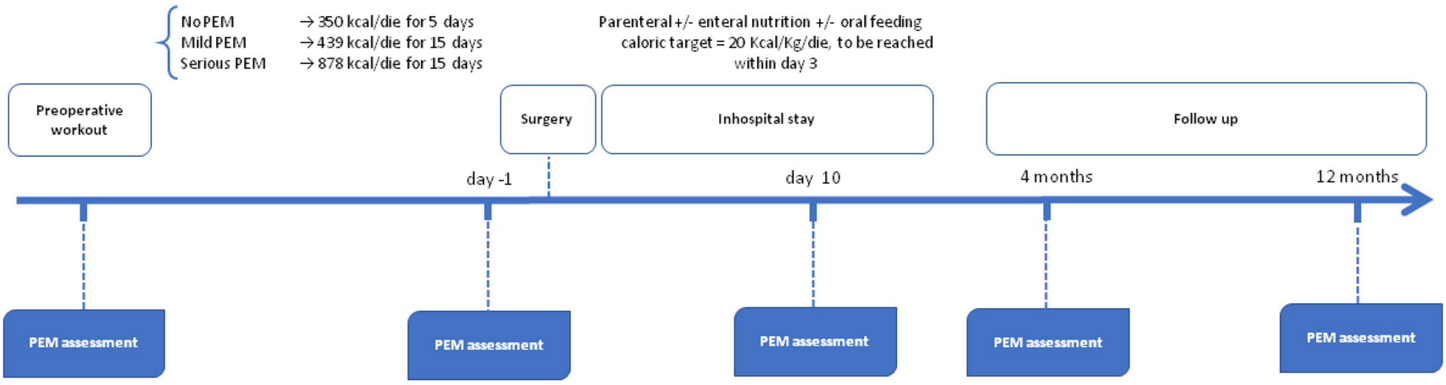

Figure 1. Perioperative nutritional support and study protocol workflow.

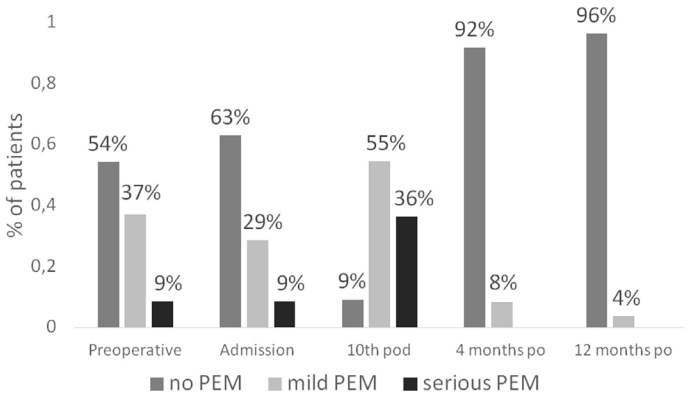

Figure 2. Protein energetic malnutrition (PEM) assessments in RPS operated patients.

Poster 387 3039242

POST-OPERATIVE RADIOTHERAPY IMPROVES OVERALL SURVIVAL IN MARGIN-POSITIVE RETROPERITONEAL SARCOMAS

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Objective: The role of radiotherapy (RT) in locoregional management of retroperitoneal sarcoma (RPS) is poorly defined, especially after incomplete resection. The goal of this study is to investigate whether post-operative RT after a margin-positive resection confers a survival benefit for RPS.

Methods: This retrospective analysis of the National Cancer Database (NCDB) from 2004 to 2015 identified all adult patients with a diagnosis of localized RPS who underwent a R1 or R2 surgical resection. Patients who underwent neoadjuvant therapy, adjuvant chemotherapy, or had metastatic disease were excluded. Logistic regression was performed to identify factors independently associated with the receipt of RT. Survival analyses were then performed adjusting for these factors. Kaplan-Meier curves with log-rank tests and Cox proportional hazards modeling were used to identify independent predictors of improved overall survival. Radiation therapy was analyzed as a time-varying covariate to account for variability in post-operative administration.

Results: 9993 RPS patients were captured. 2015 had an incomplete resection, of which the 1511 with no neoadjuvant therapy and available post-operative treatment data were included in our study. 1100 underwent surgery alone, while 411 had surgery plus post-operative RT. Median overall survival was significantly greater in the RT group compared to those having surgery alone on univariate analysis (43.4 months v. 34.2 months, $p<0.001$). Survival analysis demonstrated significantly improved overall survival for the overall RPS population ($p<0.05$), and specifically for those with leiomyosarcoma (LMS) when stratified by histology ($p<0.001$). On multivariate Cox regression, receipt of post-operative RT was an independent predictor for improved OS (HR 0.45, 95% CI 0.251-0.804, $p<0.01$), with slight attenuation of that effect over time (Δ per unit time = +0.021, 95% CI 1.001 – 1.042, $p<0.045$). Larger tumor size and higher tumor grade were unsurprisingly

independently associated with reduced overall survival, while a diagnosis of liposarcoma (LPS) conferred a survival benefit (HR 0.45, 95% CI 0.285 – 0.738, p<0.01). When stratified by histology, the significant benefit of post-operative RT persisted for LPS. Approximately 10% of the surgery alone population had been recommended RT but abstained due to medical contraindication, refusal, or other factors. Adverse event data could not be captured from the NCDB.

Conclusion: Margin-positive RPS is an understudied population and evidence for post-operative therapy in this group is negligible. We demonstrated a significant survival benefit with post-operative RT in this population. Subset analyses of predominant RPS histologies further demonstrate this benefit. Prospective studies will be required to elucidate data on adverse events, which is essential to clinical decision making in this population.

Univariate and multivariate Cox regression analyses of overall survival (OS) for all margin positive RPS.

Variable	Univariate HR [95% CI]	Multivariate HR [95% CI]	p value
Post-operative RT	0.79 [0.659 – 0.956]	0.45 [0.251 – 0.804]	0.007
Age at Diagnosis	1.04 [1.030 – 1.045]	1.03 [1.020 – 1.046]	0.000
Female Sex	0.73 [0.617 – 0.857]	0.67 [0.484 – 0.928]	0.016
Race White Black Other	- ref 1.07 [0.813 – 1.410] 0.77 [0.492 – 1.205]	- ref 1.53 [0.983 – 2.407] 2.57 [1.024 – 6.464]	- - 0.060 0.044
Charlson Comorbidity Score	1.48 [1.311 – 1.682]	1.40 [1.081 – 1.815]	0.011
AJCC Cancer Stage	1.69 [1.535 – 1.856]	1.29 [0.895 – 1.881]	0.169
Tumor Histology Other Liposarcoma Leiomyosarcoma	- ref 0.38 [0.308 – 0.479] 0.44 [0.332 – 0.578]	- ref 0.45 [0.285– 0.738] 0.96 [0.375 – 1.103]	- - 0.001 0.109
Tumor Grade I II III	- ref 4.39 [2.606 – 7.399] 6.85 [4.339 – 11.062]	- ref 3.64 [0.971 – 6.704] 3.87 [1.767 – 8.455]	- - 0.000 0.001
Tumor Size Category*	1.13 [1.016 – 1.254]	1.32 [1.045 – 1.660]	0.020
Covariate change per unit time			
Post-operative RT		1.021 [1.001 – 1.042]	0.045

*per increase in category: 20cm

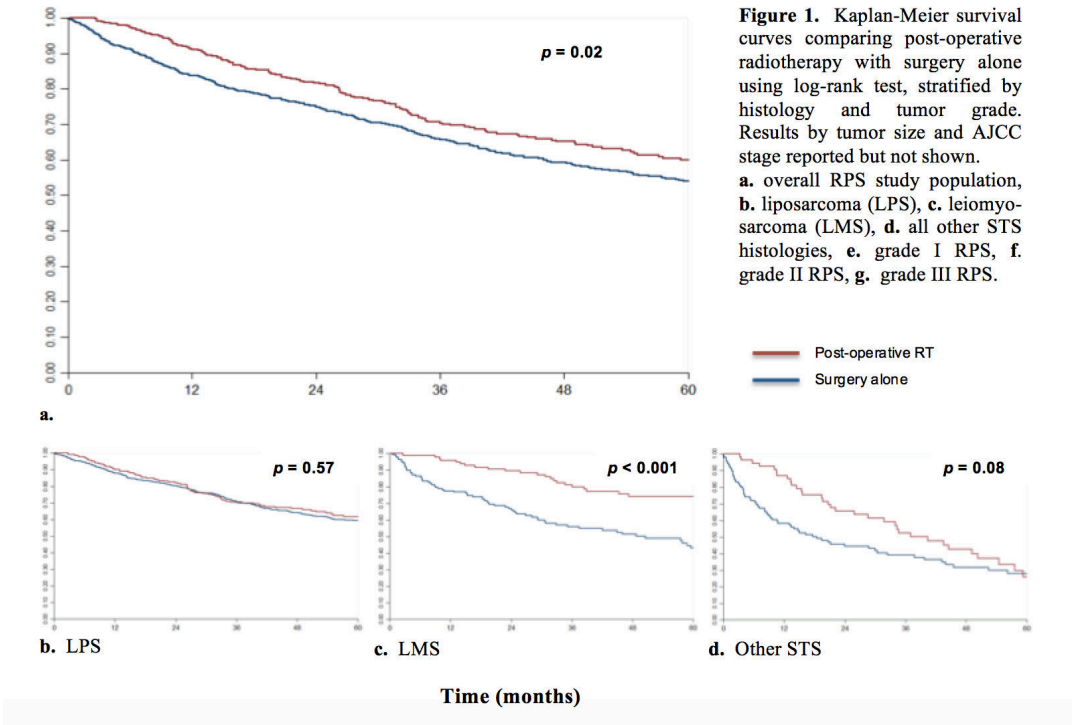

Figure 1. Kaplan-Meier survival curves comparing post-operative radiotherapy with surgery alone using log-rank test, stratified by histology and tumor grade. Results by tumor size and AJCC stage reported but not shown.
a. overall RPS study population, **b.** liposarcoma (LPS), **c.** leiomyo-sarcoma (LMS), **d.** all other STS histologies, **e.** grade I RPS, **f.** grade II RPS, **g.** grade III RPS.

Figure 1. Kaplan-Meier survival curves comparing post-operative radiotherapy with surgery alone using log-rank test, stratified by histology and tumor grade. Results by tumor size and AJCC stage reported but not shown.
a. overall RPS study population, **b.** liposarcoma (LPS), **c.** leiomyo-sarcoma (LMS), **d.** all other STS histologies, **e.** grade I RPS, **f.** grade II RPS, **g.** grade III RPS.

Poster 388 3042844

MEASURING THE IMPACT OF COMPLICATIONS AFTER SURGERY FOR RETROPERITONEAL SARCOMA (RPS): IS COMPREHENSIVE COMPLICATION INDEX (CCI) BETTER THAN CLAVIEN-DINDO CLASSIFICATION (CDC)?

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Objective: Surgery for primary retroperitoneal sarcomas (RPS) often requires a technically demanding, en bloc multivisceral resection to optimize outcomes. Clavien-Dindo Classification (CDC) is a validated method to report complications in different type of surgery; comprehensive complication index (CCI) is a more recent system to report comorbidities, based on a linear ranging scale and, differently from CDC, it takes into account all complications. CCI has been already validated in abdominal surgery; however no studies investigated yet its validity in surgery for RPS. The aim of our study is to compare CDC and CCI in describing the impact of complications after surgery for RPS on length of postoperative stay (POS).

Methods: We retrospectively analyzed data on 285 procedures, randomly selected among a consecutive series of 503 operations for both primary and recurrent RPS between January 2000 and December 2017. Patient demographics, pathology, complications and their treatments, and postoperative stay (POS) were reviewed. The CCI was calculated for each patient. Linear regression was used to assess whether the CCI and CDC correlate to POS.

Results: Out of 285 reviewed procedures, 135 (47.4%) involved female patients; median age was 61.5 years [interquartile range (IQR) 22-83 years]. In 216 procedures (76%), tumor was resected with at least one more structure or organ, and the median number of resected organs was 1 (IQR 0-3). Median diameter was 100mm (IQR: 6-180mm), while more frequent histologic subtypes were: well-differentiated liposarcoma in 104 procedures (36.5%), dedifferentiated liposarcoma in 63 (22.1%), leiomyosarcoma in 42 (14.7%), synovial sarcoma in 11(3.8%), undifferentiated pleomorphic sarcoma 6 (2.1%).
In 97 procedures (34%) postoperative complications occurred; perioperative mortality was observed in 2 out of 285 patients (0.7%); 2.1% of procedures presented a grade I complication according to CDC; 16.1% grade II, 3.2% grade IIIa, 9.8% grade IIIb, 1.7% grade IVa and 0.3% grade IVb.
Median CCI was 0 (IQR 0-20.9) and mean CCI was 11.23. Mean POS was 13.5 days, while median POS was 9 days (IQR 6-15).
Univariate linear regression selected age, number of resected organs, comorbidity, diameter of the neoplasm, length of stay in the intensive care unit (ICU), CDC and CCI as predictive factors for length of POS.
When multivariable linear regression was applied, the model with CDC selected number of resected organs, length of ICU stay and CDC as independent prognostic factors for length of POS ($p<0.001$); the model with CCI instead selected only CCI as independent prognostic factor for length of POS ($p<0.001$). The AIC and BIC for the CCI model were smaller (1704.07 and 1731.07 respectively) than for CDC (1729.15 and 1756.15, respectively), suggesting CCI to fit better than CDC. CCI resulted to be strongly related to length of POS with coefficient of 0.57 [95% confidence interval 0.46-0.68, $p<0.001$].

Conclusion: CCI is a useful tool to describe complications and their impact of postoperative course of patients underwent surgery for RPS, as it describes the real impact of complications better than CDC.

Poster 389 3042913

MANAGEMENT AND OUTCOME OF INTERMEDIATE-HIGH GRADE RETROPERITONEAL SARCOMAS: A SINGLE INSTITUTION STUDY

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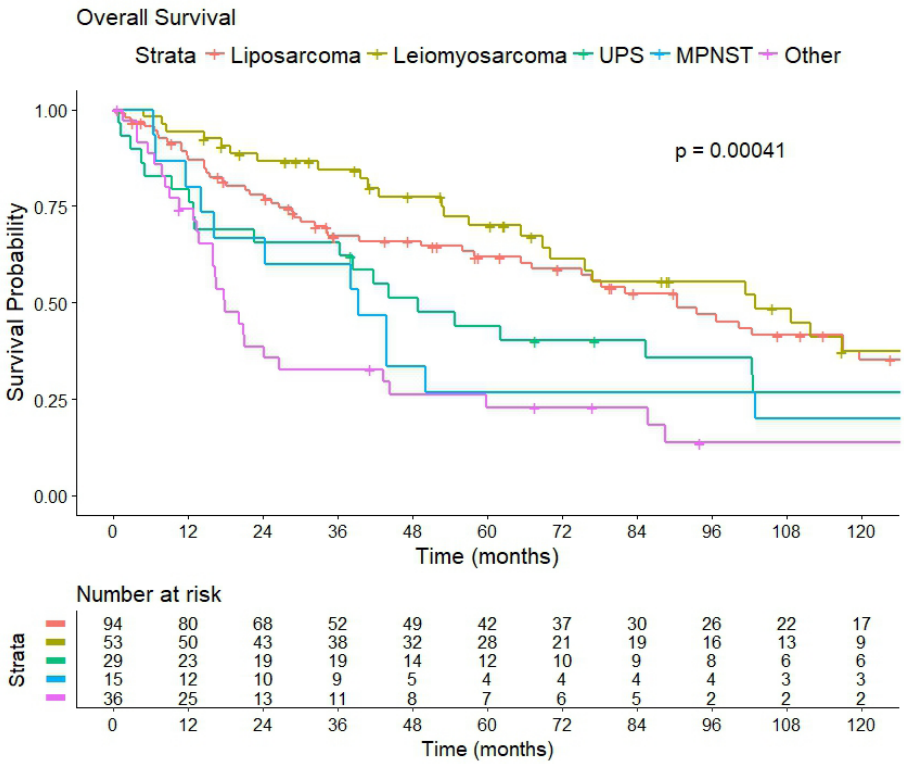
Objective: Retroperitoneal sarcomas can recur with local, intraperitoneal, and/or distant failures. Treatment requires a tailored, multidisciplinary strategy. We present our results of patients with retroperitoneal sarcoma treated at a single institution to gain insights on treatment outcomes after definitive therapy.

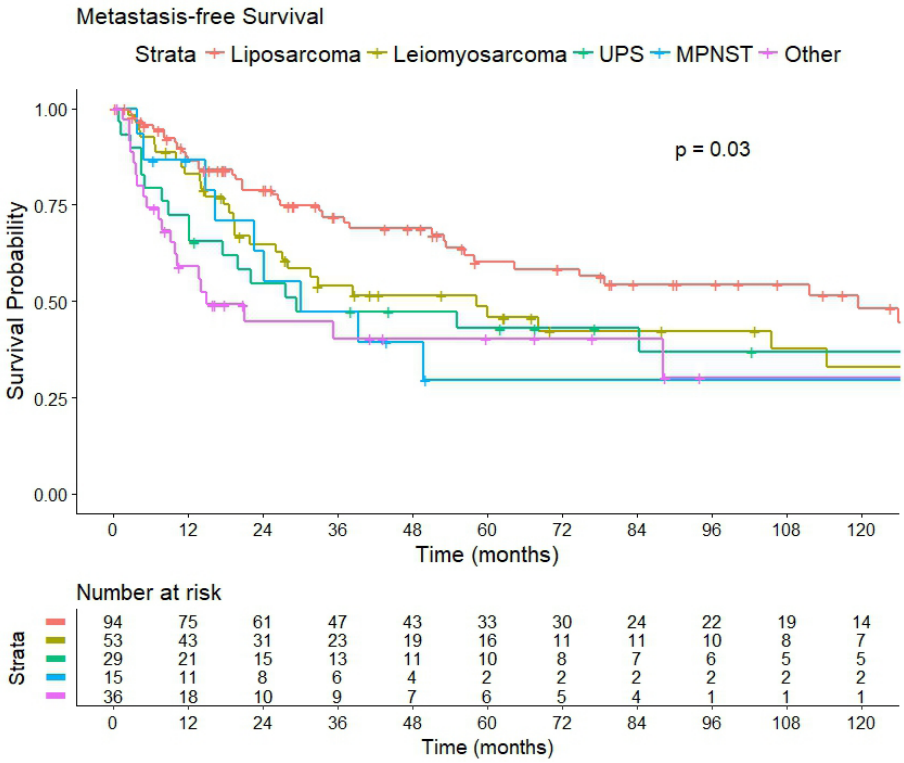
Methods: In an IRB approved protocol, we analyzed clinicopathologic characteristics, treatment, and outcomes of patients with non-metastatic grade 2-3 retroperitoneal sarcomas treated at our institution between 1975-2016. Overall survival (OS), local relapse-free survival (LRFS), and metastasis-free survival (MFS) were estimated using the Kaplan-Meier method. The multivariate Cox proportional hazards regression was used to analyze survival outcomes and risk variables.

Results: We found 267 grade 2-3 retroperitoneal sarcomas: 39% had liposarcoma, 24% leiomyosarcoma, 6% malignant peripheral nerve sheath tumor (MPNST), and 21% other histological types. Patients presented as non-metastatic (85%), with positive lymph node (6%), peritoneal extension (9%), or distant metastasis (15%; liver most common). Rate of metastatic disease at presentation was no significantly different by histology (leiomyosarcoma 17%, liposarcoma 10%, and MPNST 6%). Of 227 non-metastatic patients (median age 59 years), 41% had liposarcomas, 23% leiomyosarcomas, 13% undifferentiated pleomorphic sarcomas, 7% MPNSTs, and 7% others. Surgical extent was 41% R0, 31% R1, and 22% R2. Radiotherapy (RT) was given preoperatively in 48%, postoperatively 29%, 11% both, and 12% alone. Chemotherapy was given in 19% using single/combined doxorubicin (84%), ifosfamide (37%), dacarbazine (21%), or others (44%). 11% did not undergo surgery for unresectable disease or rapid metastases preoperatively. At median follow-up of 44 months (range: 1-326), 5-year OS, LRFS, and MFS rates were 52%, 52%, and 49%, respectively. The risk of subsequent peritoneal or distant metastasis differed by histology: 5-year MFS was 61% in liposarcoma, 46% in leiomyosarcoma, and 27% in MPNST (p=0.03). On univariate analysis, chemotherapy was associated with better OS (P=0.05). On multivariate analysis, increased age (HR: 1.02), MPNST (HR: 2.68), and positive lymph node (HR: 2.43) were associated with worse OS. No resection was associated with poor OS (HR: 7.09), LRFS (HR: 4.61), and MFS (HR: 3.81), while RT (HR: 0.56) reduced local and peritoneal failures.

Conclusion: Surgical resection remains the most significant predictor of survival. More trials are warranted to assess the optimal treatment for retroperitoneal sarcoma histologies at high risk for local and distant failure.



Kaplan-Meier curves of overall survival in patients with retroperitoneal sarcoma according to histology.



Kaplan-Meier curves of metastasis-free survival in patients with retroperitoneal sarcoma according to histology.

Poster 390 3028735

MANAGEMENT OF LOCOREGIONAL RECURRENCE AFTER RADICAL RESECTION OF A PRIMARY NON-METASTATIC RETROPERITONEAL SOFT TISSUE SARCOMA: RESULTS OF A RETROSPECTIVE SERIES IN A TERTIARY CARE CENTER

Charles Honoré[3]*; Matthieu Faron*[3]*; Olivier Mir*[1]*; Leila Haddag*[2]*; Sarah N. Dumont*[1]*; Julien Adam*[4]*; Philippe Terrier*[4]*; Cécile Le Péchoux*[5]*; Axel Le Cesne*[1]

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Objective: Retroperitoneal soft tissue sarcomas (RPS) are rare tumors. Despite surgery, 35% of patients experience locoregional recurrence (LR) the optimum treatment of which is still debated. The aim of the study is to report our experience in treating LR.

Methods: All 297 consecutive patients operated for a non-metastatic primary RPS between 1994 and 2017 were retrospectively analyzed to identify patients who developed LR. Demographic data, treatment variables and long-term outcome were recorded to calculate disease free survival (DFS), overall survival (OS) and predictive factors of recurrence.

Results: After a median follow-up of 97 months, 55 patients (19%) developed LR. The first site of recurrence was locoregional in 100% with associated peritoneal metastases in 45% and distant metastases in 5%. The median disease free interval (DFI) was 24 months. After recurrence treatment, the 1-, 3- and 5-year OS rates were 71%, 46% and 33%, and 1-, 3- and 5-year DFS rates were 50%, 22%, and 15%. Low tumor grade, DFI above 24 months, exclusive LR and well-differentiated liposarcoma were predictive of better OS and DFS. Despite finding no statistical difference between treatment strategies, median OS was less than 1 month after best supportive care, 44 months after chemotherapy (including patients who underwent subsequent LR radiotherapy or surgery) and was not reached after upfront surgery or radiotherapy. Fourteen patients underwent initial surveillance for low-grade liposarcoma and eventually required treatment in 86% after a median delay of 20 months during which no patient developed distant metastases.

Conclusion: The management of LR in RPS is complex. An initial surveillance may not alter survival in asymptomatic low-grade and slow-growing LR. A LR decision scheme is proposed.

Poster 391 3003334

OUTCOME AND QUALITY OF LIFE AFTER RESECTION FOR RETROPERITONEAL SARCOMA

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Objective: Retroperitoneal sarcomas are often treated with multivisceral resection. Little is known on how extent and outcome of resection affect quality of life. We tried to identify factors associated with risk for morbidity and mortality after multivisceral resection of retroperitoneal sarcomas, and its effect on quality of life.

Methods: Patients who underwent primary or recurrent surgery for retroperitoneal sarcoma, RPS, at Lund University Hospital between January 2005 and December 2015 were identified from hospital databases. In this study, RPS included lipo- and leiomyosarcoma, malignant solitary fibrous tumour, and malignant peripheral nerve sheath tumour, but gastrointestinal stroma cell tumour (GIST) was not included. Patients were followed until 28th February 2017, or death, whichever came first. Morbidity was noted from patient records using a prespecified form. Survival was evaluated with the Kaplan Meier method with the log-rank test, and with multiple Cox's regression adjusting for age (less than and over 60 years), sex, radio- and/or chemotherapy or not, type of sarcoma (well differentiated, dedifferentiated, leiomyosarcoma, other), and radicality (R0, R1 or R2). Quality of life in patients alive at 28th February 2017 was examined with the European Organisation of Treatment and Research into Cancer (EORTC) generic questionnaire QLQ-C30. This questionnaire was sent to patients by regular mail, with one reminder. Questionnaire data were transformed into scores as specified in the EORTC manual. The impact of treatment, histopathology and complications on quality of life scores was evaluated with multiple linear regression.

Results: In all, 92 patients underwent resection, 80 for primary tumors and 12 for recurrent tumors. The 5-year overall-survival rate was 64 % (95 % CI 52-74 %). For dedifferentiated liposarcoma, well-differentiated liposarcoma and leiomyosarcoma, the 5-year overall-survival rate (95 % CI) was 28 (10-49) %, 84 (CI 61-94) % and 72 (39-89) % respectively. Recurrence-free survival at three years were 33% (95% CI 13-54%), 71 (95% CI 44-87%) and 79 (95% CI 59-90%), respectively. In multiple Cox's regression, risk factors for death were male gender, dedifferentiated liposarcoma

and R2-resection, whereas risk factors for recurrence were R1/R2-resection and dedifferientiated liposarcoma. On the 28th February, 2017, 58 (63 %) patients were alive, to which the questionnaire was sent. Some 45 (78 %) responded. Quality of life was good among responders, with a median score of 75 of 100 on overall quality of life, and 97 of 100 for physical health. Having had chemotherapy, having more than four organs resected, and having known tumour recurrence, were all associated with worse quality of life in mulitple linear regression analysis.

Conclusion: Overall survival was similar to previous reports. Survival depended on surgical radicality and histopathologic type of sarcoma, with less favourable survival in dedifferentiated liposarcoma and leiomyosarcoma. Quality of life in survivors was overall very good, but worse in patients treated with chemotherapy, patients who had more than 4 organs resected, and in patients with recurrent disease.

Poster 392 3029453

NO BENEFIT OF PREOPERATIVE CHEMOTHERAPY FOR PRIMARY RETROPERITONEAL SARCOMAS: RESULTS FROM A SINGLE CENTER PROPENSITY MATCHED ANALYSIS

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Objective: Surgery for retroperitoneal sarcomas (RPS) is more and more standardized worldwide. Yet, the potential benefits of preoperative chemotherapy remain elusive.

Methods: All consecutive patients operated on for a primary RPS were retrospectively identified. Preoperative chemotherapy was mostly a doxorubicin-based chemotherapy regimen for 2 to 6 cycles. Surgery was performed according to the “cluster resection” principles. A caliper restricted, propensity score matched analysis was used to balance the groups.

Results: 249 patients were identified, 49(20%) of whom had receive preoperative chemotherapy. After matching, 40 pairs of patients were available and well balanced for baseline characteristics. Seven patients (8%) had intermediate adipocytic tumors, 30 (38%) had malignant adipocytic tumor, 19 (24%) had smooth muscle tumors and 24 (30%) had other subtypes. The median tumor size at diagnosis was 20 cm (IQR: 12-26 cm). Sixteen tumors (20%) were FNCLCC’s grade 1, 28 (35%) grade 2 and 36 (45%) grade 3. Univariate analysis identified the size of the tumor (p=0.036), the histological subtype (p=0.0015), the FNCLCC’s grade (p=0.0027) and the postoperative chemotherapy (p=0.01) as prognostic factors. In the multivariate analysis, only the sarcoma histotype (0.013) and the FNCLCC’s grade (p=0.022) were retained as independent prognostic factor. Preoperative chemotherapy was neither associated with overall survival (p=0.41) nor disease-free survival (p=0.11).

Conclusion: Routine use of chemotherapy should be avoided in the preoperative setting of primary RPS. Targeted treatments and/or accurate selection criteria are needed.

Poster 393 3039706

EVALUATION OF TREATMENT RESPONSE TO PREOPERATIVE THERAPY IN RETROPERITONEAL LEIOMYOSARCOMA

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Objective: Retroperitoneal leiomyosarcoma is a treatment challenge, characterized by frequent need for extensive resection and high propensity of distant recurrence. Preoperative therapy is often utilized; however, whether radiologic or pathologic response affects treatment outcomes is unknown.

Methods: We retrospectively reviewed the institutional database of retroperitoneal leiomyosarcoma patients to identify those who underwent curative-intent resection following preoperative chemo- or chemoradiation therapy. Patients who did not have pre- and post-treatment imaging with the same modality (CT or MRI) were excluded. Radiographic response was evaluated based on RECIST criteria. Pathological response was categorized into minimal, moderate, and major response

group based on viable tumor proportion (>50%, 11-50%, and ≤10%, respectively). Descriptive statistics were performed to evaluate the relationship between radiologic and pathologic response, and the effect of pre-operative treatment on overall and recurrence free survival (OS and RFS).

Results: *Thirty-two patients were included in this study; 25 (78%) were female, and 22 (69%) were white. Fourteen (44%) had tumors involving IVC, and 21 (66%) had tumors at least 10 cm in diameter. All patients received preoperative chemotherapy, and 11 (34%) received preoperative radiation therapy[W1] . On radiographic assessment, 5 (16%) had partial response, 24 (75%) had stable disease, and 3 (9%) had progressive disease during preoperative therapy. On pathological assessment, 3 (9%) had major response, 7 (22%) had moderate response, and 22 (69%) had minimal response. There was no correlation between radiographic and pathological response (fisher's exact test; p-value=0.372).* Median follow up was 3.3 years, the median OS of the entire cohort was 5.7 years, and the median RFS was 5.0 years. By log-rank test, radiographic response was associated with better RFS (p=0.0391, figure 1), but pathological response was not (p=0.8841). Neither radiographic nor pathologic response was associated with OS (p=0.2097 for radiographic, and p=0.838 for pathologic response).

Conclusion: In this retrospective single-institutional study, we observed that it was rare to have major radiographic or pathological response to preoperative therapy in retroperitoneal leiomyosarcoma patients. In this series, pathological response did not correlated with prognosis. However, Radiographic response to preoperative treatment would be the most reliable clinical information to help determine which patients might benefit from surgical intervention.

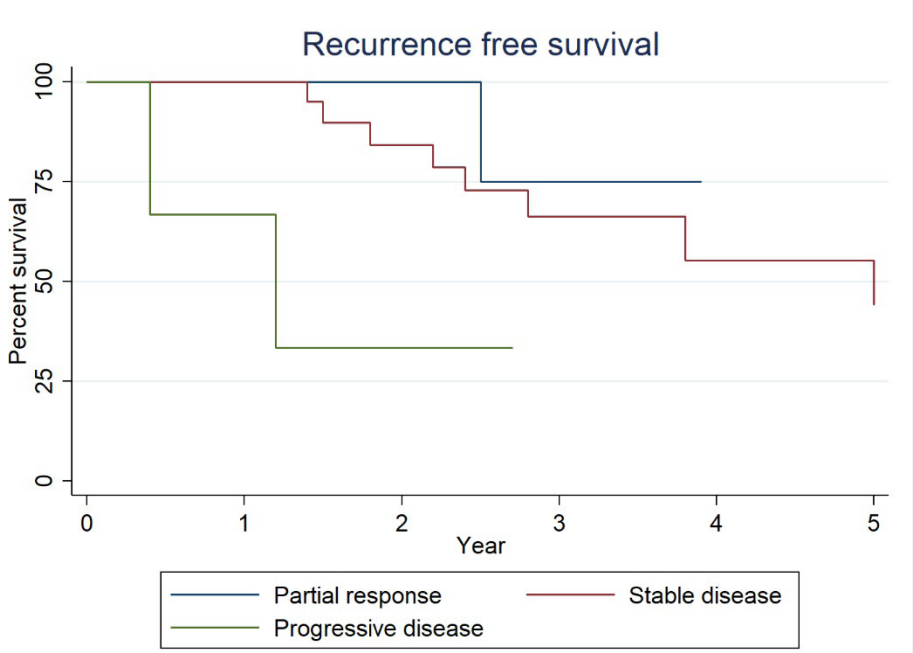

Figure. Recurrence free survival by radiographic response to preoperative therapy

Poster 394 3042182

ROLE OF NUTRITIONAL STATUS IN THE EARLY POSTOPERATIVE PROGNOSIS OF PATIENTS OPERATED FOR RETROPERITONEAL LIPOSARCOMA (RLS): A SINGLE CENTER EXPERIENCE

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Objective: To assess the nutritional status and its role in the outcome of patients operated for retroperitoneal liposarcoma (RLS).

Methods: Retrospective study on consecutive patients operated with *en bloc* compartment resection for primary or local recurrence of RLS between 2016 and 2017. Preoperative nutritional and laboratory assessment comprising serum albumin, serum transthyretin, orosomucoid, and CRP was systematically performed. The following preoperative parameters were analysed: weight, body mass index (BMI), significant weight loss (>5% in one month and/or > 10% in 6 months), serum albumin, transthyretin, CRP, orosomucoid. PINI were calculated.

Results: There were 40 patients operated for RLS: 22 women and 18 men with a median age of 61 years (34-90). Median tumour was 280 mm (80-530). Median preoperative BMI was 24.8 (18-42) and median postoperative BMI was 23 (17.8-44). Twenty-one patients (52.5%) were considered to be malnourished: 3 with biological signs of malnutrition and 18 with weight loss. Eleven (47.6%) in the group of malnourished patients and 4 (26.3%) in the group with satisfactory nutritional status

developed postoperative complications (p=0.042). A PINI score>1 was related to significantly longer hospitalisation time 21.8 days (10-58) in comparison with 14.9 (9-30) in patients with PINI < 1, p=0.003.

Conclusion: The malnourished patients with RLS experienced more postoperative complications and longer hospitalisation. Nutritional status and biological markers contribute to the global management of RLS with improved postoperative behaviour including fewer complications and shorter hospitalisation. A prospective larger study with longer follow-up is necessary to refine these results.

Poster 395 3042575

WHY WERE NON-METASTATIC PRIMARY RETROPERITONEAL SARCOMAS NOT RESECTED?

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Objective: Complete macroscopic resection, which remains the cornerstone of curative-intent treatment of Retroperitoneal Sarcoma (RPS), often involves extensive multivisceral resection. Though postoperative mortality is low in experienced centres, morbidity and length of stay can be significant. Distant metastatic disease at the time of primary presentation is considered a contraindication to resection. Even in the absence of distant metastases, a proportion of patients do not undergo resection. Little is known about the characteristics of this patient cohort, because few centres systematically collect prospective data regarding RPS patients who do not undergo resection. We investigated the incidence of and reasons for non-resection of primary non-metastatic RPS in our own sarcoma reference centre.

Methods: We identified all consecutive patients who presented to the Princess Margaret Cancer Centre/Mount Sinai Hospital Toronto with primary RPS between January 2012 and April 2017 from our prospective database. Patients with distant metastases were excluded from the present analysis. Patients who did not undergo resection were compared to those who did (Table 1), and reasons why patients did not undergo surgery and their subsequent treatment and outcomes were recorded (Table 2). Performance status (PS) was scored as per WHO criteria; “Poor” PS was defined as PS ≥ 3. Decision against resection was made by the treating surgeon following discussion at multidisciplinary tumor board.

Results: We identified 130 patients who presented to our centre with primary RPS and no distant metastases on initial cross-sectional imaging over the study interval. Of these, 96 (74%) underwent resection (±preop XRT ±preop chemo), while 34 (26%) did not.

Patients who did not have resection were slightly older, and were more likely to be male (Table 1). Tumour size was not different between the groups. Thirteen (38%) of the 34 non-resected patients had significant comorbidities. A minority had multifocal disease in the peritoneal cavity.

In nine patients, the primary RPS was deemed upfront unresectable, due to vascular involvement (SMA, SMV, portal vein, aorta or a combination) or extensive involvement of the mediastinum or spinal canal (Table 2). 13 patients had “borderline” unresectable tumours at presentation; of these, 9 progressed prior to/ on planned preoperative Rx (2 with local and 7 with distant progression), while 4 did not undergo resection due to poor PS. In 12 patients, the tumour was felt to be upfront resectable; in this group, 4 progressed prior to/ on planned preoperative Rx, 4 were not resected due to poor PS, 3 declined resection and 1 patient had a second significant competing malignancy.

Following the decision against resection, 7 patients were treated with palliative XRT, 8 with palliative chemo, and the remainder with best supportive care. For the cohort of 34 non-resected patients, 3yr OS estimated by the Kaplan Meier method was 18% and median OS was 12 months. Median survival and 3yr OS were 11 vs 20 mos and 0 vs 30 % respectively, in the patients who progressed prior to/ on planned neoadjuvant Rx (n=13) vs the remainder of the cohort (n=21).

Conclusion: A quarter of patients who presented to our centre with non-metastatic primary RPS did not ultimately undergo resection. Poor performance status, upfront technical unresectability, rapid progression with development of distant metastases, and a combination of these factors accounted equally for the decision against resection. In patients with poor PS presenting with locally advanced primary RPS, planned preoperative treatment allowed adverse biology to declare itself.

Table 1 Demographics and tumour characteristics in Non-Resected vs Resected RPS patients

	Total (n=130)	Resected (n=96)	Not resected (n=34)
Age, median (range)	65 (24-91)	62.5 (24-88)	70 (30-91)
Male Female	60 70	41 (68%) 55 (79%)	19 (32%) 15 (21%)
Tumor size, median (range), cm	14.9 (3.2-61.4)	17.5 (3.2-61.4)	15 (5.5-35)
Histology, number, % of each subtype			
WD LPS	15	12 (80%)	3 (20%)
DD LPS	72	50 (69%)	22 (31%)
LMS	26	21 (81%)	5 (19%)
MPNST	1	1 (100%)	-
SFT	3	3 (100%)	-
UPS	7	6 (86%)	1 (14%)
Other	6	3 (50%)	3 (50%)
Multifocality	4	0	4

Table 2. Reasons why patients did not undergo resection, grouped by upfront technical resectability

	Upfront technically resectable:			
Reason for non-resection	No (n=9)	Borderline (n=13)	Yes (n=12)	Total (n=34)
Poor Performance Status	-	4	4	8
Progressed prior to/ on planned preoperative Rx	-	9	4	13
Local progression Distant metastasis	-	2 7	3 1	5 8
Patient declined	-	-	3	3
Second primary malignancy	-	-	1	1

Poster 396 3042602

WHY PRIMARY RETROPERITONEAL SARCOMA (PRPS) PATIENTS (PTS) UNDERGOING TREATMENT AT STRASS INSTITUTIONS DID NOT ENROLL IN STRASS: THE STREXIT STUDY FROM EORTC STBSG AND TARPSWG

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Objective: Randomizing pts to clinical trials that evaluate the addition of unproven neoadjuvant treatment to standard–of-care surgery can be challenging. We explored the reasons why pts with pRPS treated at institutions accruing to the phase 3 trial of preoperative radiation therapy (RT) plus surgery versus surgery alone (STRASS) did not enroll in the study and evaluated their outcomes, to put the forthcoming STRASS data in perspective and guide future trial development.

Methods: We gathered treatment and outcome data on prospectively tracked, consecutive patients with pRPS and no distant metastases at presentation who underwent resection with or without perioperative therapy from 01/12 through 04/17 (STRASS enrollment window) at TransAtlantic Retroperitoneal Sarcoma Working Group (TARPSWG) referral centers that enrolled at least 1 pt in STRASS. Reasons why pts were deemed ineligible and why eligible pts did not enroll were tabulated.

Results: We identified 816 pts treated at 6 high-volume centers that met inclusion criteria for the STEXIT study, out of 31 STRASS-enrolling centers. Of these, 532 pts (65.2%) were considered eligible for STRASS, and 282 (35% of total, 53% of eligible) were offered enrollment. Of those offered trial enrollment, 156/282 (55%) enrolled and are excluded from the present analysis, while 126 declined participation in STRASS and are included here (Table 1).
The reasons that 284/816 pts (35%) were deemed ineligible for STRASS were: technical factors (97, 34%), prior treatment of pRPS (63, 22%), prior/concurrent malignancy (51, 18%), pt co-morbidities/poor performance status (38, 13%), prior RT (15, 5%), psychosocial factors (15, 5%), and other (5, 2%).
The reasons that 250/532 eligible patients were not offered enrollment included surgeon preference (107, 43%), radiation oncologist preference (64, 26%), trial not yet open (47, 19%), pt preference (24, 9%), and other/unclear (8, 3%). There was significant inter-institutional variability in use of neoadjuvant RT outside of STRASS (5-74%), offering STRASS enrollment to eligible pts (40-70%), and successful enrollment of pts offered STRASS (25-92%) (Table 2). Of the 660 pRPS pts who underwent treatment outside of STRASS (STREXIT cohort), 543 pts had surgery only and 117 had RT + surgery. Disease status at last follow-up is shown in Table 1.

Conclusion: Remarkably, a significant proportion of STRASS-eligible patients were not offered participation, even at high-volume reference centers; a major barrier to participation was surgeon preference. Delays in trial activation precluded offering enrollment to a large group of pts. These data will help inform future multimodality non-drug trial development, for not only sarcomas but also other operable solid tumors.

Table 1

Characteristics	Total (n=660) (STRASS pts excluded)	Surgery Alone (n=543)	Surgery + Radiotherapy (n=117)
Histology			
WDLPS	138	130 (94%)	8 (6%)
DDLPS	286	236 (83%)	50 (17%)
LMS	122	97 (80%)	25 (20%)
MPNST	12	7 (58%)	5 (42%)
SFT	39	31 (79%)	8 (21%)
UPS	30	19 (63%)	11 (37%)
Other	33	23 (70%)	10 (30%)
Eligible pts offered STRASS	282		
Eligible pts offered STRASS, pt declined	126	109	17
Eligible pts not offered STRASS	250	192	58
Reasons ineligible for STRASS	284	242	42
Prior RT	15	12	3
Pt factors (morbidity, PS)	38	32	6
Prior/concurrent malignancy	51	45	6
Previously treated	63	55	8
Operative factors	97	83	14
Psychosocial factors	15	12	3
Other	5	3	2
Reasons eligible patients were not offered			
Pt preference	24	20	4
Surgeon preference	107	74	33
Radiation oncologist preference	64	62	2
Trial not open	47	28	19
Other/unclear	8	8	0

Disease status (06/18)			
No evidence of disease	397	334	63
Alive with disease	132	108	24
Dead of disease	107	85	22
Dead of other causes	24	16	8

Table 2

Center	STREXIT (n=660)			Total STRASS Eligible Patients (n= 532)	Trial Participation Offered to Patient (n=282) (% of those eligible)	Patients enrolled on STRASS (n=156) (% of those offered)
	Total	Surgery Alone (n=543)	Surgery + Radiotherapy (n=117)			
A	61	47 (77%)	14 (23%)	46	23 (50%)	7 (30%)
B	73	19 (26%)	54 (74%)	71	50 (70%)	25 (50%)
C	198	172 (87%)	26 (13%)	126	78 (62%)	50 (64%)
D	93	88 (95%)	5 (5%)	89	48 (54%)	44 (92%)
E	203	189 (93%)	14 (7%)	160	67 (42%)	17 (25%)
F	32	28 (88%)	4 (12%)	40	16 (40%)	13 (81%)

Poster 397 3042735

SHOULD LOCALIZED RETROPERITONEAL SARCOMAS BE TREATED IN REFERENCE CENTERS?: RESULTS OF A SINGLE INSTITUTION

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Objective: To evaluate long-term outcomes after curative surgery for localized retroperitoneal sarcoma (RPS), in primary and sub-sequent surgical treatments and the clinical short-term benefit.

Methods: We perform a retrospective analysis of our prospective database of the Sant Pau Hospital of sarcoma patients registered between 2008 and 2018. We analyzed exclusively patients with localized RPS treated by primary surgery at our institution, and patients treated by less than 2 surgical procedures out of our center. Ethics committee approval was obtained for this study.

Results: A total of 58 patients with localized RPS were included in this study. The median age at diagnose was 60 years (range 30-84). The median tumor size was 23 cm (range 3.4-54 cm). The most frequent histological subtypes were de-differentiated liposarcoma (45%), well-differentiated liposarcoma (21%) and leiomyosarcoma (12%). 67% of the cases were high grade tumors. Most of them were localized in the abdominal retroperitoneum, with 24% localized in the pelvic, and 8,6% where multicentric at diagnosis. Thirty-five primary resections (60%) were performed by the sarcoma team in our hospital. The rest of the patients (n=23) were refered from non-specialized hospitals after surgery (2 with more than 1 previous surgical treatment). “En-bloc” surgery was performed in 79% of cases by the specialized team compared to only 52% of cases resected at a non-specialized hospital. In 79% (n=46) of cases resection was macroscopically complete. This resection was multivisceral (>1 resected viscera) in the 53.4 % (n=31) of the cases. With a medium follow-up of 45 months (range 3-196), the recurrence rate after primary surgery was 50%. The initial site of recurrence was local in 76% (n=28) of the cases, distant in 13% (n=5) and both local and distant in 11% (n=4). 70% of the recurrent cases were high grade and, regarding histology, 23% (n=6) of the cases were well-differentiated liposarcoma, 53.8% (n=14) de-differentiated liposarcoma, 7.6% (n=3) leiomyosarcoma and 15.3% (n=4) had other histologies. Twenty-six patients underwent a second surgery. The 73% resections was “en-bloc” surgery. The macroscopically resection rate for second surgery was 92.3% and in 59% of the cases was a multivisceral resection. The recurrence rate after second surgery was 73% (n=19). A total of 10

patients underwent a third surgery. Four patients died due to postoperative complications: 1 after the primary surgery, 1 after second surgery and 2 patients after subsequent surgeries. The median progression-free survival (PFS) after the first surgery was 40.3 months (95% CI 27.9-52.8) and after the second surgery 25.9 months (95% CI 13.25-38.66). The median overall survival (OS) of this series was 120.7 months (95% CI 92.21-149.33). The median OS from the second surgery was 56.4 months (range 36.3-76.5). After first surgery, a statistically significant difference in OS was found in favor of the "en-bloc" surgery (109.9 vs 46.16 months, p=0.019). A worse survival is observed after second surgery in the "en-bloc" surgery group, probably related to a worse prognosis of the malignancy (51.51 vs 72.67 months, p=0.5). The macroscopic complete resection predicts a better OS after first (103.31 vs 48.44 months, p = 0.23) and second surgery (60.86 vs 8.50 months, p=0.01). Of the 10 patients undergoing a third retroperitoneal surgery, 40% remain alive (n=4), with an OS of 24.95 months (12.59-37.31).

Conclusion: Despite extensive surgery, the recurrence rate of RPS is high. The performance of "en-bloc" surgical resection as first treatment has a statistically significant impact on survival after first surgery. However, those patients who underwent an en-bloc surgery after first recurrence have worse survival. This may reflect a greater extension of the recurrence and a worse prognosis of these patients. The survival results of our series suggest that patients diagnosed with RPS should be referred to referral centers.

Poster 398 3026103

PREDICTIVE FACTORS FOR COMPLICATIONS AFTER SURGICAL TREATMENT FOR SCHWANNOMAS OF THE EXTREMITIES

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Objective: Schwannomas are well encapsulated, benign neoplasms, and enucleation is a standard operation procedure. The incidence of neurological complications after surgical treatment for schwannomas of the extremities varies, and there is no consensus concerning predictive factors for complications. The aim of this study was to elucidate predictive factors for complications after surgical treatment of schwannomas.

Methods: A total of 139 patients with 141 schwannomas arising in major nerves were enrolled. Data regarding preoperative clinical features and the postoperative neurological complication rate were obtained. Predictive factors for complications were statistically analyzed.

Results: Postoperative complications occurred in 49 patients (35.2%), including 42 patients with sensory disturbance and 8 with motor weakness. In univariate analysis, older age, upper extremity tumor origin, and major motor nerve involvement were associated with a high complication rate ($p = 0.03$, $p = 0.003$, and $p = 0.001$, respectively). In multivariate analysis, major motor nerve involvement was an independent predictive factor for postoperative complications ($p = 0.03$). This was confirmed by Bayesian estimation, integrating results from 5 previous studies. Almost all complications gradually improved, but 6 out of 8 patients with motor weakness did not show full recovery at final follow up.

Conclusion: Schwannomas arising from major motor nerves may be at higher risk for postoperative complications.

(a)

Study	Nerve origin	
	Major motor nerves	Others
Fujibuchi et al	18/62	0/4
Siqueira et al	10/69	1/3
Sawada et al	11/16	1/2
Oberle et al	7/15	0/0
Kim et al	23/30	0/0
Present study	44/103	5/38

Complication number/Total

(b)

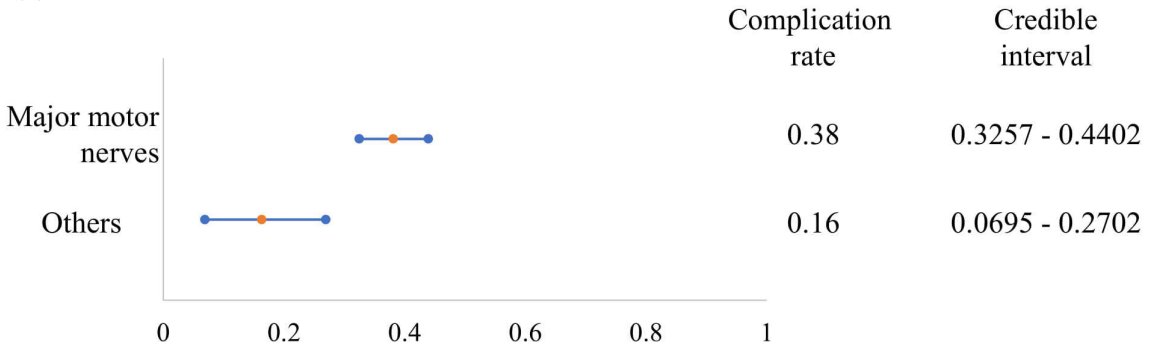

Figure. Correlation between nerve origin and postoperative complications. (a) Complication number/total number of cases in previous reports and in the current study. (b) Comparison of complication rates between tumors originating in major motor nerves and others .

Poster 399 3027924

CLINICOPATHOLOGICAL AND RADIOLOGIC FEATURES OF GASTRIC SCHWANNOMA

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Objective: Schwannomas are usually benign, slow-growing neurogenic tumors that originate from Schwann cells in the neural sheath and gastric schwannomas are rarer mesenchymal tumors that arise from the nerve plexus of gut wall. It accounts for only 0.2% of all gastric tumors and 4% of all benign gastric neoplasms. They are usually asymptomatic and found accidentally by medical checkups. The diagnostic accuracy is low when adequate amount of tissue is not obtained in endoscopic ultrasound-guided fine-needle aspiration biopsy (EUS-FNA) for gastric submucosal tumors (SMTs), on the other hand, gastric SMTs were known to have nonspecific radiological features by pathological differences. The aim of this study is to clarify the clinical and radiologic characteristics of gastric schwannomas.

Methods: We retrospectively reviewed 1714 patients with gastric tumor who underwent surgical resection and definitive pathological findings were available from April 2008 to May 2018 in a single institution. Among them, the following characteristics of gastric schwannomas were examined: patient demographics, clinical presentation, preoperative imaging, examination results, operating data, histopathology and prognosis.

Results: There were 4 patients with gastric schwannoma among 1714 patients (0.2%). Four patients were females and the median age was 52.5 years (range, 49-75). One patient had GI bleeding and the others were asymptomatic. All the 4 patients underwent EUS-FNA, but none were diagnosed as schwannoma preoperatively, mainly due to small amount of tissue samples. In upper gastrointestinal endoscopy, tumor located at middle body of the stomach for 2 patients and lower for 2 patients, and all lesions were seen as SMTs. In CT examination, median tumor diameter was 30mm (range, 22-76) and 3 lesions were seen as ovoid, well-defined and homogeneous enhancement. Growth patterns of the three patients were extra-luminal type and the other was mixed type. Three patients had perigastric lymphadenopathy. All the patients met three of the following four radiologic characteristics of schwannoma: 1) extra-luminal or mixed growth pattern, 2) homogeneous enhancement, 3) round-shaped, 4) perigastric lymphadenopathy. Two patients with suspicious lymph node metastasis underwent laparoscopic distal gastrectomy with lymphadenectomy, but there were no lymph node metastases and peripheral lymphoid cuffs were shown in pathological finding. All the 4 tumors had no malignant findings with few

mitoses.

Conclusion: Our results suggested that the combination of several nonspecific radiological findings might be helpful to diagnose gastric schwannoma, especially when tumors were not diagnosed by EUS-FNA. Development of more reliable diagnostic methods including radiologic findings may contribute to decide indication of treatment for gastric SMTs.

Poster 400 3041682

SOLITARY FIBROUS TUMOR - A SINGLE INSTITUTION RETROSPECTIVE STUDY

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Objective: Solitary Fibrous Tumor (SFT) is a rare neoplasm that usually arise from serosal membranes in any anatomical locations, however, pleura is the most frequent site affected. The primary treatment is surgery and/or radiotherapy. The prognosis is difficult to predict since most tumors never relapse, but a minor group of patients suffer from recurrent disease several years after initial treatment. Following the rare prevalence of SFT treatment recommendations are lacking and published data is highly insufficient at present. The aim of this study is to evaluate a risk assessment tools proposed by Demicco et al. based on age, tumor size and mitotic index.

Methods: We retrospectively analyzed a population-based cohort of SFT. 72 patients diagnosed with SFT in the Central, North and Southern Denmark Region between 1979 and 2013 were included in the study. Patients with uncertain diagnosis or insufficient data were excluded. Patients, tumor, treatment and follow-up data were achieved from journals, pathology database and the Aarhus Sarcoma Registry (ASR). The primary endpoint is local recurrence (LR).

Results: 17 of 62 patients developed recurrence with either local or distant disease. The 5-year recurrence free survival was 83% (95%CI: 70-90) and the 10-year was 69% (95%CI: 53-81). The median time to recurrence was 4.3 years. Metastatic or inoperable SFT has a poor prognosis with a median overall mortality of 0.7 year (range: 0.3-2.2) and a 5-year overall mortality of 89% (95%CI: 70-98).
Further validation of the risk assessment tool proposed by Demicco et al. was done on 51 patients with extra-cranial tumors and patients classified as high-risk, had a significantly decreased overall survival with a hazard ratio of 3.7 (95%CI: 1.1-12.3).

Conclusion: Validation of the Demicco et al. risk assessment tool found high-risk patients to have a significantly worse prognosis than other patients. 10 years follow-up for moderate and high-risk patients is recommended.

Poster 401 3041744

HIGH-GRADE UNDIFFERENTIATED SMALL ROUND CELL SARCOMA (USRCS): A CLINICAL-PATHOLOGICAL STUDY BY THE ITALIAN SARCOMA GROUP (ISG)

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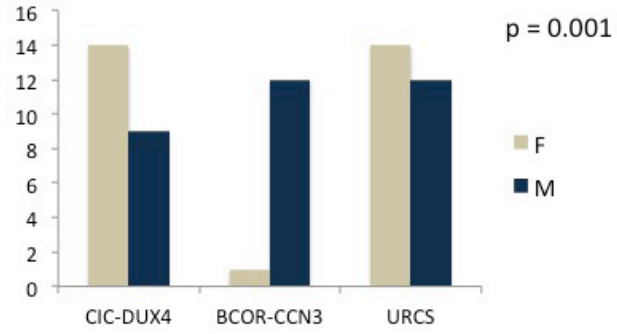
Objective: Undifferentiated small round cell sarcomas (USRCSs) are a diagnostic challenge. The use of molecular techniques led to the description of a variety of new, rare sarcoma subtypes, which have a morphological appearance similar to Ewing sarcomas ("Ewing-like" sarcomas) but carry different gene fusions; *CIC-DUX4* and *BCOR- CCNB3* are the most comon alterations. Natural history and optimal treatment for these ultra rare tumors is not well defined.

Methods: All cases with a diagnosis of USRCSs were reviewed, and *CIC-DUX4*/*BCOR-CCNB3* translocations were

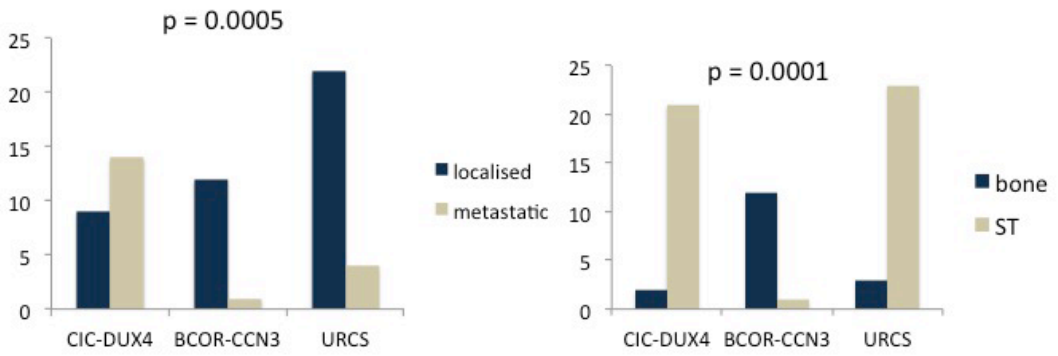
tested by FISH or RT-PCR. Inclusion criteria for the present study were 1) a diagnosis of USRCSs (negative for all Ewing translocations, *CIC-DUX4* and *BCOR-CCNB3*), a diagnosis of *CIC-DUX4* or *BCOR-CCNB3* sarcoma; 2) clinical and outcome data available. Treatments and outcome were examined. Pathologic response to neo-adjuvant chemotherapy was assessed by Bologna System as for Ewing (micro-foci or not viable tumor defining good response). Good radiologic response in the primary tumor was defined as any decrease in tumor size in pre- surgical staging, while RECIST 1.1 was used in metastatic patients.

Results: 62 patients treated from 1983 to 2018 met the inclusion criteria: 45 cases were reclassified: *CIC-DUX4* fusion was detected in 23 (51%) patients, *BCOR-CCNB3* in 13 (29%), 9 (20%) cases were USRCSs, while in 17 cases molecular analysis is ongoing. Median age was 33 years (range 5-75 years); 43 (69%) patients had localized disease and 19 (31%) presented with metastases (15 (79%) to the lungs, 3 to the nodes, 1 to bone and 1 to liver). Forty-five (73%) of the patients had soft tissue primary tumors, 17 (27%) bone tumors. Differences in presentation were observed amongst the specific entities (Figure 1).
Survival analysis was performed in 45 re-classified patients, while addictional data on 17 patients will be presented at the meeting.
The local treatment was surgery in 22 (49%) patients, surgery + radiotherapy in 13 (29%) and radiotherapy in 6 (13%), whereas 2 patients (4.5%) did not undergo local treatment and in 2 it was not reported. No differences were apparent amongst the different entities. Chemotherapy was given to 41/45 (91%) patients: Ewing-like in 27 (66%), Doxo/IFO in 8 (19%), osteosarcoma-like in 2 (5%), unknown in 4 (10%). When chemotherapy was given preoperatively, a good pathological response was observed in 6/8 (75%) *BCOR-CCNB3* patients (1/1 after Doxo/IFO, 5/5 after Ewing-like, 0/2 after osteosarcoma-like), and in 1/9 (11%) *CIC-DUX4* patients (0/1 after Doxo/IFO, 1/8 after Ewing-like); a radiological response defined as good on primary tumor was observed in 6/9 (67%) *BCOR-CCNB3* patients (1/1 after Doxo/IFO, 5/8 after Ewing-like), and in 5/10 (50%) *CIC-DUX4* patients (0/1 after Doxo/IFO, 5/9 after Ewing-like).
Best response according to RECIST in 8 *CIC-DUX4* positive metastatic patients undergoing Ewing-like chemotherapy was 1 CR (13%), 3 PR (38%), 2 SD and 2 PD, while in 2 *CIC-DUX4* patients undergoing ADM-IFO 1 PR and 1 SD were reported.
With a median follow-up of 19 months (range 1-212), The 3-year EFS rate was 82% (95% CI 59-100) in *BCOR-CCNB3* patients, 16% (95%CI 3-61) in *CIC-DUX4*, and 75% (95% CI 33-100) in USRCSs. The 3-year OS rate was 92% (95%CI 78-100) in *BCOR-CCNB3* patients, 31% (95% CI 8-55) in CIC-*DUX4*, and 100% in USRCSs.

Conclusion: Our retrospective study confirms that “Ewing-like” sarcomas are not a single entity. Molecular analysis should be undertaken in all patients classified as USRCSs, with *CIC-DUX4* and *BCOR-CCN3* tumors having highly discrepant clinical behaviour. Specifically, *BCOR-CCN3* tumors are more often bone localized tumors, with good pathologic responses in most of the patients, while *CIC-DUX4* often present as metastatic soft-tissue tumors, with a low rate of good pathologic responses and inferior survival.
Due to the extreme rarity of these entities, a worldwide effort should be undertaken to prospectively validate these findings and identify new treatment strategies.



Differences in presentation amongst *CIC-DUX4*, *BCOR-CCN3* and *USRCSs*: a higher prevalence for female gender, presence of metastases and soft tissue primary tumor location in *CIC-DUX4* patients, vs a male prevalence, bone presentation and a low rate of synchronous metastases in *BCOR-CCN3* patients



Poster 402 3008451

DESIGNING A RATIONAL FOLLOW-UP SCHEDULE FOR SOFT TISSUE SARCOMA

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Objective: The objective of this study was to determine the frequency and timing of local recurrence and metastasis following resection of extremity STS, and apply these findings to design a rational follow-up schedule.

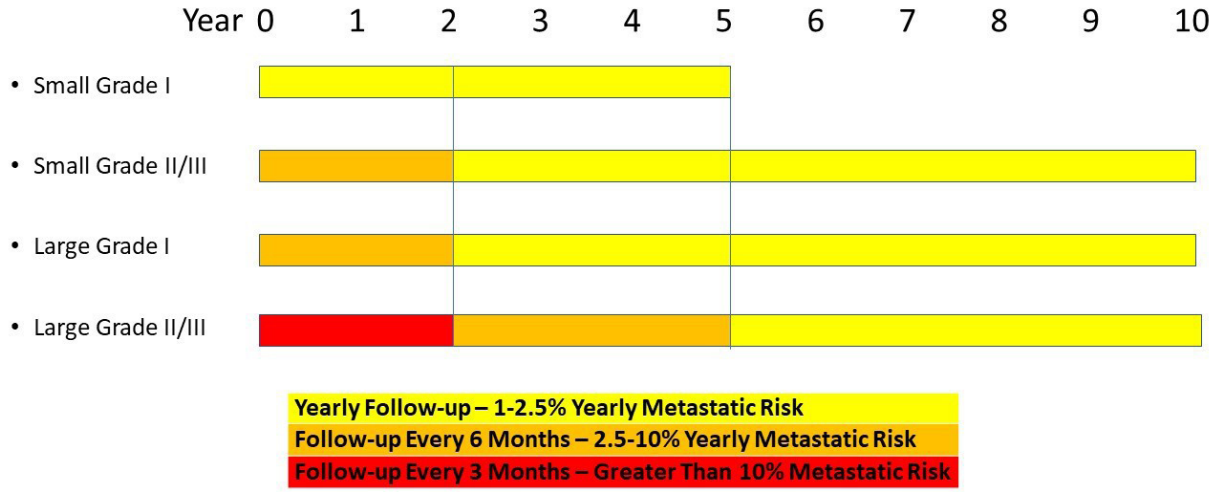
Methods: Utilizing a prospective database, a retrospective single center review was performed on all patients with minimum 2 year follow-up who had surgically resected localized extremity STS. Low grade liposarcoma and dermatofibrosarcoma protuberans were excluded. The standard follow-up protocol at the study center included a chest x-ray and physical exam every 3 months for 2 years, then every 6 months until 5 years and yearly until 10 years for intermediate and high grade tumors. For low grade tumors it was every 6 months until 10 years. Kaplan-Meier curves were calculated based on histologic grade (low, intermediate, high), tumor size (greater than or less than 5cm), and the event rate for local recurrence and metastatic disease was calculated on an annual basis for 10 years. Based on the yearly event rate for each grade of tumor stratified by size, a follow-up protocol was established. An event rate greater than 0.1 per year (i.e. >10% chance of developing metastasis) was used to define patients who would require a follow-up every 3 months. An event rate of 0.025-0.1 would necessitate follow-up every 6 months, an event rate of 0.025-0.01 would suggest a follow-up on a yearly basis, and patients with an event rate of less than 0.01 events would require no further follow-up.

Results: A total of 1816 extremity STS patients were reviewed. At the conclusion of the study 1115 were alive with no evidence of disease, 92 were alive with evidence of disease, 450 had died of disease, and 160 had died of other causes.
There were 121 small low grade tumors with 8 metastatic events (6.6%) and 5 local recurrences (4.1%). There were 244 small intermediate grade tumors with 31 metastatic events (12.7%) and 18 local recurrences (7.4%). There were 261 small high grade tumors with 53 metastatic events (20.3%) and 28 local recurrences (10.7%).
There were 109 large low grade tumors with 20 metastatic events (18.3%) and 8 local recurrences (7.3%). There were 382 large intermediate grade tumors with 112 metastatic events (29.3%) and 27 local recurrences (7.1%). There were 699 large high grade tumors with 359 metastatic events (51.4%) and 66 local recurrences (9.4%).
The event rate of development of metastasis was greater than that of local recurrence at all time points. Therefore the event rate for metastatic spread was used to develop the protocol. For the development of a clinically applicable algorithm, consolidation of the tumor groups was performed. High grade and intermediate grade tumors both met the highest threshold event rate in the first 2 years and they were grouped together due to similar proposed follow-up schedules. This left four remaining groups necessitating a follow-up protocol (Table 1). Based on the results, for small low grade tumors we propose a yearly follow-up with chest imaging and physical exam for 5 years. Large low grade tumors and small intermediate/high grade tumors can be followed with the same suggested protocol: every 6 months for 2 years then yearly to 10 years. Large intermediate and high grade tumors should be seen every 3 months for 2 years, every 6 months for years 3-5, then yearly until 10 years (Figure 1).

Conclusion: Based on the results of this study, we can recommend 3 distinct follow-up protocols based on tumor grade and size that are easy to apply clinically (Figure 1). These results can streamline patient care by providing optimal follow-up while minimizing resource utilization. Follow-up for extremity STS should be tailored to the risk of recurrence or development of metastatic disease and using this proposed schedule, overutilization of medical resources and patient anxiety can be reduced.

Table 1: Yearly Metastatic Event Rate Based on Size and Grade

	0-1 Years	1-2 Years	2-5 Years	5-10 Years
Small Low Grade	1.7%	0.0%	1.1%	0.6%
Small Int/High Grade	6.0%	3.4%	1.6%	0.9%
Large Low Grade	6.4%	2.9%	1.3%	1.2%
Large Int/High Grade	26%	11%	2.8%	1.1%



Poster 403 3014026

RADIATION-ASSOCIATED SARCOMA AFTER BREAST CANCER IN FINLAND DURING 1953-2014: A STRONG INCREASE OF ANGIOSARCOMA

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Objective: Treatment of early breast cancer (BC) consists of breast-conserving surgery and radiotherapy (RT). Radiation-associated sarcoma (RAS) occurring after BC is a well known secondary malignancy. RAS is defined as a sarcoma occurring at or close to the RT target. During the past two decades a sizeable number of studies have focused on radiation-associated angiosarcoma (AS) after BC. However, a substantial proportion of previous studies of RAS after BC are case reports and several studies are based solely on registry data with a lack of detailed treatment information.
Our current study presents an overview of RAS after BC in a nationwide population in Finland and provides an analysis of the evolution of this malignancy during 1953-2014.

Methods: This investigation involved the analysis of patients with sarcoma after BC obtained from the files of the Finnish Cancer Registry (FCR). The FCR was queried for patients with an invasive breast carcinoma and subsequent sarcoma during 1953-2014. Registry data, patient records and pathology reports were analyzed by a physician (S.S.). Patients with no RT for BC or sarcoma outside the RT field were excluded to identify actual RAS patients. BC and RAS treatment data was collected directly from the hospitals in question. All RAS samples, excluding eight unavailable specimens, underwent a histological re-examination by an experienced sarcoma pathologist (T.B.). RAS latency was defined as the time elapsed from RT for BC to RAS diagnosis.

Results: Our query in the FCR yielded a total of 355 patients with a sarcoma diagnosed after BC between 1953-2014. Standardized incidence ratio (SIR) for all sarcomas during study period was 1.89 (95% CI, 1.7-2.09). For AS the SIR was 10.81 (95% CI, 8.53-13.47) and for other sarcomas 1.55 (95% CI, 1.38-1.74).
After exclusion of ineligible patients, the study population consisted of 96 RAS patients (Figure 1). The mean age (SD) at BC and RAS diagnosis was 56 (11) and 68 (10) years, respectively. The majority (54%) of BC patients were operated with breast-conserving surgery. The overall median latency of RAS was 11.0 years (range 0.6-29.9). For AS the median latency was 7.7 years (range 0.6-24.5) and for other RAS 13.8 years (range 2.3-29.9). RAS median latency varied depending on the year of BC diagnosis (Figure 2). The most common RAS location was breast (Table 1). The Kaplan-Meier estimate for 5-year sarcoma-specific survival was 64.8% for all patients and 75.1% for patients treated with curative intent.
AS was the most common RAS subtype (Table 2). However, in current study the first AS was diagnosed in a patient treated for BC in 1984, after which the frequency of AS was considerably larger compared to RAS of other types as presented in Figure 2.

Conclusion: Present study discovered that AS was the prevalent RAS subtype after BC. The first AS was diagnosed in 1984; thereafter the proportion of AS has strongly increased. Only a few similar observations, underlining the change in RAS subtypes towards AS, have been made previously. It is possible that current BC treatment strategies favoring breast-conserving surgery and RT are contributing to this phenomenon. Future work should explore the causes of this finding.

Table 1. Radiation-associated sarcoma location

Site	Total no. of patients	Angiosarcoma	Other sarcoma
Breast	46	37	9
Upper trunk	16	7	9
Ablation scar	11	6	5
Shoulder	6	0	6
Sternum	5	0	5
Axilla	4	0	4
Lung	4	0	4
Scapula	3	0	3
Upper arm	1	0	1

Table 2. Radiation-associated sarcoma histology (n)

Angiosarcoma	50
Undifferentiated pleomorphic sarcoma	27
Osteosarcoma	5
Fibrosarcoma	3
Extraskeletal osteosarcoma	3
Chondrosarcoma	2
Leiomyosarcoma	2
Myxofibrosarcoma	2
Extraskeletal chondrosarcoma	1
Neurofibrosarcoma	1

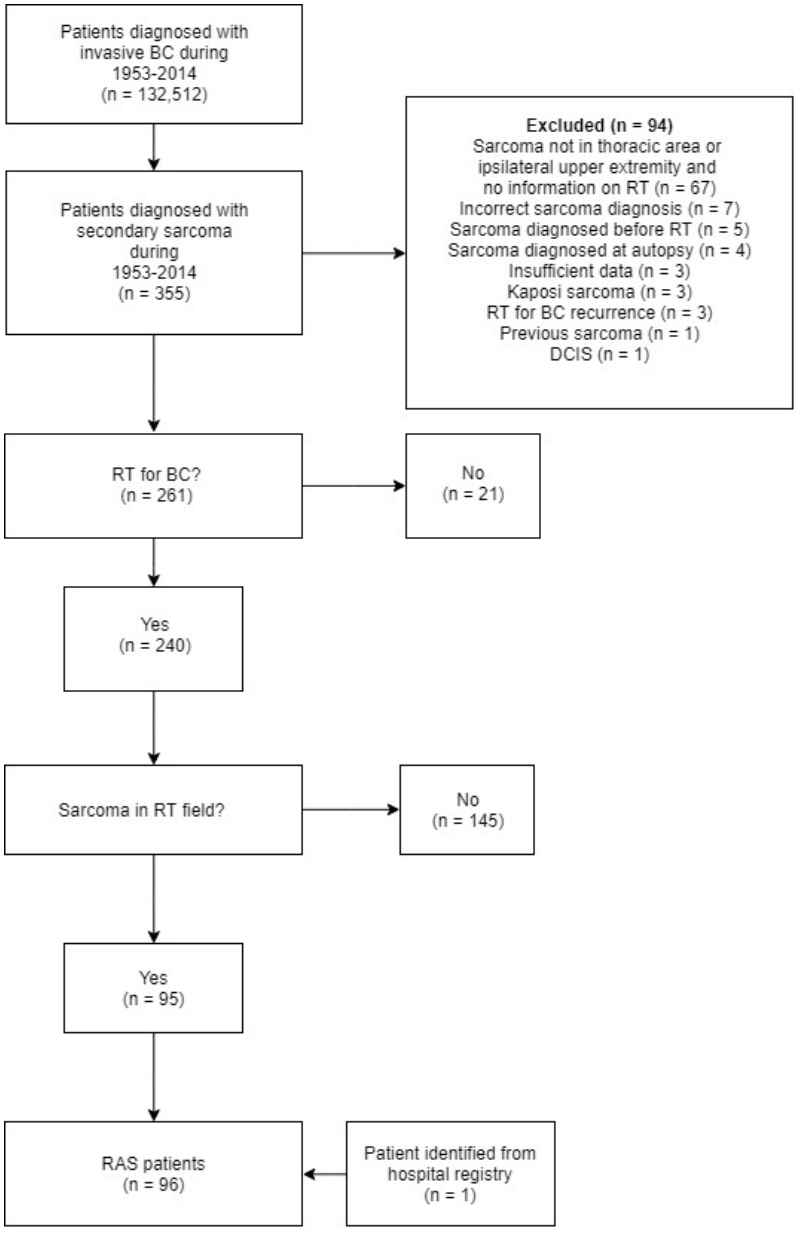

Figure 1. Flow chart of the study population; BC breast cancer; RT radiotherapy; RAS radiation-associated sarcoma; DCIS ductal carcinoma in situ

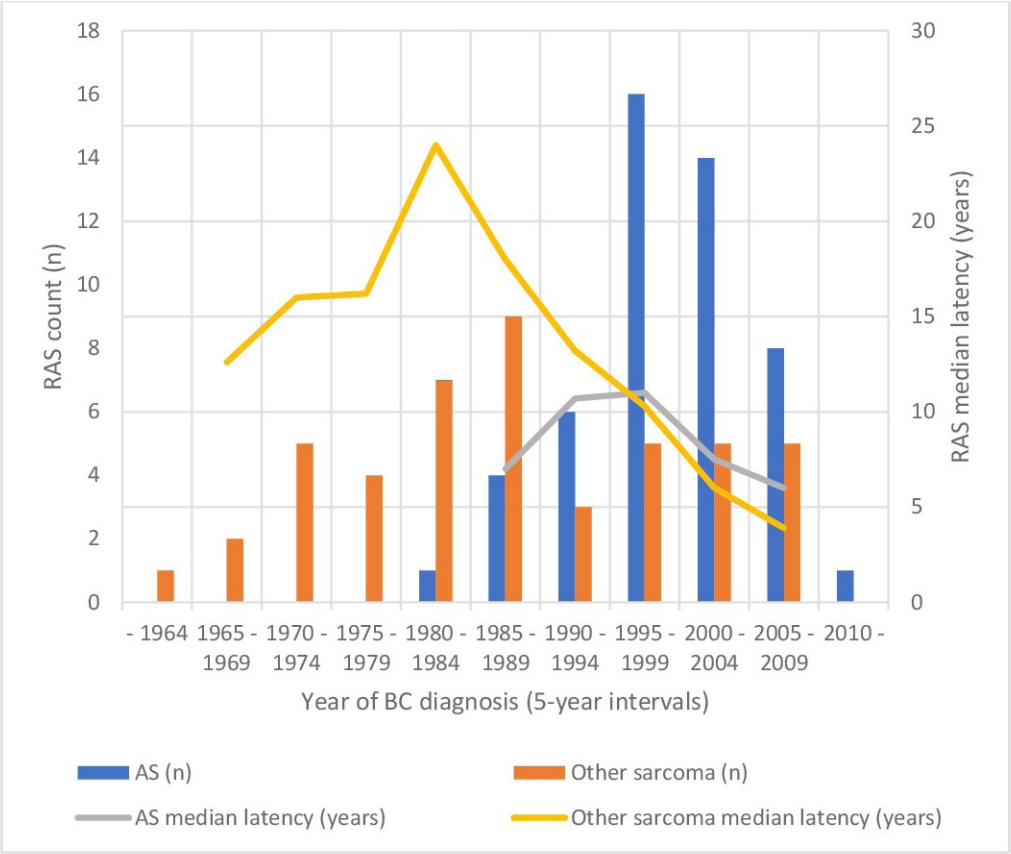

Figure 2. Trends in RAS incidence and median latency; RAS radiation-associated angiosarcoma; AS angiosarcoma; BC breast cancer

Poster 404 3042577

MULTIDISCIPLINARY TUMOR BOARD RECOMMENDATIONS FOR SARCOMA PATIENTS WITH OLIGOMETASTATIC DISEASE

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Objective: Oligometastatic disease is challenging since systemic as well as localized treatment options may be rational and few data exist to guide treatment decisions. We prospectively analysed the multidisciplinary sarcoma board held weekly at the University Medical Center Mannheim.

Methods: This prospective observational study analyzed 164 patients that were discussed in the multidisciplinary sarcoma board between 02/2017 and 07/2017. We included patients with 1-5 metastases. Patient characteristics as well as tumor stage and previous treatment modalities were documented. Primary aim of the study was to evaluate the treatment decisions that were taken for sarcoma patients with oligometastatic disease. Treatment decision were classified in systemic vs. regional treatment. Regional treatment was classified in surgery, radiation therapy and other interventional treatment modalities.

Results: Sixtyseven (41%) out of 164 patients had metastatic disease. Eleven patients (7% of all patients and 16 of those with metastases) had oligometastatic disease. The most frequent histology of patients with oligometastastic disease was undifferentiated pleomorphic sarcoma (n=3). The most frequent site of oligometastases was the lung (n=6). Ten out of eleven patients with oligometastases had metachronic metastatic disease (median time to metastases 20 months, range 0 to 127 months). Treatment recommendations for oligometastatic disease was as follows: watchful waiting n=1, systemic chemotherapy n=3, regional therapy n=7 (surgery plus irradiation n=3, irradiation n=2, surgery n=1 and radiofrequency ablation n=1). There was no obvious difference in age, ECOG performance status, number of metastases and time to first metastasis between patients who received regional or systemic treatment.

Conclusion: Patients with oligometastatic disease represent a considerable proportion of all patients discussed in the multidisciplinary sarcoma board (7%). In most patients with oligometastatic disease regional treatment was recommended. These data may be used for the design of prospective trials to optimize the treatment of oligometastatic disease.

Poster 405 3007777

ULCERATING SOFT TISSUE SARCOMAS

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Objective: Although cutaneous involvement of tumors is seen frequently in squamous cell carcinomas and dermatofibrosarcoma protuberans, skin ulceration is an uncommon presentation of malignant soft tissue sarcomas of the extremities. Fungating soft tissue sarcomas present a treatment challenge, as they can lead to infection and clinically significant bleeding. The standard soft tissue sarcoma approach of neoadjuvant radiation and wide local resection can worsen these issues and also lead to tumor rupture. Prior literature has focused on the prognostic aspect of sarcoma ulceration, however, there is no literature, to our knowledge, to direct treatment in these cases. Our objective is to examine treatment methods and subsequent outcomes in an ulcerating soft tissue sarcoma cohort. This should allow us to identify a sequence of administering systemic therapy, radiation, and surgery such that patients are at lower risk for complication.

Methods: A query of our institution's tumor registry was performed and identified 588 patients treated for soft tissue sarcoma between January 1, 2000 and January 29, 2018. This cohort was further filtered to select all extremity sarcomas except dermatofibrosarcoma tuberans and epithelioid sarcoma. Our final cohort of fungating sarcomas was identified by then searching pathology, physical exam, and operative notes for the terms "fungating" or "ulcerating". Due to the expected rare occurrence of these tumors, multi-institution collaboration was undertaken. Patient demographic, treatment, and outcome information were collected via retrospective chart review.

Results: Seventeen patients met criteria for the study. Median follow up was 11 months, mean was 21 months (range: 3-120 months). Only four patients had a tumor under 5cm, four had tumors over 10cm. Eight patients had a biopsy prior to presentation; ulceration began after biopsy in four of these patients; the other four did not have documentation as to when ulceration was noticed. Twelve patients were AJCC stage III at presentation, three were stage IV. All but one patient had a negative margin resection, none had neoadjuvant radiation, seven had post-operative radiation. Wound complications developed in 4 patients; only one of those patients received radiation and developed a wound infection. Five developed recurrence: one patient recurred with local and pulmonary disease, one with pulmonary metastases alone, two with local recurrence alone, and one had recurrence in spine, ilium and lymph nodes. Both pulmonary recurrences eventually succumbed to their disease, as did one of the local recurrence patients. Three more patients died from unrelated causes. Five patients required skin graft, four required local muscle flaps, and five underwent primary amputation. Four patients underwent systemic treatments, one with known lymph node metastases at presentation and three for development of distant metastases. Seven patients had pathologic diagnosis of UPS, five had myxofibrosarcoma, three had leiomyosarcoma, one had angiosarcoma, and one had extra-osseous Ewing's sarcoma.

Conclusion: Ulcerating soft tissue sarcoma of the extremity is a poor prognostic factor, and fungation requires reassessment of the typical soft tissue treatment sequence. In our cohort, only two patients developed surgical site infection, and two more had delayed healing without infection. Only one required operative intervention. Although our numbers are small, we believe approaching an ulcerating soft tissue sarcoma with wide local resection prior to radiation allows for a low risk of wound complications for the patient; systemic therapy is only offered if the pathology requires it or if the disease is not localized.

Clinical data on ulcerating sarcoma patients

Patient	Pathology	Location	Size (cm)	Mets at presentation	Surgery	XRT	complications	Recurrence	FU (mos)
1	UPS	ASIS	9	no	WLE	no	infection	yes	12 DOD
2	UPS	tibia	8	no	WLE	no	no	no	11
3	MyxoFS	prox calf	5	no	WLE	post-op	no	no	10
4	LMS	ankle	10.5	no	WLE	no	no	no	6
5	MyxoFS	post calf	4.5	no	WLE	post-op	no	no	11
6	LMS	lat calf	21	pulmonary	WLE	no	delayed healing	no	12
7	UPS	forefoot	6.3	lung nodules, not certain	amputation	no	dehiscence	no	4
8	UPS	elbow	8.3	no	amputation	no	no	no	18
9	LMS	forearm	1	no	WLE	no	no	no	120 DNED
10	UPS	calf	4	no	WLE	post-op	infection	no	90 DNED
11	UPS	low back	5.5	no	WLE	post-op	no	no	21
12	Ewing	heel	3.6	inguinal LN	amputation	no	no	yes	8 DOD
13	UPS	arm	12	no	WLE	post-op	no	yes	5 DWD
14	MyxoFS	thigh	6.1	no	WLE	post-op	no	no	3
15	MyxoFS	ankle	13.5	satellite	amputation	no	no	yes	14 DOD
16	Angiosarc	ankle	8.3	no	amputation	no	no	yes	14 AWD
17	MyxoFS	thigh	6.5	no	WLE	post-op	no	no	6

Table 1. UPS – undifferentiated pleomorphic sarcoma; MxyoFS – myxofibrosarcoma; LMS – leiomyosarcoma; Angiosarc – angiosarcoma; DOD – died of disease; DNED – died, no evidence of disease; DWD – died, with evidence of disease; AWD – alive with disease.

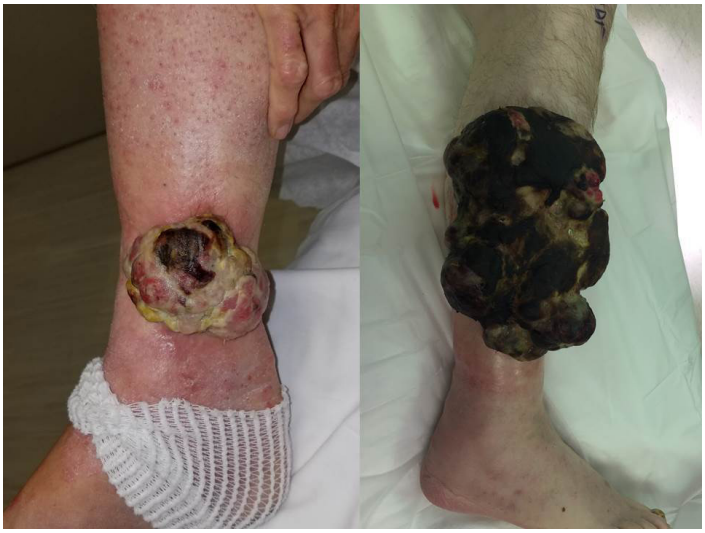

Image 1. Two of the leiomyosarcoma patient presentation photographs.

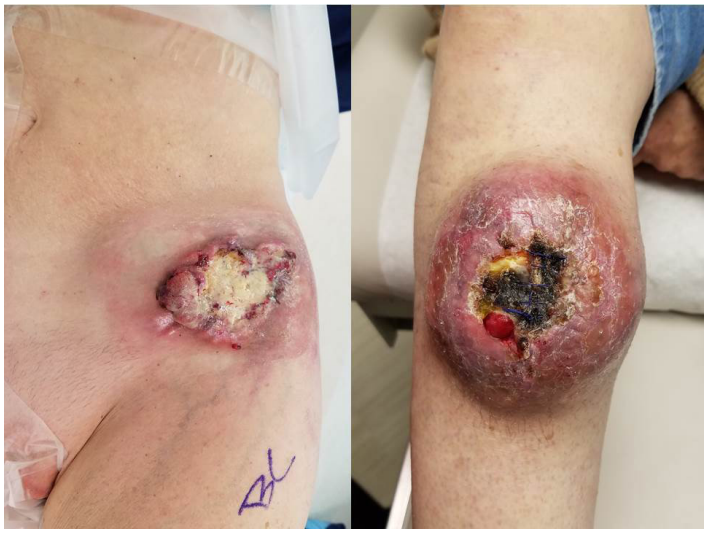

Image 2. Both of these tumors are UPS pathology; both had invaded into bone. Limb salvage was accomplished for both patients; the pelvis patient recurred and developed pulmonary metastatses.

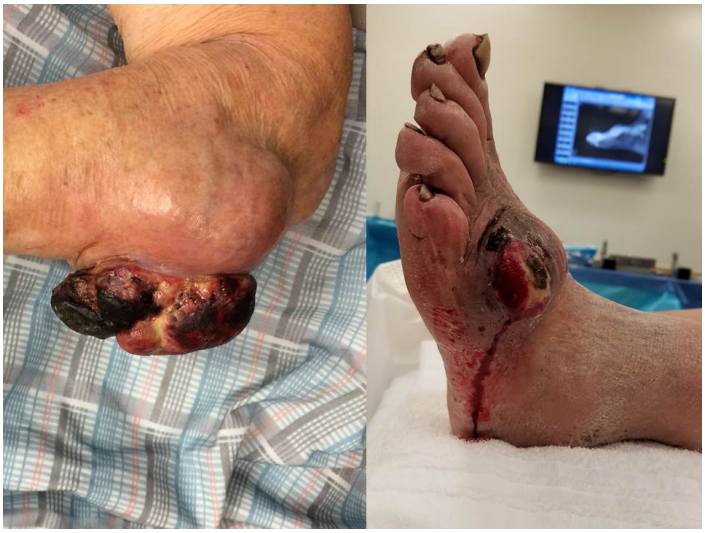

Image 3. Both of these patients underwent amputation to treat their disease.

Poster 406 3030992

THE PROGNOSTIC VALUE OF INTERLEUKIN-6 IN PATIENTS WITH SOFT TISSUE SARCOMA

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Objective: Several relevant prognostic factors have been identified in patients with soft tissue sarcoma (STS). The histological tumor grade, size, depth, and age were reported to be predictive factors for predicting survival. Recently, the presence of systemic inflammation has also been reported associate with poor prognosis in patients with STS. Pretreatment serum interleukin-6 (IL-6) levels were reported to be significantly associated with survival in patients with several types of cancer. However, little is known about the association between IL-6 and STS. The aim of this study is to investigate the possible value of IL-6 to predict survival in patients with STS.

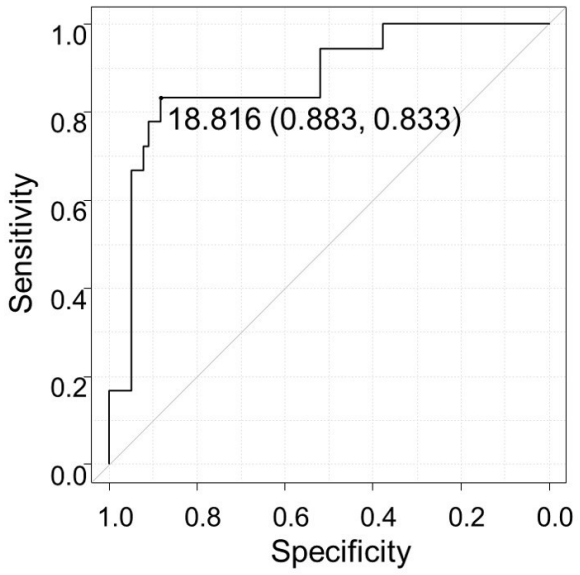
Methods: A total of 95 patient with STS who underwent surgical resection were retrospectively reviewed. Patients who presented with recurrent disease or/and metastasis or who referred for additional resection after the inadequate excision were excluded from the study. Patients with an obvious history of cardiac infarction or infectious disease were also excluded. Blood samples from all patients were obtained prior to initial treatment. All samples were stored at -80 degrees until measurement followed by centrifugation at 1,000 x g for 15 minutes. IL-6 levels were measured using ELISA kit (Quantikine®).

Results: The cohort included 55 males and 40 females with a mean age of 65.3 (10-88) years old at first presentation. The mean follow-up period was 34.4 (2.3-97.2) months. The histological diagnosis is detailed in Table 1. The IL-6 varied from 0 to 552.58 pg/ml (median 6.57, mean 28.85). CRP levels were correlated with serum IL-6 levels based on the Spearman rank correlation test (Spearman ρ=0.612, p<0.0001). Furthermore, hemoglobin (Hb) levels (Spearman ρ=-0328, p=0.001) and tumor histological grade (p=0.0002) were associated with IL-6 levels. The 5-year overall survival rate was 72.5% and the 5-year event-free survival rate was 46.7%. In the receiver operating characteristic (ROC) analysis, a value of 18.82 pg/ml was found to be an appropriate threshold for identifying patients at risk for death at 5 years (Figure I). The area under the curve was 0.87 (95% CI: 0.774-0.966). The patients with elevated serum IL-6 levels before initial treatment had poorer overall and event-free survival than those with lower IL-6 levels. When the patients were divided into two groups according to IL-6 levels of 18.82 pg/ml, the estimated overall survival at 5 years was 23.7% for the patients with higher IL-6 levels, while 93.0% for those with lower IL-6 levels (p<0.0001, Figure II). Concerning event-free survival at 5 years, 17.4% for the patients with higher IL-6 levels, while 57.2% for those with lower IL-6 levels (p<0.0001). The univariate analysis also revealed tumor histological grade was prognostic factor for overall survival (p=0.003) and event-free survival (p=0.001). On multivariate analysis, tumor grade and IL-6 level remained significant factors for survival (p=0.009, p=0.009, respectively) and events (p=0.004, p=0.001, respectively).

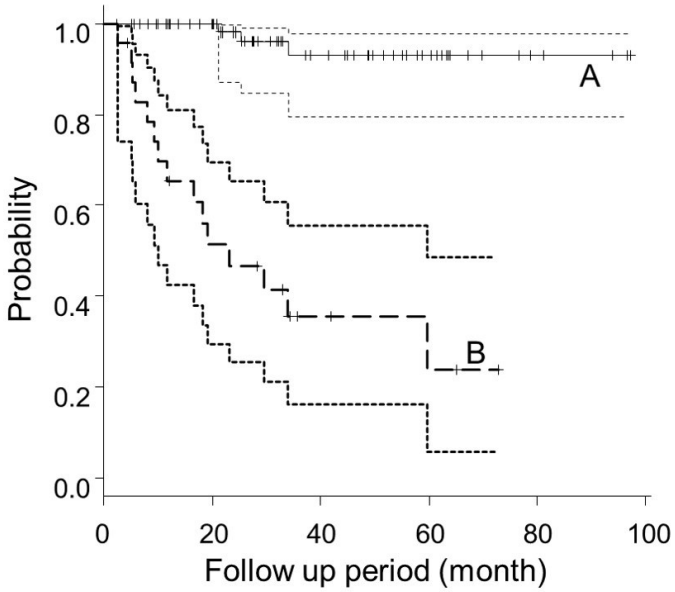
Conclusion: We found that the elevation of serum IL-6 levels was prognostic factor for predicting overall and event-free survival with patients with STS. In conclusion, IL-6 may play an important key role in the inflammatory circumstance in STS.

Histological diagnosis of 95 patients with STS.

Histological diagnosis	N
Well-differentiated liposarcoma	24
Undifferentiated pleomorphic sarcoma	15
Dedifferentiated liposarcoma	14
Myxofibrosarcoma	13
Leiomyosarcoma	9
Malignant peripheral nerve sheath tumor	4
Synovial sarcoma	4
Myxoid liposarcoma	3
Others	9



ROC for the appropriate serum IL-6 level for overall survival at 5 years.



The Kaplan-Meier curves show the overall survival of STS patients: A; patients with low IL-6 (18.82 pg/ml).

Poster 407 3033650

TRABECTEDIN IN 473 PATIENTS WITH ADVANCED SOFT TISSUE SARCOMA (STS): AN ITALIAN SARCOMA GROUP (ISG), OBSERVATIONAL, MULTICENTER, RETROSPECTIVE STUDY

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Objective: Trabectedin is approved for patients with STS after failure of anthracyclines (A) and ifosfamide (I), or patients unsuited to receive AI. The ISG performed a retrospective study to assess trabectedin in real-life clinical practice.

Methods: Patients enrolled in clinical trials were excluded. trabectedin was given as 24-h infusion every 3 weeks. According to National Health Service reimbursement rules, tumor response evaluation was performed after two cycles.

Results: From 1/2010-12/2015 a total of 473 patients (56% female) with a median age of 57.5 years (range: 21-87) were included. Performance status (in 457/473) was: 0 in 297 (65%), 1 in 139 (30%) and >1 in 21 (5%) patients. Leiomyosarcoma 37% (uterine: 14%) and liposarcoma (32%) were the most prevalent histological types. Patients received a median of 3 trabectedin cycles (range: 1-10) either at a recommended dose of 1.5 mg/m2 (n=170, 36%) or at a lower dose of 1.3 mg/m2 (n=303, 64%), and as a 2nd (n=281, 59%), 3rd (n=137, 29%) or ≥4th (n=55, 12%) line of treatment. The objective response rate (ORR) in 462/473 patients was 13%: 5 CR (1%), 57 PR (12%), and with 157 patients (33%)) achieving stable disease (SD) and 243 (51%) PD. ORR was 16% in leiomyosarcoma (uterine 21%, non-uterine 13%) and 17% liposarcoma (MRCL 24%, dedifferentiated 11%, pleomorfic 13%), 15% synovial sarcoma and 7% in the remaining histotypes (p = 0.02). Also ORR was 16% when trabectedin was delivered as 2nd line treatment vs 10% in ≥ 3rd line (p = 0.08). No difference in ORR according to trabectedin dose was observed (1.3 mg: 13%, vs. 1.5 mg: 15%) (p = 0.9). The 4- and 6-month PFS rates were 44% and 36%, respectively, with better results for leiomyosarcoma (52%/45%) and liposarcoma (54%/46%), and no differences according to trabectedin dose (1.3 mg: 47%/38% vs. 1.5 mg: 42%/33%). The 1-year survival rate was 67% (89% for patients with CR/PR, 82% for SD, 50% for PD, p=0.001). Grade 3-4 adverse events (in 442 pts) were recorded in 20% of pts (1.3 mg: 15% vs. 1.5 mg: 31%; p<0.001). Dose reduction occurred in 26% of pts (1.3 mg: 20% vs. 1.5 mg: 37%; p< 0.01). A treatment discontinuation not PD-related was reported in 80 patients (patient's choice 16, worsening PS 14, toxicity 28, surgery 11, other 11 patients). Cardiac toxicity was reported in 3 patients, with fatal outcome in one patient previously irradiated for a NH-lymphoma, while toxic death after febrile neutropenia occured in 2 patients.

Conclusion: In clinical practice, trabectedin shows results comparable to those achieved in patients enrolled in phase II/III trials. In patients treated with a lower dose (1.3 mg/m2), toxicity was less pronounced, with similar activity compared to the recommended dose (1.5 mg/m2). Clinical trial information: NCT02793050

Poster 408 3040775

"FASCIA-INFILTRATING SARCOMA": A CATEGORIE OF HIGH RISK OF RECURRENCE AND POOR OUTCOME

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Objective: Tumor depth referring to fascia infiltration has been withdrawn from the recent 8th. AJCC classification for soft-tissue sarcoma (STS). However, there are indications that infiltration of the fascia may confer a poor outcome to STS patients.

Methods: We compared the characteristics of limb and trunk wall STS involving the fascia either from outside in (of superficial origin) or from inside out (of deep origin), named fascia-infiltrating sarcoma (FIS). We compared retrospectively outcome of FIS patients to those with strict superficial (sSTS) and deep sarcoma (dSTS).

Results: Of 728 patients, 146 (20%) had FIS, 156 (21%) sSTS and 426 (59%) dSTS. FIS patients presented unfavourable characteristics with more undifferentiated STS (42% vs 26% and 24%) and more Grade 3 tumors (59% vs. 29% and 42%), respectively. FIS of superficial origin were typically Grade 2 myxofibrosarcoma with extensive fascial involvement. FIS of deep origin were represented by large, Grade 3 undifferentiated pleomorphic sarcoma. Comparing FIS to sSTS and dSTS, postoperative complications were 12% vs 4% and 8% (p = 0.04) and functional impairment 16% vs. 5% and 15% (p = 0.002), respectively. Overall survival and time to distant progression of FIS patients neared those of dSTS. Loccal recurrence-free survival of FIS vs. sSTS and dSTS were 81% vs 92% and 90% (p = 0.01).

Conclusion: Our data highlight poorer outcome in FIS patients, supporting their need of specific therapeutic strategies. FIS of superficial origin require enlarged resections combined to reconstructive surgery. Patients with FIS of deep origin may benefit from neoadjuvant chemotherapy discussed in multidisciplinary tumor board.

Outcome according tumor depth in 728 patients treated for primary, non-metastatic soft-tissue sarcoma of the limbs or trunk wall

	sSTS (N = 156)	FIS (N = 146)	dSTS (N = 426)	p - value
Oucomes	N (%)	N (%)	N (%)	
Major complications	6 (4)	17 (12)	35 (8)	0.04
Poor function	7 (5)	22 (16)	64 (15)	0.002
5-y OS	88%	75%	78%	logrank p = 0.02
5-y MFS	95%	77%	80%	logrank p = 0.0006
5-y LRFS	92%	81%	90%	logrank p = 0.01

sSTS: strict superficial sarcoma; FIS: fascia-infiltrating sarcoma; dSTS: deep sarcoma

Poster 409 3042580

ESOPHAGEAL GASTROINTESTINAL STROMAL TUMOR VERSUS LEIOMYOSARCOMA: NATIONAL CANCER DATABASE COMPARATIVE STUDY

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Objective: Esophageal gastrointestinal stromal tumors (E-GIST) and leiomyosarcomas (E-LMS) are rare tumors. Prior studies had small numbers of patients and it was challenging to draw conclusions about their clinicopathological characteristics and prognosis. We performed a comparative study of E-GIST and E-LMS using a large national database.

Methods: The National Cancer Data Base 2004-2014 was queried for patients with E-GIST and E-LMS. The primary outcome was overall survival (OS). Comparative analysis using t-test and chi square was performed to study their baseline characteristics. Uni- and multivariate Cox regression models were used to study the impact on OS.

Results: A total of 141 E-GIST and 38 E-LMS patients were included. Mean age and male gender were: 66 year and 54% for E-GIST vs. 65 year and 61% for E-LMS. Tumor size was comparable in both with mean diameter of 6.2 and 6.1cm for E-GIST and E-LMS. Esophagectomy and systemic treatment rates were 55% and 49% for E-GIST and 50% and 26% for E-LMS. Median and 5-year OS were for E-GIST vs. E-LMS (97 vs 19 months and 62% vs. 23%, p<0.0001) (figure 1). In multivariate analysis: younger age, tumor diameter <10cm, esophagectomy, E-GIST vs. E-LMS had significantly superior OS (table 1).

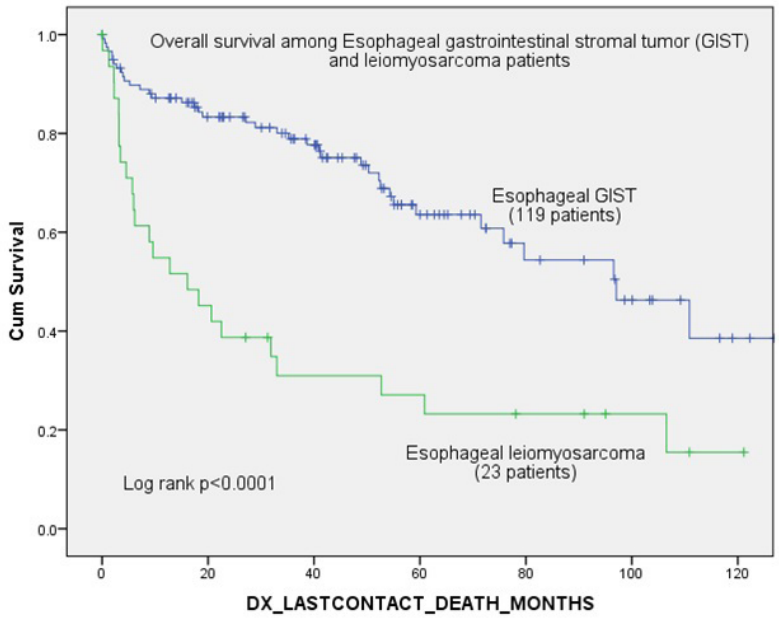
Conclusion: E-GIST has an independent superior OS compared to E-LMS. Surgery is the cornerstone treatment modality for both tumors to achieve survival benefit. E-GIST has a much better[LASM1] prognosis than E-LMS. Our results suggest the need for better systemic treatment of E-LMS.

Cox regression analyses for Predictors of Mortality among Esophageal Gastrointestinal Stromal Tumor (E-GIST) and Leiomyosarcoma (E-LMS) Patients.

	Univariate analysis		Multivariate analysis	
	HR(95%CI)	P value	HR(95%CI)	P value
Age(per year)	1.07(1.04-1.10)	0.001	1.1(1.03-1.10)	0.001
Sex(male)	1.4(0.87-2.40)	0.2		
Tumor size				
Tumor size 5-9.9cm (Ref <5cm)	0.8(0.42-1.62)	0.6		
Tumor ≥ 10cm(Ref <5cm)	2.2(1.14-4.42)	0.02	2.6(1.25-5.45)	0.01
Tumor grade(high)	2.1(0.77-5.72)	0.2		
Esophagectomy	0.4(0.26-0.72)	0.001	0.5(0.25-0.95)	0.03
Systemic treatment	1.0(0.59-1.65)	0.9		
E-GIST vs. E-LMS	3.1(1.83-5.11)	0.001	5.0(2.41-10.42)	0.001

HR=hazard ratio, CI=confidence interval

The Overall Survival among Esophageal Gastrointestinal Stromal Tumor (GIST) and Leiomyosarcoma patients.



Poster 410 WITHDRAWN

Poster 411 3042634

PRIMARY SARCOMA OF LUNG (PSL). A RETROSPECTIVE SERIES.

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Objective: PSL is a rare disease that comprises only 0.15 to 0.30% of primary neoplasms of the lung and 9% of all soft tissue sarcomas. Lack of data for this location is a fact. We herein present a small series to increase the knowledge of PSL.

Methods: For a period of 10 years (01/06/2008 to 31/05/2018), experience from 5 centers were gathered and analyzed retrospectively.

Results: A total of 25 cases were diagnosed in this period. Median age at diagnosis was 68 (31-75). Histological subtypes were synovial sarcoma (40%), undifferentiated pleomorphic sarcoma (40%), epithelial sarcoma, angiosarcoma, fibrosarcoma, inflammatory fibroblastic tumor and SMARCA1-deficient sarcoma (1 case each). Median follow-up of the sample was 8.5 mo (1-43). 8 pts (32%) presented with metastases at diagnosis. Data for survival analysis were available for 7 pts (median OS 12 mo (2-24)). From 17 pts (68%) with localized disease, 12 pts (70.6%) underwent surgery (1 pt is still receiving neoadjuvant chemotherapy and 5 pts had extensive disease not surgically amenable). Median OS for inoperable pts was 10mo (5-10). Margin status was negative for 10 out of 12 operated pts. For operated patients, the recurrence rate was 58.3% (7/12). None of these pts received adjuvant chemotherapy or radiotherapy. Median relapse-free survival was 7.5 mo(1-37). The median OS from diagnosis for pts who relapsed was 9 mo (2-43).

Conclusion: PSL is a rare disease and scarce data are available. Thus, optimal management is still unknown. With 16 cases, this is the largest series reported so far. Prognosis of PSL seems somber, with a high recurrence rate after surgery and a short survival after metastatic disease is diagnosed. However, due to the short median follow-up of 8.5 months, a new analysis of these data is needed in a future.

Poster 412 3042713

SCLEROSING EPITHELIOD FIBROSARCOMA OF SOFT TISSUE AND BONE: REPORT OF 12 CASES.

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Objective: Sclerosing epithelioid fibrosarcoma (SEF) is a rare soft tissue sarcoma first described in 1995 by Meis-Kindblom. It shares genetic features with low-grade fibromixoid sarcoma and hybrid tumors. Despite relatively low cellularity in hyaline matrix and absence of marked cytologic atypia and minimal mitotic activity, SEF has a dismal prognosis with high incidence of local recurrence (40%)and distant metastases (80%). Overall a 50% has been described to die for it. Differential diagnosis is primarily with metastatic carcinoma, sclerosing lymphoma, and osteosarcoma. The majority of cases show immunohistochemical positivity for MUC4 and contain an EWSR1-CREBL1/2 fusion genes.Only case reports have been reported since 1995. Chemotherapy treatment of advanced disease has been reported with mainly unsatisfactory results. The drugs most employed have been antracyclin, ifosfamide, cisplatin,metothrexate,but also vincristine, actinomycin, etoposide, idarubicine,irinotecan. We reviewed clinical outcome of 12 cases of SEF treated at our Institution.

Methods: We reviewed our data base to find all cases of with a diagnosis of sclerosing epithelioid fibrosarcoma between 1993 and 2018. Diagnosis was confermed by pathologist expert in sarcoma (GM,RA,DTA). Patients were divided in soft tissue and bone primary tumor and metastatic and localized.

Results: 14 cases with pathologic diagnosis of SEF have been found in our database : 12 of these had adequate informations and are reported in Tab 1. Seven cases originated from the soft tissues while 5 originated from bone. Median age was 32 (16-75). Seven patients were male and 5 were female. Ten had localized disease at diagnosis; two patients were metastatic. Median follow up 18,5 months (4-84). All patients except two had surgery for primary disease ;2 patients had adjuvant chemotherapy , 2 adjuvant radiotherapy.2 patient had chemotherapy for advanced disease.

In patients with localized disease 5/10 (50%) developed distant metastases with a median DFS of 16 ms (3-84). Six patient out of 12 (50%) died of disease (1 metastatic and 5 with localized disease at diagnosis). Those two patients with metastatic disease at diagnosis had a progression free survival of 11 and 4 months (one is on treatment in June 2018). One male patient (case 1) with localized disease of a cervical vertebra (C3) after vertebrectomy (margins focally contaminated) received adjuvant chemotherapy with cisplatin/etoposide +doxorubicin, neck djuvant protontherapy (68 Gy) was administrated after chemotherapy and he is free from of 14 ms from diagnosis. One female patient (case 4) with localized disease of L5 received neoadjuvant chemotherapy according to E.U.R.O.B.O.S.S. protocol with cisplatin, doxorubicin and ifosfamide after 2 months had vertebrectomy (necrosis 70%) followed by adjuvant chemotherapy with the same drugs. She relapsed with lung metastases after 18 months from diagnosis and died 5 months later after two lines of other chemotherapy (trabectedin and pazopanib) without response. One female patient (case 11) with SEF of thigh and metastases of L3 vertebra at diagnosis, she received 2 cycle of ifosfamide-doxorubicin with stable disease; had resection of thigh primary SEF (necrosis 10%) followed by chemotherapy with 2 cycles of Cisplatin and Etoposide with reduction of L3 metastases that made vertebrectomy possible , she developed lung metastases 11 months after first diagnosis. One male patient (case 12) with diagnosis on February 2018 of SEF with multiple bone and lung metastases has received Cisplatin alone (due to comorbidity) and has stable disease at 4 months.

Conclusion: Conclusions: SEF is a rare tumor with high incidence of relapse even in localized tumor as previously reported , chemotherapy in advanced disease with Cisplatin with o without Etoposide has shown some activity that must be confirmed by further study.

Tab 1

N	Sex	age	status	Site	IHC	Stage	site of M	Chemotherapy	CT response	Relapse	DFS ms	FUP ms
1	M	42	NED	C3	MUC4+	localized		CDP/VP16/Doxo	adj		14	14
2	M	28	DOD	L1	NO	localized		no		bone, multi	35	54
3	F	29	DOD	L2	MUC4+	localized		no		lung	3	8
4	F	44	DOD	L5	MUC4+	localized		CDP/Doxo/Ifo;Trab,PZP	Adj; PD-PD	lung	18	23
5	M	28	NED	leg	NO	localized		no			84	84
6	M	16	NED	thigh	MUC4+	localized		no			6	6
7	M	32	DOD	leg	NO	localized		no		lung	18	51
8	M	48	DOD	girdle	MUC4+	localized		no		lung/bone	62	75
9	F	32	NED	thigh	MUC4+	localized		no			11	11
10	F	75	NED	buttock	MUC4+	localized		no			7	7
11	F	29	DOD	thigh	MUC4+	metastatic	bone	Ifo/Doxo-CDP/VP16	SD-PR	lung/bone	11	43
12	M	50	AWD	humerus	MUC4+	metastatic	lung/bone	CDP	SD		4	4

NED= non evidence of disease , DOD =death of disease, AWD= alive with disease, ST= soft tissue; IHC= Immunoistochemical ; adj= adjuvant chemotherapy; CDP= cisplatin; Doxo=doxorubicin; Ifo=ifosfamide; VP16=etoposide; Trab= trabectedine;PZP=pazopanib; DFS=Disease Free Survival ; TTP= time to progression; FUP=follow up

Poster 413 3042830

PREDICTORS OF VENOUS THROMBOEMBOLISM IN PATIENTS WITH PRIMARY SOFT TISSUE SARCOMA

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Objective: Venous thromboembolic event (VTE) is one of the most common life threatening diseases, causing approximately 200,000 deaths each year. Cancer is known to be associated with VTE, as patients have an almost 4x increased risk. Orthopedic surgeries have also been identified as a risk factor for VTE. The increased risk of VTE in soft-tissue sarcoma patients is partially explained by increased levels of activated platelet-derived macrovesicles. Therefore it is logical that patients undergoing surgery for soft tissue malignancies are at an increased risk for postoperative thromboembolic events. The literature reports the incidence of VTE in this patient population to be between 0.6 and 14.8% with the use of mechanical and/or chemical prophylaxis. Prophylactic anticoagulation medication may help reduce VTE and the resulting morbidity and mortality; however, it can lead to bleeding and wound complications, especially in patients undergoing radiation and removal of large volumes of tissue. Patients must be carefully assessed to mitigate unnecessary risk of prophylaxis-associated complications.
There are currently no guidelines that take into account the unique risk factors of the orthopedic oncology patient. The risk of complication involved with many pharmacologic prophylactic agents necessitates a thorough understanding of the relevant risk factors of DVT guiding the decision of which agents to employ. Previous studies have combined both soft tissue and primary bone sarcomas to assess the risk of VTE, but a large study of soft tissue sarcomas has not been conducted. As a

result, the aims of this study were to 1) analyze the rate of VTE in patients with soft tissue sarcoma; 2) identify risk factors for VTE in patients with soft tissue sarcoma; and 3) discuss the complications associated with prophylactic anticoagulation in patients with soft tissue sarcomas.

Methods: This retrospective study includes any patients older than 18 years of age who have been treated at our institution from 1/1976 to 12/2017 for soft tissue sarcoma of the lower extremity independent of the modality of treatment. The outcome event is defined as a radiographically (CT scan or ultrasound) confirmed deep vein thrombosis (DVT) or pulmonary embolism (PE) within 90 days of the index surgery. Only patients with follow-up for at least 90 days from the index of surgery were included. In total, 44 variables were tested for association with VTE including patient characteristics such as demographics, details about the outcome event, tumor characteristics, treatment variables or recurrence, preoperative and postoperative clinical variables, and any complications. Patients with VTE events were compared to those without them to identify any potential predictors of VTE.

Results: VTE was detected in 17 patients (3.12 %) within 90 days of surgery and confirmed radiographically. Metastasis at diagnosis (OR 3.15, 95% CI 1.30-11.48) and tumors larger than 125mm (OR 3.40, 95% CI 1.25-9.08) were found to be statistically significant predictors. Furthermore, post-operatively, chemotherapy (OR 3.27, 95% CI 1.31-8.05) was found to be a significant predictor. However, different prophylaxis and varying chemotherapy drugs did not affect the rate of VTE.

Conclusion: We assessed an institutional database for possible predictors of VTE. Metastasis at diagnosis, tumor size larger than 125mm, and post-operative chemotherapy were found to be independently associated with VTE. The increase in risk of VTE due to metastasis reflects the idea that the diffuse nature of the tumor leads to hypercoagulability, increasing the risk of thrombosis. We were expecting to find wound complications and radiation to be predictors but they were not found to be significant. The lack of differences between medications suggests that medications with fewer risks such as aspirin could be utilized more to reduce VTE. The results support the literature but further research is required to assess the relative risk factors in a prospective study.

Poster 414 3043002

DYNAMIC PREDICTION FOR PATIENTS WITH HIGH-GRADE EXTREMITY SOFT TISSUE SARCOMA - PERSONALIZED SARCOMA CARE (PERSARC DYNAMIC)

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Objective: The develop a model that includes updated information, as well as to model time-varying effects to make predictions of overall survival at different time points during follow-u, a dynamic prediction model was build. Increasing interest lies in a personalized prediction of disease progression for patients with soft tissue sarcoma. Many prediction models available at present are applicable only at the time of baseline, such as time of diagnosis or surgery. However, updated patient information during the follow-up as well as changing covariate effects over time may change the prognosis of a patient, which is not accounted for in these models. Dynamic prediction models include updated information and time-varying effects, that can be used to provide better individualized treatment which depends on the dynamic assessment of a patient's prognosis.

Methods: Data of 2232 patients with high-grade Extremity Soft Tissue Sarcoma who underwent surgery at specialized sarcoma centres was used to develop a dynamic prediction model with primary endpoint overall survival. A landmark supermodel is used to give updated 5-year survival probabilities from a particular prediction time point during follow-up. Landmark models are able to make predictions from a particular time tLM, by using (updated) information of patients still alive and in follow-up at that time. Such models may be estimated at different time points tLM using the Cox proportional hazards model and combined to form one landmark supermodel.
Several patients and tumour-specific risk factors at baseline were included in the model as well as time-dependent covariates, such as status of local recurrence (LR) and distant metastasis (DM). Furthermore, covariates were allowed to have a time-varying effect on the outcome.

Results: Median follow-up was 6.42 (95% CI 6.17 to 6.72) years, during which 302 LRs and 715 DMs were observed. The effect of risk factors was tested for changes in time and time-varying effects were found for surgical margin and tumour histology. The protective effect associated with a free surgical margin compared to an intralesional margin is strongest shortly after surgery, however, fades as time progresses. Furthermore, LR and DM were found to have a strong association

with survival, which is used in the Landmark model to make adequate updated predictions for patients who experience these events.
To illustrate the personalized outcome see figure 1 for the 5-years dynamic overall survival for two fictional patients without distant metastases. Note the different predicted outcome due to histopathological subtype, surgical margin and the use of radiotherapy.

Conclusion: The finding of time-varying effects as well as the importance of time-dependent covariates such as LR and DM found in this analysis confirm the inadequacy of baseline models for predictions later on in follow-up. A model designed for dynamic prediction, which updates survival probabilities is needed and it is provided in this work.

Poster 415 3036211

SPONTANEOUS REGRESSION OF SOFT TISSUE SARCOMA

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Objective: Unexpected regression of malignancy is a well-known phenomenon, albeit rare. Carcinomas account for majority of spontaneous regression reported to date, but the phenomenon is extremely rare in sarcomas. Although the mechanism behind spontaneous regression is unknown, it has been hypothesized as due to immune modulation, infection, cancer antigen elimination, hormonal mediation and infarction from thrombotic occlusion. In this study, we report three rare cases of soft tissue sarcoma that spontaneously regressed and tried to elucidate the clinical course and the potential mechanism behind this rare phenomenon.

Methods: We analyzed 3 cases of soft tissue sarcomas which regressed spontaneously since 2012. The average age was 55.3 years, and the median follow up period was 31.3 months (range 2 - 66 months). Histological diagnosis included dedifferentiated liposarcoma, myxofibrosarcoma and extraskeletal myxoid chondrosarcoma. Location included two thighs and a groin. Any episode before spontaneous regression, time to regrowth after regression, operative methods, and oncological outcomes were analyzed.

Results: Regression of the tumor occurred before a biopsy in one case and 2 cases regressed after an open biopsy. There were 2 complete disappearance and one 30% partial disappearance of the tumor. Regrowth of the tumor was observed after 4 months in two cases: one case in the primary site and the other in one lung metastatic lesion among multiple pulmonary nodules. Neither chemotherapy nor radiotherapy was performed in each case before the regression. There was no accompanying inflammatory event such as an infection. All the tumors were eventually resected with wide margin, but one case in the thigh recurred and underwent re-excision and radiation. Interestingly, extraskeletal myxoid chondrosarcoma of the groin has not seen any regrowth after 5 years after biopsy and resection of the regrown lung metastasis. Due to the unclear nature of regression, the most recent patient with myxofibrosarcoma of the thigh underwent wide resection of the tumor after spontaneous partial reduction of the mass after biopsy. Histology of all 3 cases revealed moderate to high amount of lymphocyte and neutrophil infiltration with partial necrosis, which suggested some kinds of immunological response. At the final follow-up, oncological outcomes were 1 CDF and 2 NED.

Conclusion: The mechanism behind spontaneous regression of sarcoma is still unclear and our histological findings could not confirm any definitive response; nevertheless, sarcomas have the potential to regress, possibly due to immune response. Although one case of extraskeletal myxoid chondrosarcoma has not seen any regrowth, unpredictable nature of spontaneous regression should be treated with standard treatment until further data is accumulated. Novel new approaches are needed to improve the prognosis of sarcoma, and analysis of spontaneous regression might be correlated to recent advances in immunotherapy. However, further studies are needed to elucidate the mechanism behind this phenomenon to utilize its effect in the treatment of soft tissue sarcomas.

Poster 416 3037922

SOFT TISSUE SARCOMA OF THE EXTREMITY: THE IMPACT OF TREATMENT AT MULTIPLE FACILITIES

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Objective: Patients with soft tissue sarcoma (STS) often obtain treatment at multiple facilities. It is unclear how the number of treatment facilities is related to clinical characteristics and patient survival. We sought to identify differences in clinical features and outcomes between patients with (STS) of the extremity treated at a single facility and those treated at multiple facilities.

Methods: Data on patients diagnosed with STS of the extremity between 2006 and 2015 was obtained from the National Cancer Database. The study sample was stratified by treatment source (whether treatment was received at a single Commission on Cancer (CoC) facility or at multiple CoC facilities). Characteristics of patients treated at a single facility were compared to those treated at multiple facilities using Chi-square tests. One-way analysis of variance was used to compare mean age at diagnosis, and Wilcoxon rank-sum test was used to compare median time to treatment initiation. The odds ratios for obtaining treatment at multiple facilities were calculated. Kaplan-Meier analysis was used to calculate survival estimates, and the log-rank test compared survival estimates. Cox regression was used to estimate the risk of death based on treatment source. Both crude and adjusted (covariates included age, grade, stage, histology, facility type and treatment type) hazard ratios were calculated. A p-value of < 0.05 was used for all tests.

Results: The study sample included 18,491 patients with STS of the extremity, of which 79.7% were treated at a single CoC facility and 20.3% were treated at multiple CoC facilities. The mean age was 64.5 years, 54.5% were male and 84.6% were white. The median time to treatment initiation was 13 days for those treated at a single facility and 19 days for those treated at multiple facilities ($p < 0.001$). Compared to patients treated at a single facility, those treated at multiple facilities were less likely to be Black (OR = 0.79; 95% CI: 0.69 – 0.89) or Asian (OR = 0.58; 95% CI: 0.45 – 0.74) than white, and were more likely to have private insurance (OR = 1.30; 95% CI: 1.04 – 1.60), or Medicare (OR = 1.27; 95% CI: 1.01 – 1.59) rather than no insurance. In addition, patients who received treatment at multiple facilities were more likely to have undifferentiated rather than well-differentiated tumors (OR = 2.27; 95% CI: 1.99 – 2.59) and stage IV rather than stage I disease (OR = 1.31; 95% CI: 1.13 – 1.52) compared to patients treated at a single facility. Furthermore, patients treated at multiple facilities were more likely to have received radiation (OR = 2.35; 95% CI: 2.18 – 2.54) and chemotherapy (OR = 1.36; 95% CI: 1.24 – 1.49). Finally, the risk of death was 11% lower for patients treated at multiple facilities compared to those treated at a single facility (HR = 0.89; 95% CI: 0.82 – 0.95).

Conclusion: Although patients with STS of the extremity treated at multiple CoC facilities were more likely to present with advanced disease and had a greater time to treatment initiation, their survival was superior to that of patients treated at a single facility. Treatment at multiple facilities may be necessary to optimize the survival of patients with STS of the extremity.

CLINICAL CHARACTERISTICS STRATIFIED BY TREATMENT SOURCE.

Characteristic	Treatment Source		
	Single Facility, n (%)	Multiple Facilities, n (%)	OR (95% CI)
Grade			
Well Differentiated	2,591 (17.6)	362 (9.7)	Reference
Moderately Differentiated	1,897 (12.9)	506 (13.5)	1.91 (1.65 – 2.21)*
Poorly Differentiated	3,685 (25.0)	1,162 (31.0)	2.26 (2.00 – 2.57)*
Undifferentiated	2,997 (20.3)	951 (25.4)	2.27 (1.99 – 2.59)*
Unknown	3,575 (24.3)	765 (20.4)	1.53 (1.34 – 1.75)*
Clinical Stage			
I	4,525 (30.7)	924 (24.7)	Reference
II	2,797 (19.0)	864 (23.1)	1.51 (1.36 – 1.68)*
III	3,097 (21.0)	1,051 (28.1)	1.66 (1.50 – 1.84)*
IV	1,060 (7.2)	284 (7.6)	1.31 (1.13 – 1.52)*
Unknown	3,266 (22.2)	623 (16.6)	0.93 (0.84 – 1.04)
Surgery Type			
No Surgery	1,328 (9.0)	290 (7.7)	Reference
Excision/Partial Resection	5,237 (35.5)	1,143 (30.5)	1.00 (0.87 – 1.15)
Limb-sparing Resection	7,298 (49.5)	2,107 (56.3)	1.32 (1.15 – 1.51)*
Amputation	790 (5.4)	179 (4.8)	1.04 (0.84 – 1.28)
Unknown	92 (0.6)	27 (0.7)	1.34 (0.86 – 2.10)
Radiation			
No	7,562 (51.3)	1,170 (31.2)	Reference
Yes	7,032 (47.7)	2,562 (68.4)	2.35 (2.18 – 2.54)*
Unknown	151 (1.0)	14 (0.4)	0.60 (0.35 – 1.04)
Chemotherapy			
No	11,813 (80.1)	2,854 (76.2)	Reference
Yes	2,413 (16.4)	793 (21.2)	1.36 (1.24 – 1.49)*
Unknown	519 (3.5)	99 (2.6)	0.79 (0.63 – 0.98)*

Notes: OR = odds ration; CI = confidence interval. *p-value significant at < 0.05.

Poster 417 3038292

TREATMENT AND FOLLOW-UP OF 5 PATIENTS WITH INFANTILE MYOFIBROMATIS - A SINGLE CENTER EXPERIENCE

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Objective: Infantile Myofibromatosis (IM) is a rare benign fibrous tumor that can arise in the skin, muscle, bone, subcutaneous tissue, or viscera. Solitary form, generalized (multicentric) form, and generalized form with visceral involvement are described. The solitary form usually regresses spontaneously but the generalized form especially with visceral involvement carries significant morbidity and mortality.

There is no established treatment or follow-up protocols for the treatment of infantile myofibromatosis. Single case reports or small series reported successful treatment using low dose methotrexate and vinblastine in generalized form with visceral involvement.

Methods: Five patients (1 male, 4 females) were treated in the department of Pediatric Hematology-Oncology, Tel Aviv Medical Center between the years 2014-2018. All were below 1 year of age at diagnosis (new-born [1], 1 month old [1], 2 month old [2], 8 months old [1]). Four had multicentric form and 1 had solitary lesion. The patient with solitary lesion involving bone and soft tissue underwent biopsy, received no treatment and had spontaneous improvement during follow up. The 4 patients with multicentric form had generalized visceral involvement that included lesions in the CNS (3 patients), cardiac (2

patients), gastrointestinal (2 patients), muscle (4 patients), bone and subcutaneous tissue (4 patients). All underwent total body MRI in order to demonstrate disease extension, as well as cardiac function tests. Those modalities were used later for follow-up.

Results: All 4 patients received low dose methotrexate and vinblastine chemotherapy, 3 survived and 1 died. His death occurred after the first course of chemotherapy due to respiratory failure and cardiac involvement. Two patients received 1 year of chemotherapy, improved dramatically and are alive 4-12 months thereafter. Another patient completed 1 year of chemotherapy but relapsed a year later only to improve again after renewal of the same chemotherapy.

Conclusion: IM is a rare disorder mainly arising in the infant age period. In our experience, solitary form should be operated or closely observed until spontaneous remission occurs. On the other hand, multicentric visceral involvement should be treated early using weekly methotrexate and vinblastine for at least 1 year. Intensive supportive care may be needed in case of visceral involvement. Initial evaluation after confirming IM should include whole body MRI and cardiac function tests.

Poster 418 3042667

INTIMAL SARCOMA: A CLINICOPATHOLOGIC AND IMMUNOHISTOCHEMICAL EXPRESSION IN SEVEN CASES IN THE NATIONAL CANCER INSTITUTE.

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Miguel Angel Clara Altamirano[1]*; Mario Cuellar Hubbe*[1]*; Hector Martinez Said*[1]*; Jorge Martinez Tlahuel*[1]*;*
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Background: Intimal sarcoma is very rare and remains a diagnostic challenge to the pathologist. This unusual sarcoma carries a poor prognosis and a high rate of recurrence or metastasis. There are very few series correlating histologic features with follow-up data. We present a series of 7 intimal sarcomas, from different subsites of the economy, in a 10-year period in a third level institution; all in association with histomorphologic features and immunohistochemical findings.

Objective: To describe the different histological types and immunoexpression of distinct antibodies in a subset of patients with intimal sarcoma of diverse subsites.

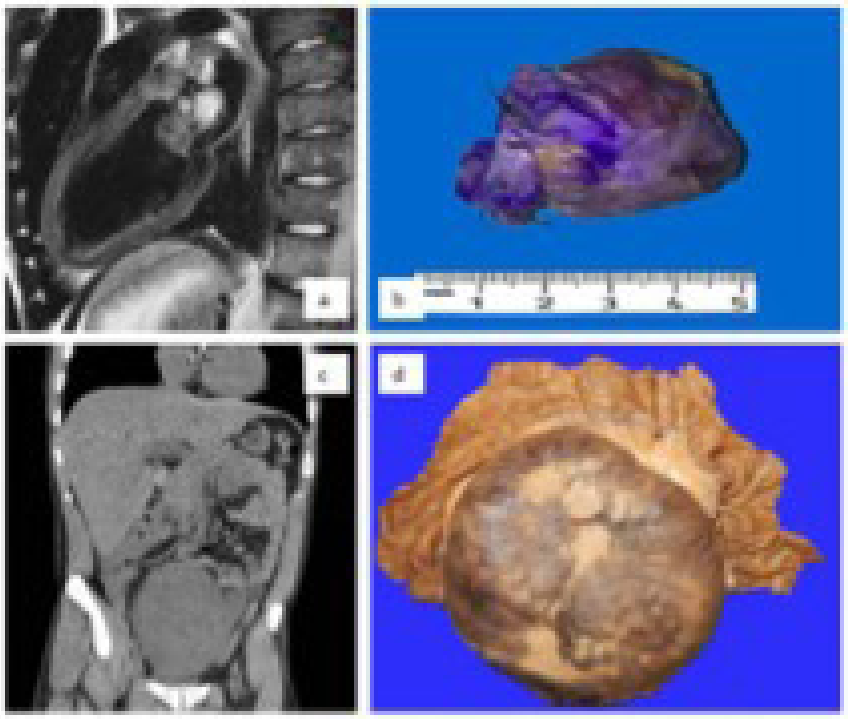
Methods: We studied seven cases of intimal sarcoma, that arrived at National Cancer Institute in Mexico City, in 10 years. Six in consultation material and one secondary to radiotherapy. All of them were analyzed by two pathologists, to determine the histological type and grade, as well as fifteen different markers by immunohistochemistry. We obtained clinical and image data. Also**,** in four cases, we had the complete surgical specimen and one necropsy material.

Results: The mean age was 48.1 years, with equal gender distribution. The mean tumour size was 8.86 cm. One in the pulmonary artery, two in the left atrium, one in the right atrium and the rest in the arm (50%) (fig 1). In 66.7% of the cases, the tumour was invading adjacent tissue. All samples were high graded intimate sarcomas. In one-hudred percent of them, three different types of sarcomas were found (osteosarcoma, liposarcoma and leiomyosarcoma). Fifty percent of patients received surgical treatment and two received radiotherapy and surgery combined. Seventy percent had progression of the disease, with just in one case of bone metasasis. Sixty-six percent are still alive with a global surviving time of 18.8 months. The immunohistochemical markers used showed heterogenic expression.

Conclusion: Intimal sarcoma is a rare and aggressive tumour, that in our population was more commonly found in arms and left atrium. All of them were big sized and with at least three different subtypes of high-grade sarcomas, those were the pathological clues to the diagnosis because of the little use of immunohistochemistry in these tumours.

TABLE 1 DEMOGRAFIC

Size	8.86 (1.8-21)
Pulmonary artery	1 (14.3%)
Left atrium	2 (28.6%)
Right atrium	1 (14.3%)
Arm	3 (42.9%)
STAGE	
II	2 (28.6%)
IIIA	1 (14.3%)
IIIB	2 (28.6%)
IV	2 (28.6%)
TREATMENT	
Surgery	4 (57.2%)
Surgery + radiotherapy	2 (28.6%)
Chemotherapy	1 (14.3%)
PROGRESSION	
Yes	5 (71.5%)
DEATH	
Yes	3 (42.9%)
CD 31	
+ FOCAL	3 (42.9%)
CD 34	
+FOCAL	2 (28.6%)
++	1 (14.3%)
FLI-1	
+ FOCAL	3 (42.9%)
+ DIFUSSE	1 (14.3%)
++	2 (28.6%)
P53	4 (57.2%)
SATB-2	
+ FOCAL	2 (28.6%)



Poster 419 3003313

MORBIDITY, QUALITY OF LIFE AND PAIN IN RETROPERITONEAL SARCOMA (RPS). RESULTS FROM A PROSPECTIVE STUDY

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Objective: Extended surgical resection is the primary approach to localized primary RPS. Prospective data on morbidity and Quality of Life (QoL) are lacking.

Methods: Patients aged ≥ 18 candidate to extended surgical resection for primary localized RPS between March 2014 and January 2016 at our center were enrolled in a prospective observational study (ClinicalTrials NCT03480399). Morbidity was recorded according to Clavien-Dindo. Renal function was monitored, and renal failure defined as mild (NKD EGFR stage 2) or moderate (stage 3). Lower limb function was assessed by Lower Extremity Functional Scale (LEFS), QoL by EORTC QLQ-C30; pain by Brief Pain Inventory (BPI-SF) and neuropathic pain by DN4. Patient reported outcomes (Qol, DN4 and LEFS) were assessed at 4 and 12 months (mos) after surgery and their average compared with baseline using paired t-test. Linear regression was used to test the association of clinical and demographic variables with baseline to follow-up differences. Associations between clinical variables were tested using the Mann–Whitney–Wilcoxon or Kruskal Wallis or Fisher-Freeman-Halton Fisher tests, as appropriate.

Results: One hundred and eleven patients were observed and operated in the study period. Sixty-two were enrolled in the study. M/F ratio: 1.6/1. Median age 61 years (CI 95%, 58.1 – 64.4); median tumor size 24 cm (CI 95%, 21.1 – 26.3): dedifferentiated liposarcoma (35, 56.5%), well differentiated liposarcoma (17, 27.4%), leiomyosarcoma (8, 12.9%), other (2, 3.2%). Perioperative treatments (chemo and/or RT) were administered in 20 (32%). Median number of resected organs was 4.3 (CI 95%, 3.9 – 4.7), and in 52 cases (84%) enbloc nephrectomy was performed. After a median follow up of 30 mos (CI 95%, 29.1 – 33.1), local recurrence was observed in 10 patients, distant metastasis in 7 and both in 1. Fifty-five patients were alive at last evaluation (8 AWD, 47 NED). Severe post-operative events (Clavien-Dindo ≥ 3) were observed in 16 patients (25.8%), reoperation was performed in 10 (16.1%); 1 patient (1.6%) died within 90 days for surgical related complications. At 12 mos, stage 2 and 3 renal failure occurred in 27/54 (50%) and 20/54 (37%) of patients, respectively (Figure 1). The chance to develop stage ≥ 3 renal failure at 12 months was significantly higher for patients with EGFR stage ≥ 2 at baseline (p=.0005), and correlated with nephrectomy (p=.01).

Clinically significant neuropathic pain was found in 48% and 43% of patients at 4 and 12 mos, respectively. Average pain was mild (2.1; CI 95%, 1.5 – 2.7), but significantly higher in 19 patients (30.6%) who reported clinically significant neuropathic pain both at 4 and 12 mos after surgery (p=.004) (Figure 2, panel C-D). Mean LEFS score was significantly lower after surgery (60 to 55 to 53.5, p<0.001) (Figure 2, panel A). Psoas muscle resection was associated to higher increase of DN4 scores in the long term (p=0.003) but not to LEFS score variation (p=0.9). Global quality of life status showed no significant change after surgery (p=0.063) (Figure 3, panel B) and baseline to follow-up variations resulted not significantly associated to number of organ resected (p=0.52), perioperative treatments (p=0.46), age (p=0.13) or gender (p=0.23).

Conclusion: In this prospective series, severe morbidity and mortality after extended surgery for primary RPS were acceptable, and similar to retrospective published series. Changes in renal function after enbloc nephrectomy are usually mild and correlate with baseline EGFR stage. Global QoL status at 12 months after surgery in surviving patients is not inferior to baseline assessment. After psoas resection, onset of clinically significant neuropathic pain may be expected; targeted rehabilitative actions are worthy to be performed in this subgroup. Specific QoL tools to be designed for RPS patients should include items regarding neuropathic pain and lower limb function.

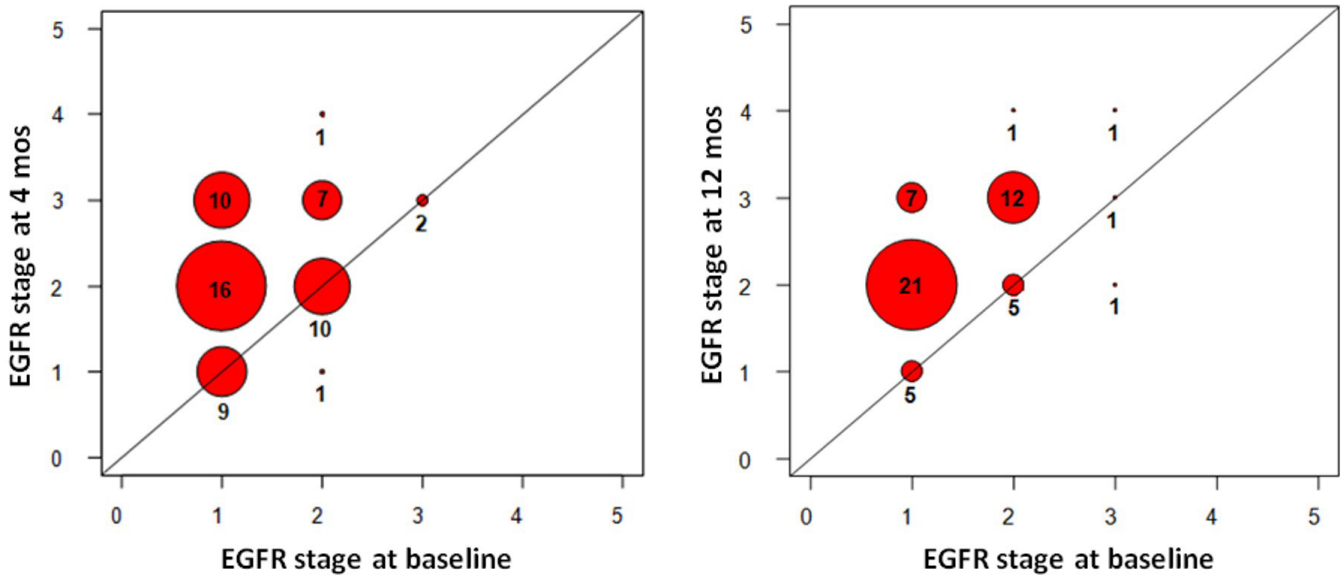

Figure 1. Renal function changes at 4 and 12 months after surgery according to NKD EGFR stage at baseline.

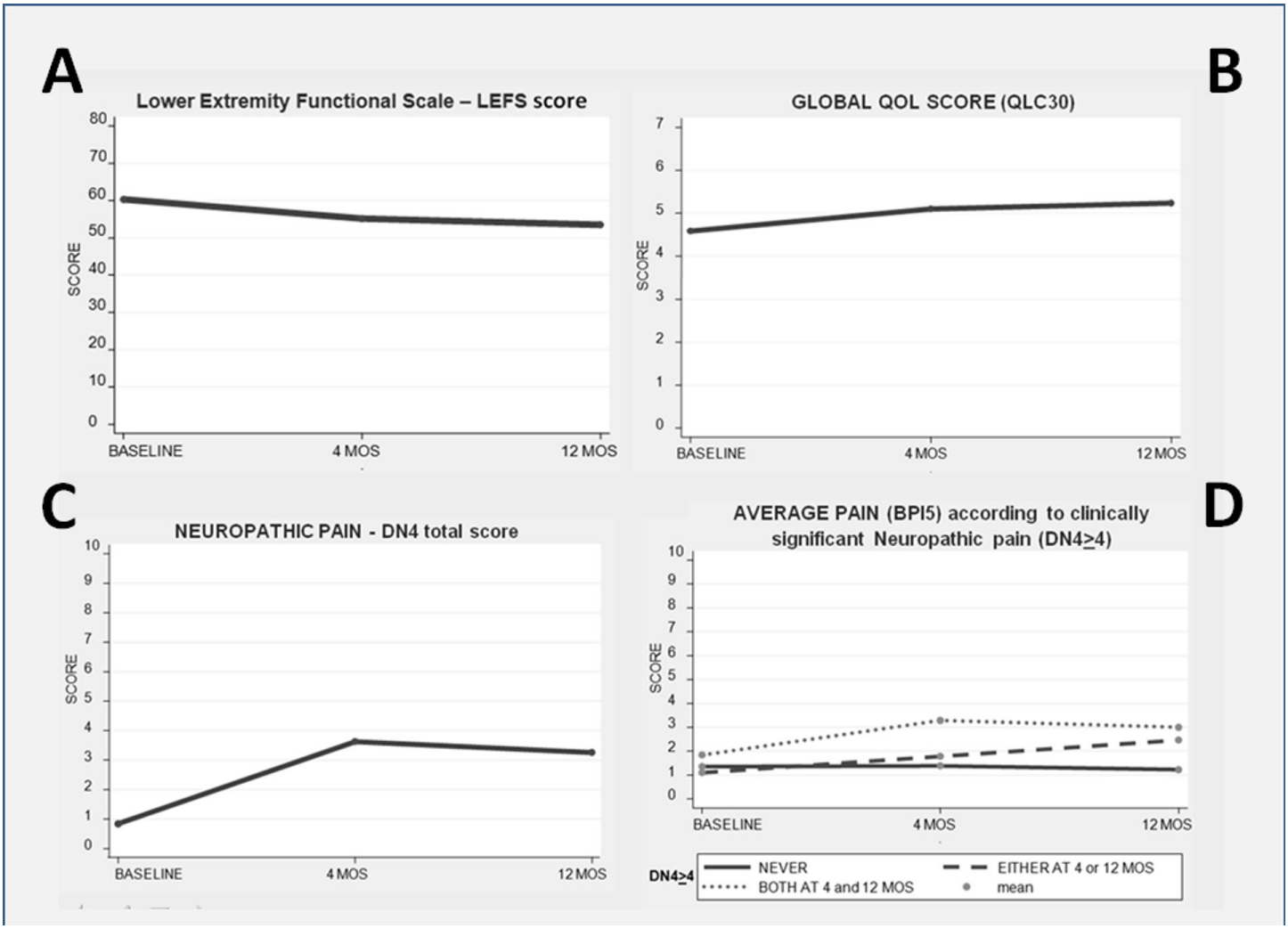

Figure 2. Lower extremity function, global QoL score and pain assessment.

Poster 420 3023377

LOCALIZED MYXOFIBROSARCOMAS: ROLE OF SURGICAL MARGINS AND (NEO)ADJUVANT RADIOTHERAPY

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Objective: The objective of this study was to describe the outcome and prognostic factors of adults treated for myxofibrosarcoma.

Methods: The authors conducted a retrospective multicenter study of 525 non-metastatic patients (pts) operated between January 1996 and December 2015 in French Sarcoma Group centers and enrolled in the "Conticabase." Pathological diagnosis was systematically reviewed by expert pathologists, and myxofibrosarcoma confirmed according to the 2013 WHO classification. The endpoints were relapse-free and metastasis-free survival. Log-rank tests and Cox models have been used to identified prognostic factors.

Results: Among 12,262 soft tissue sarcoma pts included in the conticabase, 525 (4.3%) had localized myxofibrosarcoma. Median age was 66, 53% were males, 85% of cases occurred in limbs or superficial trunk, median size was 60 mm, 37%/39% had Grade 2/3, 66% R0 resection and 34% R1 resection. Adjuvant radiotherapy was given to 65% of patients, neoadjuvant radiotherapy in 2%, neoadjuvant chemotherapy in 7% and adjuvant chemotherapy in 13%. The median follow-up was 51 months. The 5-year local relapse free survival was 67%; independent prognostic factors for local relapse were age (HR: 1.026; p=0.030), R0 resection (HR=1.24; p=0.016) and adjuvant radiotherapy (HR= 0.046; p=0.0001). In stratified analysis, adjuvant radiotherapy was beneficial after R0 resection (p=0.0020) as well as after R1 resection (p=0.0001). The 5-year overall survival was 80%. OS was highly influenced by occurrence of metastases (HR=2.015; p<0.00001). The 5-year metastasis-free survival was 83%. Independent prognostic factors for metastatic relapse were: Grade 3 (HR=1.975; p=0.0001), size (HR=1.005; p=0.001) and deep tumor (HR=2.129; p=0.038). No treatment characteristics influenced the metastasis-free survival.

Conclusion: This is the largest data base study on myxofibrosarcoma confirming its propensity for local relapse. Combination of R0 resection and adjuvant radiotherapy provided the best local control. Given the uncertainty of infiltration extent on MRI, after pre-treatment biopsy, upfront combined aggressive local treatment strategy is necessary.

Poster 421 3026885

MANAGEMENT AFTER UNPLANNED EXCISION IN ADULT EXTREMITY AND SUPERFICIAL TRUNK SOFT TISSUE SARCOMA: ABSTENTION OF SYSTEMATIC RE EXCISION DOES NOT AFFECT OVERALL SURVIVAL, NOR AMPUTATION RATE

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Objective: The role of systematic re-excision (RE) after initial complete -R0/R1- unplanned excision (UE) of soft tissue sarcoma (STS) is not clearly established.

Methods: Evaluate the impact on local relapse free survival (LRFS), metastatic relapse free survival (MRFS), overall survival (OS) and rate of amputation after: systematic RE in labeled center (Group A), systematic RE outside labeled center (Group B), or absence of systematic RE (Group C). All patients with UE for extremity or superficial trunk STS between January 2007 and December 2013 were analyzed. Patients referred secondarily with distant metastasis, macroscopic residual disease, piecemeal resection or requiring straightaway amputation were excluded.

Results: A total of 1037 patients underwent UE, among which 622 fit criteria of inclusion. A, B and C groups included 300 (48.2%), 71 (11.4%) and 251 (40.4%) patients, respectively. Following characteristics differed across the 3 groups: gender (p=0.042), primary site location (p=0.0001), muscle involvement (p=0.024), tumor size (p=0.001), deep tumor (p=0.0001), adjuvant CT (p=0.0001) and adjuvant RT (p=0.001). The median follow-up was 61 months. 123 patients experienced local relapse. All of them were re-operated and 0/28 patients, 1/15 patients and 5/80 patients, in Group A, B and C respectively required amputation (p=0.41). The 5-year LRFS rates were 83%, 73.5% and 63.8% in groups A, B and C, respectively (p=0.00001). In multivariate analysis, factors influencing LRFS were: adjuvant radiotherapy (HR=0.21; p=0.0001), R0 resection at the time of WS (HR=0.26, p=0.0001) and Group A (HR= 0.44; p=0.0101). The 5-year MFRS were 85.4%, 86.2% and 84.9% in Groups A, B and C, respectively (p=0.938). Re-excision (p=0.55) and RT (p=0.36) did not influence MRFS. The 5-year OS were 88.4%, 87.3% and 88% in groups A, B and C respectively (p=0.228).

Conclusion: Systematic RE in labeled center significantly improves LRFS but did not influence MRFS or OS. Patients without systematic RE after UE did not present higher amputation or metastatic rates. The role of immediate RE must be assessed with a prospective trial.

Poster 422 3041962

INCREASED SURVIVAL AFTER SURGICAL MANAGEMENT OF HIGH-GRADE AND DEEP-SEATED SOFT TISSUE SARCOMA IN HIGH-VOLUME HOSPITALS: A NATIONWIDE STUDY

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Objective: Diagnosing and treating soft tissue sarcomas (STS) remains challenging, stressing the urgency for centralization into dedicated multidisciplinary hospitals. This nationwide study on behalf of the Dutch Sarcoma Study Group (DSSG) aimed to evaluate the centralization of surgical treatment of STS and the effect of surgical volume on survival.

Methods: Patients operated for primary STS from 2006-2015 were queried from the Netherlands Cancer Registry. Hospitals performing STS surgery were allocated into three categories: low-volume (1-9 resections per year), medium-volume (10-19 resections) or high-volume (≥20 resections). Differences in grading, depth, size, and net survival rates were calculated. A multivariate Poisson regression analysis was performed to explore the effect of surgical volume on survival after adjustment for case-mix.

Results: In total, 5,282 patients were identified. Low-volume hospitals treated 41.6% of all STS patients, medium-volume hospitals 7.7% and high-volume hospitals 50.7%, with a significant trend over time towards treatment in a high-volume hospital ($p<0.01$). High-volume hospitals more often treated patients with high-grade, large and deep-seated tumors than low-volume hospitals. There was no survival benefit for patients treated in high-volume hospitals, with 10-year net survival rates of 76% (low-volume), 68% (medium-volume) and 68% (high-volume). After case-mix adjustment, multivariate analysis showed no significant influence of surgical volume on survival (relative rate 0.92, $p=0.503$). However, a subgroup analysis including only high-grade and deep-seated tumors revealed a survival benefit for patients treated in high-volume hospitals with 10-year survival rates of 54% (high-volume), 49% (low-volume) and 42% (medium-volume), and a relative rate of 0.61 ($p=0.012$) after case mix adjustment.

Conclusion: Centralization of STS surgery into high-volume hospitals has improved in the past years. Since surgery in a high-volume hospital had a beneficial effect on net survival for patients with high-grade and deep-seated tumors (i.e. more complex surgery and more multidisciplinary treatment required), these patients should be referred to a high-volume hospital. Other STS patients should be at least discussed in a multidisciplinary high-volume hospital before start of treatment.

Poster 423 3042165

CHARACTERISTICS OF THE UNPLANNED RESECTION OF A SOFT-TISSUE SARCOMA

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Objective: The objective of this study is to determine if there is any correlation with size, histopathology, and grade of soft-tissue sarcoma (STS) and unplanned resection (UR).

Methods: After IRB approval was obtained, a retrospective review was performed on all patients that presented to a tertiary sarcoma center with a diagnosis of sarcoma between 1996 and 2017. Using the Electronic Medical Record Search Engine (EMERSE), 2,600 patients were identified and in depth chart reviews were performed. Only patients with a primary diagnosis of STS in an upper or lower extremity were included in this study. In total, 848 patients met inclusion criteria. Data collected included STS histology, grade, size, resection status, demographics and referral information. Due to the current guidelines for tumor size and referral to a tertiary sarcoma center, tumor size was broken down into two categories, >5cm and <5cm. The histology of the STS tumors were recorded based on in-house pathology evaluation including outside biopsies and surgical specimens. A total of 36 unique STS pathology types were noted. Finally, tumor grade of all tumors (high, intermediate, or low) were compared. Rates of UR were compared between each of the groups using a chi-square analysis to assess for statistical significance between groups.

Results: There were a total of 769 of the 848 patients with primary STS that recorded the tumor size and tumor grade. Size was measured in 3 dimensions, the largest dimension determined the size of the tumor. The mean age of patients on presentation was 54 years (2 to 94). The group included 41.9% females and 58.1% males. The mean rate of all UR was 26.2%. STS that were >5cm underwent UR occurred in 19% of the cases (104/567) compared to 41% of those <5cm (83/202). This finding was determined to be statistically significant with p<0.0001. In regards to histopathology, UR occurred in significantly lower rates for Ewing sarcoma (0/12, p = 0.037), myxoid liposarcoma (5/36, p = 0.036), pleomorphic sarcoma (3/30, p = 0.022). Significantly higher rates of UR occurred in malignant fibrous histiocytoma (MFH) (37/67, p 0.021) and myxofibrosarcoma (34/58, p = 0.013). Tumor grade of UR was not determined to be significant p=0.878.

Conclusion: With high national UR rates, further understanding of STS presentation is needed in order to prevent the devastating consequences that occur. This retrospective study of 848 patients with STS found a high percentage of URs in presumed low-risk masses based on size. It was also determined that certain types of STS were found to be more and less likely to undergo UR, while grade did not affect UR. Our results suggest that the current recommendation to refer any patient with a tumor greater than 5 cm to a tertiary sarcoma center may no longer be valid. Further research is needed to determine the tumor size at which a patient should be referred. We recommend the evaluating physician have a high index of suspicion for STS in any sized soft tissue mass.

Tumor Size and Unplanned Resection

Tumor Size	Total	UR	%
<5cm	202	83	41.1%
>5cm	567	104	18.3%
Total	769	191	24.8%

p<0.001

Tumor Grade and Unplanned Resection

Unplanned Resection	Grade 1	Grade 2	Grade 3	Total
No	121	23	428	572
Yes	44	9	144	197
Total	165	32	572	769

p=0.878

Poster 424 3042300

OUTCOMES OF SOFT TISSUE SARCOMA RESECTED WITH CLOSE OR POSITIVE MARGINS ON PRIMARY SURGERY

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Objective: The benefit of adjuvant radiotherapy (RT) after complete surgical resection of soft-tissue sarcoma (STS) has been demonstrated in two randomized trials. Planned R0 surgical resection for STS followed by adjuvant RT is thereby a standard of care. However, clinical practice shows a significant proportion of patients with primary planned R1 resection or being addressed to a referral center for salvage surgery after unplanned (R1) resection. The aim of this study was to evaluate the outcomes of STS primary resected with close or R1 margins, from a single sarcoma referral center experience.

Methods: Between 1996 and 2015, 411 patients with STS of the extremities and trunk wall underwent conservative primary surgery with close or positive margins. Dermatofibrosarcoma Protuberans, Lipoma-Like sarcomas and Tumors of Uncertain Malignant Potential were excluded.
Surgical resection was considered “Planned” when previous MRI and guided core-needle biopsy was performed and when it was executed at our referral center by one of the five sarcoma-specialist surgeons (GV, PM, PP, MG, JG). Planned surgery was defined marginal when tumor distance from ink was < 2 mm but ≥ 1 mm. It was defined R1 when tumor distance from ink was < 1 mm or ink marked. Surgical resection was considered “Unplanned” when performed outside of a referral center. According to this classification, patients were allocated into primary Planned (n = 167) and Unplanned surgery (n = 244) groups. Planned-surgery patients were divided into marginal-R0 (n = 56), and Planned-R1 (n = 111) subgroups. Among Planned-R1 tumors, 51 were resected with ink-marked margins and 60 with infra-millimetric margins. Unplanned-surgery

patients were divided into Re-excision with residual disease (n = 90), Re-excision without residual disease (n = 84), and Unplanned surgery without re-excision (n = 70) subgroups.
Adjuvant RT was performed for 314 patients (76 %) with a median delivered dose of 50 Grays (range 44 - 66) in 25 fractions.

Results: Median follow-up was 80 months (range 3-288). On the entire cohort, overall survival (OS) and local recurrence free survival (LRFS) at 10 years were respectively 72 and 71 %. Univariate analysis of specific subgroups shows that patients who underwent primary Planned (marginal R0 or R1) surgery achieved better LRFS than patients who underwent Re-excision after Unplanned surgery (80 vs 66% at 10 years, $p < 0.001$) but there was no difference in OS, Disease Specific Survival (DSS) and Metastatic Free Survival (MFS).
After Planned resection, patients in the marginal-R0 subgroup obtained better OS and DSS than those in the planned-R1 subgroup (88 vs 70% at 10 years, $p = 0.018$), but no difference in LRFS and MFS was observed. Adjuvant RT did not improve LRFS after marginal-R0 resection.
After Unplanned resection, the benefit of Re-excision was major since patients who underwent re-excision had significantly better LRFS, OS and DSS ($p < 0.001$) than patients who did not. Adjuvant RT improved LRFS after Re-excision without microscopic residual disease (83 vs 62% at 10 years, $p = 0.002$).
Overall, adjuvant RT was associated with better LRFS (74 vs 58 % at 10 years, $p < 0.001$) whereas no difference in OS, DSS and MFS was observed.

Conclusion: Planned resection achieving even close but negative margins was prognostic for OS. Re-excision after unplanned R1 resection is mandatory and seems to reach similar OS and DSS outcomes than planned resection. To our knowledge, this is the first study to display a benefit of adjuvant RT after Re-excision even if it shows no microscopic residual disease.

Poster 425 3027922

CLINICAL OUTCOME IN PATIENTS WITH SOFT TISSUE SARCOMA WHO RECEIVED ADDITIONAL EXCISION AFTER UNPLANNED EXCISION: REPORT FROM THE BONE AND SOFT TISSUE TUMOR REGISTRY IN JAPAN

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Objective: When unplanned excisions (UEs) were performed in patients with soft tissue sarcoma (STS), there is no intent to achieve tumor-free margins and the direction of the skin incision is not considered. This significantly increases the risk of local recurrence. To reduce the possibility of relapse, surgeons perform additional excisions after UEs. Additional excisions require more extensive surgical margins than do conventional wide-margin excisions because reactive changes after UEs and inappropriate skin incisions can cause tumor cell contamination of non-tumor areas.
The Bone and Soft Tissue Tumor (BSTT) Registry is a nationwide organ-specific cancer registry for bone and soft tissue tumors in Japan. The aim of this study was to elucidate the clinical outcomes of patients with STSs who received additional excisions after UEs using data from the BSTT Registry.

Methods: We examined patients with STSs who received an additional excision after a UE. Data from 2006 to 2013 were obtained from the BSTT Registry. All were primary STSs. Therefore, patients with local recurrence and metastasis at the time of registration in the BSTT Registry were excluded. The minimum follow-up period was 2 years after the additional excision except for the patients who developed additional oncological events within 2 years.

Results: Our cohort consisted of 197 patients with STSs who received an additional excision. There were 112 males and 85 females, with an average age of 54 years. The average and median follow-up duration were 48 and 41 months, respectively. The STSs were histologically classified as undifferentiated pleomorphic sarcomas/malignant fibrous histiocytomas (UPS/MFH) (n = 51), liposarcomas (n = 37), myxofibrosarcomas (n = 26), leiomyosarcomas (n = 24), synovial sarcomas (n = 12), malignant peripheral nerve sheath tumors (n = 11), fibrosarcomas (n = 11), or other (n = 25). The average tumor size at initial excision was 4.7 cm, although tumor size in 56 patients was not recorded by the hospitals. Tumor depth was superficial in 132 and deep in 65.
Residual tumor cells were observed in 115 of 197 (58%) specimens at additional excision. Microscopic residual tumor cells were observed in 83 patients, whereas macroscopic in 32 patients. Wide margins were achieved in 109 of 115 patients who had residual tumor cells, whereas marginal or intralesional margins in remaining 6 patients. One hundred and five patients (53%) required plastic reconstructions including skin grafts (n = 50), pedicled myocutaneous flaps (n = 41), free myocutaneous flaps (n = 19), and other procedures (n = 6). At the last follow-up, local recurrence occurred in 15 patients, and the 5-year local recurrence-free rate was 91%. In a univariate analysis using a Cox proportional hazards model, local control correlated with residual tumor tissue in re-excision specimens, and tumor size. The 5-year local recurrence-free

survival was significantly worse in patients with macroscopic residual tumors (80.7%) than in those without residual tumors (97.3%) (p=0.001). There was a marginal difference for local control between the patients with microscopic residual tumor cells and no residual tumors (p=0.08). The 5-year local recurrence-free survival in patients with microscopic residual tumor cells was 88.3%. In 141 patients who had information of tumor size, 38 patients had > 5cm tumors and they had significantly poorer local control (75.8% at 5 years) compared to those with ≤ 5cm tumors (95.6% at 5 years.

Conclusion: We suggest that UEs should be avoided because they require additional excisions and, in many cases, subsequent soft tissue reconstruction. Soft tissue tumors should be treated according to the clinical guideline in soft tissue tumors in each country. Additional excisions may improve local control, although patients with residual tumor cells in re-excision specimens and/or bigger tumors should be carefully followed-up.

Poster 426 3029688

ASSESSMENT OF THE TIME TO TREATMENT INITIATION = 0 COHORT IN SOFT TISSUE SARCOMA PATIENTS AT A TERTIARY CANCER CENTER: ARE WE DEFINING THIS CORRECTLY?

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Objective: Time to treatment initiation (TTI), defined as the time from tissue diagnosis to initiation of first treatment, is a quality control metric intended to improve patient outcomes in cancer referral centers. A unique aspect of a tertiary sarcoma practice is the large percentage of patient referrals with incomplete excision of a soft tissue sarcoma (STS) preceding referral, commonly as an excisional biopsy. In this scenario, the patient is defined as being diagnosed and first treated on the same day, incurring a TTI = 0. The premise of this study challenges this flawed definition, as the patient oftentimes requires further definitive treatment. For this reason, we argue TTI should be standardized at time of first “definitive” or “true” treatment, as this would serve as more accurate descriptor of the STS gold standard treatment received. The purpose of this study is to assess the accuracy of a tertiary cancer tumor registry in reporting TTI data, when using this proposed modified definition for TTI. As well, we will offer implications that this modified TTI definition may have on individual cancer centers and nationwide registries.

Methods: A retrospective analysis of a single tertiary cancer center registry between 2006-2016 was conducted to identify patients who underwent treatment of an extremity or trunk STS. First “true” treatment was defined as planned wide excision or re-excision, radiation therapy or chemotherapy. Patient demographics, tumor characteristics and TTI-related data were collected. TTI differences were compared with a Kruskal–Wallis test, and trends over time were evaluated using linear regression.

Results: Between 2006-2016, 403 patients underwent excision of an extremity or trunk soft tissue sarcoma. Of these, 118 patients (29.3%) had a recorded TTI = 0, while the remaining 285 patients (70.7%) had a recorded TTI > 0.
In the TTI = 0 cohort (Table 1), 91/118 patients (77%) were incorrectly reported according to our modified definition of TTI, as 80 underwent incomplete excisions and 11 received incisional biopsies. After adjusting the treatment date to that of the first true treatment received, the mean TTI rose to 44.6 ± 42.5 days [range 0-253] in the entire TTI = 0 cohort (P<0.001), and 58.2 ± 37.9 days [range 5-253] in the incomplete excision sub cohort (P<0.001). Patients first treated at an outside health system had higher true TTI compared to patients first treated within our sarcoma group (61.8 days vs. 36.2 days; P=0.047), though were found to have no difference in true TTI compared to non-sarcoma treating physicians within our health system (61.8 days vs. 55.8 days; P=0.462).
In the TTI > 0 cohort (Table 2), 19/285 patients (7%) were incorrectly reported according to our modified definition of TTI. For those incorrectly reported, the reported mean TTI was 33.5 ± 43.9 days [range 2-188], and the true mean TTI was 54.6 ± 34.8 days [range 4-119], with a TTI difference of 21.1 days (P=0.013). In the entire TTI > 0 cohort, the reported mean TTI was 31.2 ± 26.0 days [range 2-188], and the true mean TTI was 32.6 ± 25.8 [range 2-141], with a TTI difference of 1.4 days (P=0.421). Figure 1 demonstrates no significant change in overall reported TTI (P=0.307), overall true TTI (P=0.719), or true TTI in the TTI = 0 cohort (P=0.558) during the ten-year span. However, a significant difference was found between all three groups (P<0.001).

Conclusion: Using a modified TTI definition, nearly 80% of patients with a reported TTI = 0 were found to be inaccurate, and the true TTI in this cohort was found to be on average greater than 6 weeks. Incomplete excision procedures were the most common reason for inaccuracies in reported TTI, with the highest prevalence and greatest delay on TTI when first treatment occurred outside of our health system. This internal review of a single institution sarcoma registry suggests a significant underestimation of true TTI, which may shed light on the overall reliability of TTI data collected by national databases.

Table 1. Treatment Characteristics of TTI=0 Cohort

	Number of Patients (%)	True Mean TTI, days (SD) [range]
Total TTI=0 Cohort	118 (100)	44.6 (42.5) [0-253]
Correctly reported TTI=0*	27 (23)	0
First treatment performed by		
Sarcoma physician ϕ	8 (7)	0
Non-sarcoma physician	17 (14)	0
Outside health system	2 (2)	0
Incorrectly reported TTI=0	91 (77)	57.8 (39.7) [5-253]
Incomplete Excision reported as first treatment	80 (68)	58.2 (37.9) [5-253]
First treatment performed by		
Sarcoma physician ϕ	5 (4)	36.2 (30.4) [5-87]
Non-sarcoma physician	26 (22)	55.8 (33.2) [13-138]
Outside health system	49 (42)	61.8 (40.6) [14-253]
Method of Definitive/True treatment		
Planned Re-excision	70 (59)	57.3 (39.5) [5-253]
Radiation	9 (8)	64.3 (30.9) [27-138]
Chemotherapy	1 (1)	31
Incisional Biopsy reported as first treatment	11 (9)	54.7 (52.9) [14-190]
First treatment performed by		
Sarcoma physician ϕ	4 (3)	21.3 (11.2) [14-38]
Non-sarcoma physician	3 (3)	106.7 (81.6) [27-190]
Outside health system	4 (3)	49.3 (23.2) [28-74]
Method of Definitive/True treatment		
Excision	7 (6)	47.1 (33.7) [14-103]
Radiation	2 (2)	27 (15.6) [16-38]
Chemotherapy	2 (2)	109 (114.6) [28-190]

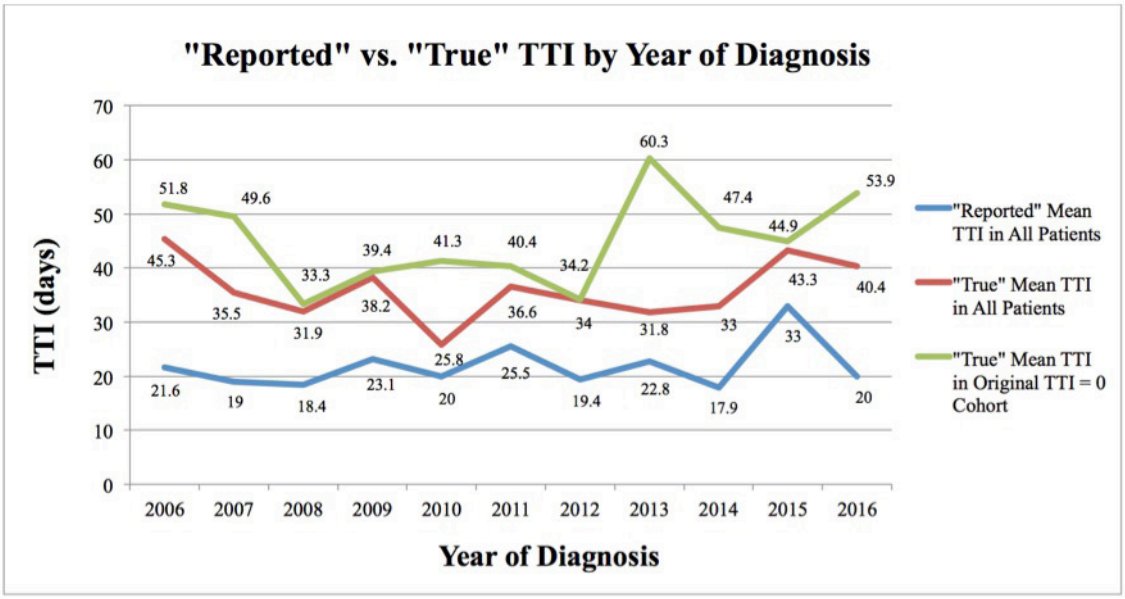
* = All were wide primary excisions; ϕ = Sarcoma physician and non-sarcoma physician providers were within our health system.

Table 2. Treatment Characteristics of TTI>0 Cohort

	Number of Patients (%)	Reported Mean TTI, days (SD) [range]	True Mean TTI, days (SD) [range]	TTI Difference, days
Total TTI>0 Cohort	285 (100)	31.2 (26.0) [2-188]	32.6 (25.8) [2-141]	1.4
Correctly reported TTI>0 Cohort	266 (93)	31.0 (24.4) [2-141]	--	--
First treatment performed by				
Sarcoma physician ϕ	164 (57)	28.7 (22.6) [3-141]	--	--
Non-sarcoma physician	83 (29)	35.5 (27.6) [2-140]	--	--
Outside health system	19 (7)	31.3 (22.6) [2-108]	--	--
Method of Definitive/True treatment				
Excision	144 (50)	31.1 (25.9) [3-141]	--	--
Radiation	86 (30)	32.5 (21.6) [3-140]	--	--
Chemotherapy	36 (13)	26.9 (24.7) [2-108]	--	--
Incorrectly reported TTI>0 Cohort	19 (7)	33.5 (43.9) [2-188]	54.6 (34.8) [4-119]	21.1
Incomplete Excision reported as first treatment	7 (2)	23.3 (14.0) [2-42]	67.6 (31.3) [23-114]	44.3
Incisional biopsy recorded as first definitive treatment	7 (2)	27.7 (34.9) [2-85]	52.6 (43.2) [4-119]	24.9
Date of definitive treatment misreported	3 (1)	24.7 (21.1) [12-49]	31.0 (18.2) [21-52]	6.3
Lymph node biopsy recorded as first definitive treatment	1 (1)	17.0	28.0	11.0
Other treatment performed prior to reported definitive treatment	1 (1)	188	76	-112

ϕ = Sarcoma physician and non-sarcoma physician providers were within our health system.

Figure 1. Time to Treatment Initiation by Year



Poster 427 3030738

PROGNOSTIC RELEVANCE OF SYSTEMIC INFLAMMATORY MARKERS IN SOFT-TISSUE SARCOMA PATIENTS TREATED WITH CURATIVE RESECTION

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Objective: Systemic inflammation has been implicated in cancer development and progression. Inflammatory markers have been identified as prognostic indicators in various malignancies. In the present study, we investigated the prognostic relevance of initial and postoperative systemic inflammatory markers (neutrophil-lymphocyte ratio, platelet-lymphocyte ratio) on progression-free survival (PFS) and overall survival (OS) in patients with soft-tissue sarcoma (STS) who performed curative resection.

Methods: We included 89 STS patients who underwent extensive and radical resection at the Kyungpook National University Chilgok Hospital (Daegu, Korea), between 2004 and 2018. Kaplan-Meier curves and multivariate Cox proportional models were calculated for PFS and OS.

Results: The median age of the patients was 55 years (range 27-86) and the ratio of males to females was approximately 1:1. Histologic subtype of STS was as follows: liposarcoma (n=32, 36%), leiomyosarcoma (n=15, 16.9%), spindle cell sarcoma (n=8, 9%), synovial sarcoma (n=6, 6.7%), rhabdomyosarcoma (n=6, 6.7%), DFSP (n=3, 3.4%), MFH (n=8, 9%), pulmonary artery sarcoma (n=2, 2.2%) and angiosarcoma (n=1, 1.1%). Sixty-seven (75.3%) patients showed high initial NLR (≥4.1) and 65 (75.3%) showed high initial PLR (≥231). After curative resection, the number of high NLR and PLR patients are forty-two (47.2%) and forty-one (46%). In univariate and multivariate analysis, elevated initial PLR ratio was significantly associated with decreased PFS (HR: 2.10; 95% CI: 1.14-3.87, p=0.016) and OS (HR: 5.2; 95% CI: 1.75-15.43, p=0.003). The patients with high PLR (PLR >231) had a median PFS of 18 months, whereas those with low PLR (PLR ≤231) had a median DFS of 35 months. Median OS was 70 and 104 months for high PLR and low PLR groups, respectively. Furthermore, postoperative high NNR and PLR ratio was also significantly associated with decreased PFS (HR: 3.80; 95% CI: 1.67-8.64, p=0.001) and OS (HR: 5.70; 95% CI: 1.09-17.57, p=0.038).

Conclusion: The present results suggest that preoperative and postoperative PLR ratio can be used as a cost-effective prognostic marker for the oncologic outcomes in the STS patients who underwent surgery.

Fig 1 Kaplan-Meier recurrence-free survival curves according to NLR and PLR

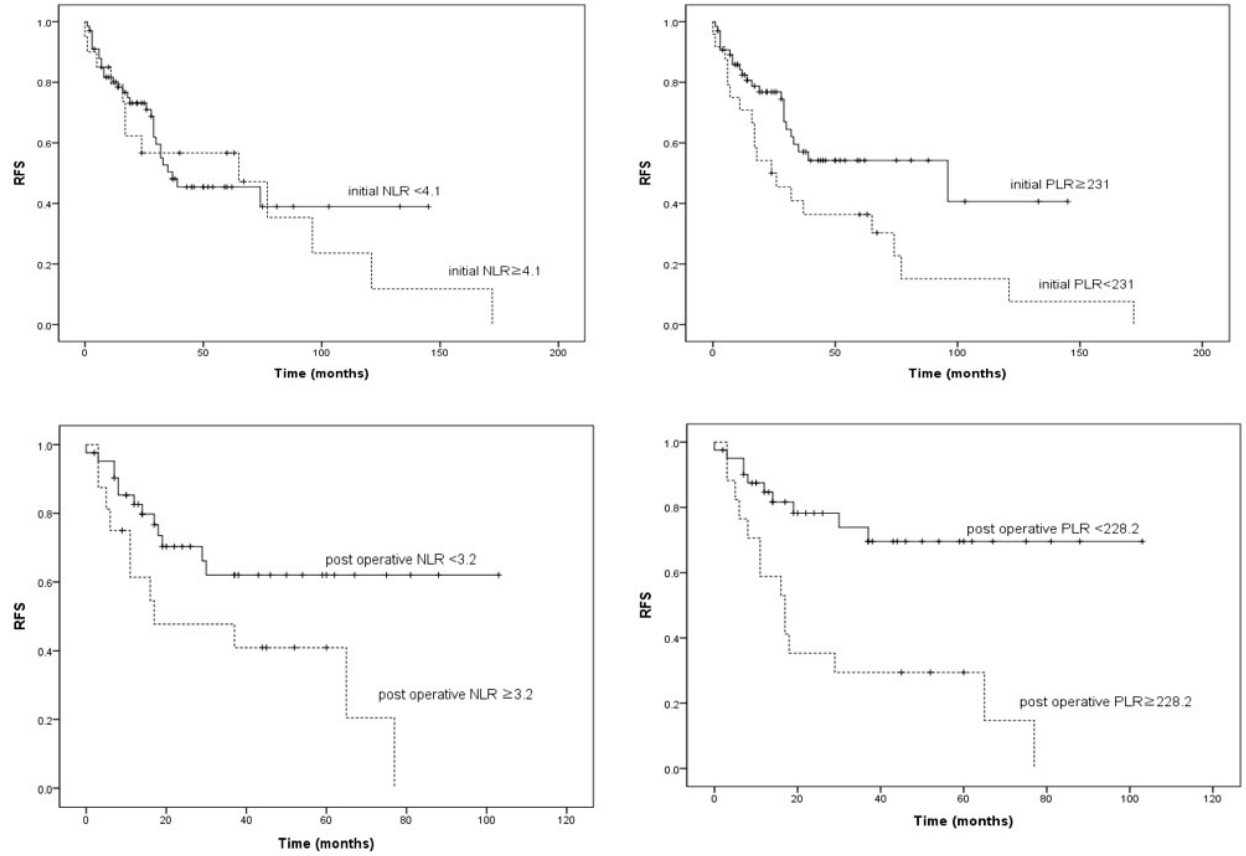
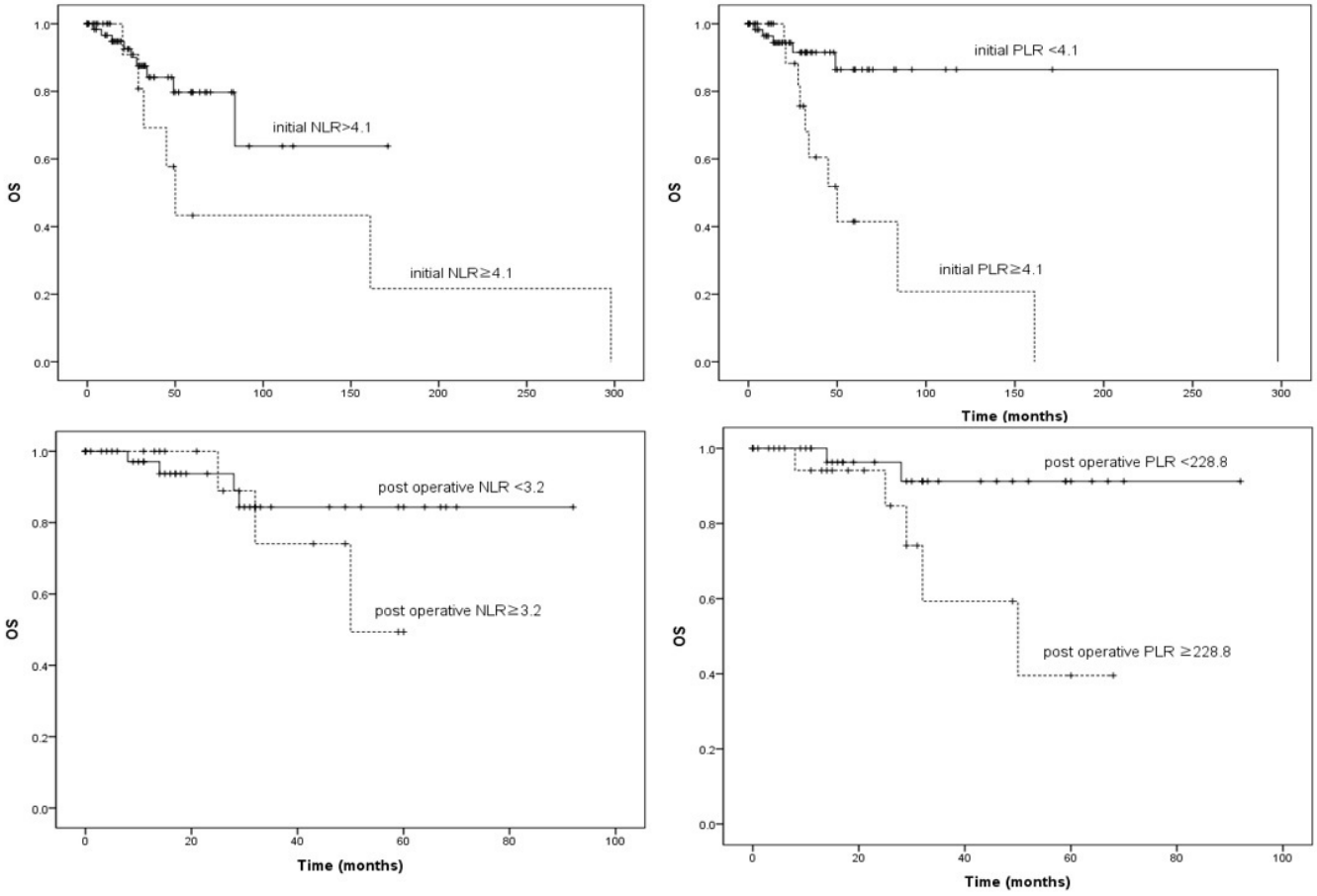


Fig 2 Kaplan-Meier overall survival curves according to NLR and PLR



Poster 428 3034536

PREDICTORS OF LYMPH NODE EVALUATION AND MANAGEMENT OF POSITIVE LYMPH NODES IN TRUNCAL/EXTREMITY SOFT TISSUE SARCOMA PATIENTS: THE WHO, THE WHEN AND THE DIFFERENCE IT MAKES

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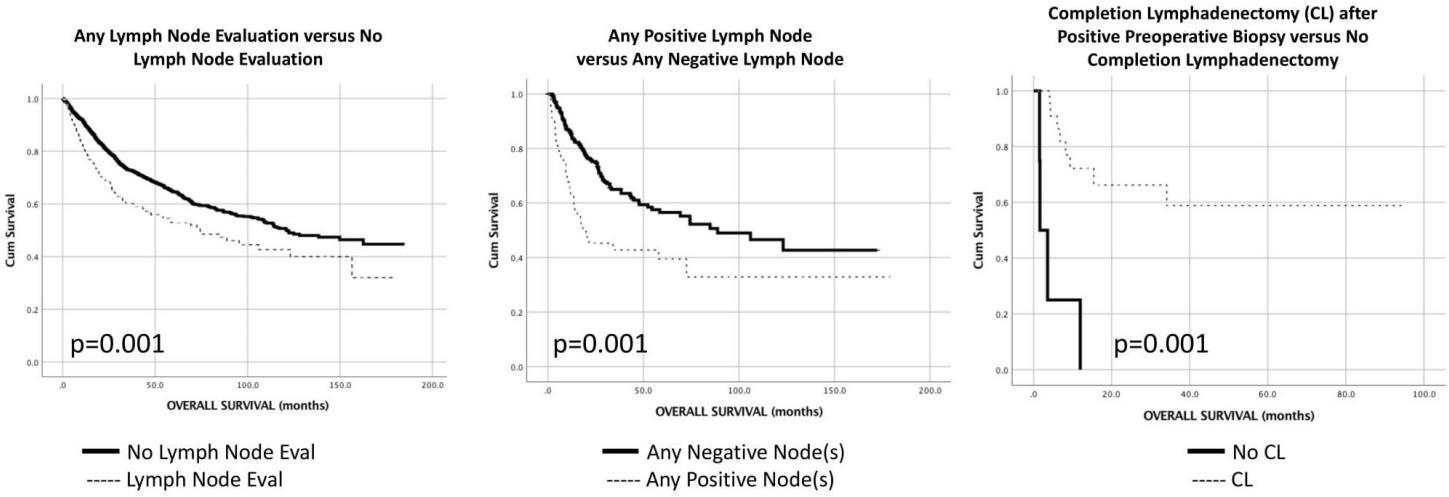
Objective: While regional lymph node (LN) metastasis in soft tissue sarcomas (STS) is rare (2-6%), it can be more common (6-32%) in certain STS subtypes--synovial, clear cell, angiosarcoma, rhabdomyosarcoma, and epithelioid sarcomas (SCARE). Although initial staging includes clinical and radiographic evaluation of LNs, there are no recommendations for the pathologic evaluation of clinically positive nodes or LNs with micrometastatic disease. Additionally, there is no consensus for sentinel node biopsy and the management of positive locoregional LN disease. Thus, our aim was to determine predictors for LN evaluation and positive LNs as well as examine the role of completion lymphadenectomy in pts with positive nodal disease.

Methods: A retrospective review of all adult pts with truncal/extremity STS who underwent resection from 2000-2016 at 7 institutions of the US Sarcoma Collaborative was performed. Patients were stratified by LN evaluation including planned, pre-operative pathologic evaluation (FNA, core, incisional, excisional, and sentinel lymph node biopsy) and incidental intra-operative LN sampling, as well as lymph node biopsy results, and completion lymphadenectomy. Recurrence free survival (RFS) and overall survival (OS) were analyzed.

Results: Of the 3086 patients with truncal/extremity STS analyzed, the mean age was 56 and 54% were male. The median tumor size was 6.5 cm and 61% were high-grade. Median f/u was 28 months. There were 394 pts (12.8%) with SCARE subtype. LNs were evaluated in 321 patients (66 planned pre-op biopsy and 255 incidental intra-operative LN sampling) of which 75pts (24%) had positive LNs (29 planned and 46 incidental). Predictors of pathologic LN evaluation included younger age (p<.001), male gender (p<.001), Caucasian race (p=.039), recurrent tumor (p<.001), SCARE pathology (p=.001), high-grade tumors (p<.001), necrosis (p=.039), lymphovascular invasion (LVI) (p=.001), metastatic disease (p<.001), and clinically positive nodes (p<.001). Patients undergoing LN evaluation had shorter RFS (24 vs 67 mo; p<.001) and OS (74 vs 121 mo; p<.001). On multivariable analysis (MVA), SCARE histology (HR 2.5, CI 1.6-2; p=.001), LVI (HR = 2.4, CI 1.4-4.2; p=.002) and clinically positive nodes (HR= 23.5, CI 10.9-50.7; p=.001) remained significant predictors for lymph node evaluation. Patients with any positive LNs, either preop or incidental, had worse RFS (10 vs 31 mo; p=0.020) and OS (18 vs 88 mo; p=0.001) compared to LN negative pts. On MVA, LVI (HR 9.9, CI 3.4-29.1; p=0.001) and clinically positive nodes (HR 3.9, CI 1.2-12.5; p=0.21) were independent predictors of LN positivity. The 66 patients who underwent planned, pre-op pathologic LN evaluation were younger (p=.038), had SCARE pathology (p<.001), high-grade tumors (p<.001), LVI (p=.007), and clinically positive nodes (p<.001). Median OS for patients undergoing preop lymph node eval, regardless of positivity, was 74 mo versus 122 mo in patients not undergoing preop eval (p=0.052). Of the 27 patients with positive preop nodes, 23 (85%) underwent completion lymphadenectomy (CL). For pts undergoing CL, the median OS was not reached and the 5-year survival was 64% vs median OS of 1.6 months and 5-year survival of 0% (p<0.01) for those not undergoing CL.

Conclusion: STS patients undergoing planned or incidental LN evaluation have a worse RFS and OS. Positive LN disease, whether discovered preoperatively or incidentally, is associated with worse RFS and OS. Predictors of LN evaluation and positive LNs include SCARE histology, high-grade tumors, LVI+ tumors, and clinically positive nodes. In patients with positive preoperative LNs, completion lymphadenectomy appears to be associated with improved survival. Further studies assessing the benefit of completion lymphadenectomy in STS patients with locoregional nodal involvement are needed.

Overall Survival based on Pathologically evaluated Lymph Nodes



Poster 429 3042841

NUTRITIONAL PREDICTORS OF WOUND COMPLICATIONS IN PATIENTS WITH SOFT TISSUE SARCOMAS OF THE LOWER EXTREMITIES

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Objective: Sarcomas of the lower extremities are frequently an indication for high-risk surgeries that leave patients with deep and complex wounds. Past studies have already identified tumor relationship to neurovasculature, use of pre-operative and intra-operative radiation and post-operative day one glucose levels as significant factors in wound complications. The purpose of this research is to identify more potential physiologic and lifestyle risk factors for wound complications in soft-tissue sarcoma removal procedures, specifically of the lower extremities.

Methods: 562 patients from our institution's patient records were identified as having a lower extremity sarcoma of soft tissue origin removed between 1992 and 2017 with adequate records for retrospective analysis. Procedures performed included 229 resections, 296 excisions, 26 amputations (above/below knee) and four hip disarticulations on sarcomas of all stages and grades. A multitude of variables were collected for further research purposes meaning some patients had missing values and therefore each analysis per variable was run only including those patients who had all relevant data available. Lab values were available most often on the day before and after a procedure for the pre/post values and, if available, always within seven days in either direction. Data was analyzed using STATA 13 by StataCorp.

Results: The average patient age at diagnosis was 54 with a range of 18 to 97 with 43% women and 57% men. Smoking status, plasma glucose, hemoglobin and plasma albumin levels were all significant variables in patients with post-operative wound complications and infections after controlling for possible confounding variables (tumor site, depth and stage, gender, procedure, age, preop chemo/radiation, etc.). Smoking status (p=0.010, odds ratio: 1.66, 95% confidence interval: 1.13, 2.44) elevated overall risk for complication with active smokers (n=57) seeing a 13.2% increase and former smokers (n=177) an 11.8% increase in their complication rates. Post-operative glucose analysis showed a mean of 148.9 mg/dL (CI: 141.2, 156.5) for those who developed wound infections compared to 123.8 mg/dL (CI: 120.1, 127.4) in those with no infections, and 146.2 mg/dL (CI: 138.4, 154.0) in those classified as having a wound complication compared to 124.6 mg/dL (CI: 120.9, 128.2) in patients with none. ROC curve analysis was also performed with an area under the curve (AUC) of 0.712 (CI: 0.655, 0.770) demonstrating predictivity positive predictivity of elevated glucose. Conversely, pre-operative albumin was an average of 0.399 g/dL lower (p=0.0000) and hemoglobin 0.970 g/dL lower (p=0.0030) in patients with infections. Pre-operative PTT, PT/INR, platelet count, WBC count, pre and post-operative use of radiotherapy and chemotherapy, along with body mass index, did not have a significant effect on wound healing.

Conclusion: Given the invasive and risky nature of sarcoma surgeries in the lower extremities pre-operative testing and post-operative monitoring are crucial to avoid adverse outcomes. While smoking status is not under the control of surgeons,

its demonstrated effects on healing in these procedures necessitate closer monitoring of patients who are smokers, quicker follow up upon discharge and cessation counseling. Similarly, patients with elevated post-operative glucose levels are at an increased risk and should be monitored more closely for wound infection, dehiscence, and other post-surgical complications. A plasma glucose threshold of >120 mg/dL produced a sensitivity of 76.3% with a false positive rate of 43.2%, which indicates that aggressive glucose monitoring and control should be carried out in patients who exceed this baseline. Although the decreases in hemoglobin and albumin among patients with infections were modest, each was found to be significant. This could assist oncologic surgeons to identify which of their patients are predisposed to infection before they enter the operating room.

Poster 430 3039866

PRIMARY VERSUS STAGED SOFT TISSUE RECONSTRUCTION HAVE SIMILAR WOUND AND ONCOLOGIC OUTCOMES AFTER SOFT TISSUE SARCOMA EXCISION

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Objective: Soft tissue reconstruction after soft tissue sarcoma (STS) excision is useful to cover large wound defects following limb salvage surgery. The ideal timing of soft tissue reconstruction requires further evaluation. The purpose of this study is to compare the wound complication rate and oncologic outcome in patients undergoing primary versus staged soft tissue reconstruction after soft tissue sarcoma excision.

Methods: A retrospective analysis of a single sarcoma referral center between 2006-2016 was conducted to identify patients who underwent excision of an extremity or trunk STS with associated soft tissue reconstruction (split-thickness skin graft (STSG) or flap coverage).Patients were divided into two groups based on the timing of reconstruction: primary (same day of excision surgery) versus staged (at a later date from excision surgery with wound vac temporization). Demographic characteristics, wound complications and oncologic outcomes were collected. Groups were compared using the Wilcoxon rank-sum test for continuous variables and the Fisher's exact test for categorical variables.

Results: Between 2006-2016, 491 patients underwent excision of an extremity or trunk soft tissue sarcoma. Of those, 81 (16%) patients received associated soft tissue reconstruction, with 26 patients undergoing primary reconstruction and 55 patients undergoing staged reconstruction. Though primary and staged groups had mostly similar patient and tumor characteristics (Table 1), differences included perioperative radiation (P = 0.003) and perioperative chemotherapy (P = 0.041), both utilized more frequently in the primary group. Surgical characteristics and clinical outcomes of the two cohorts are found in Table 2. Staged reconstruction was more frequently utilized in re-excisions of incompletely excised tumor beds, while primary reconstruction was more frequently used in index wide excision procedures (P = 0.035). There were a larger proportion of flaps performed in the primary group, and STSGs in the staged group (P = 0.002). Two patients had positive margins after primary reconstruction with no re-excision performed, while four patients in the staged reconstruction group had positive margins after excision surgery – all were taken back for re-excision prior to reconstructive surgery. A larger proportion of patients in the primary group (15, 57.7%) required SICU stay, compared to the staged group (12, 21.8%), though overall length of SICU stay was no different. The total number of surgeries required was greater in the staged reconstruction group (3.9 ± 2.1) versus the primary group (2.5 ± 2.4) (P = 0.002), though the number of surgeries after reconstruction and the total anesthesia time was no different. The mean time from excision to reconstruction in the staged group was 17 ± 15 days.
Wound complication rates were similar, found in 15 patients (57.7%) in the primary group and 25 patients (45.5%) in the staged group (P = 0.347). The number of patients with more than one wound complication, the mean number of wound complications and the proportion of reconstructions healed at final follow up were no different between the groups. Local recurrence (7.7% vs. 7.3%), metastasis after reconstruction (19.2% vs. 20.0%), and mortality (26.9% vs. 27.3%) were not significantly different between the primary and staged groups, respectively. Mean final follow up was 38 ± 33 months (range 1-135) for all patients.

Conclusion: There was no difference in the wound complication rate and oncologic outcomes between patients undergoing primary versus staged soft tissue reconstruction after soft tissue sarcoma excision. Staged reconstructions did lead to significantly fewer SICU stays, while also affording easy opportunity for re-intervention after positive margins with little additional morbidity. Further prospective research is necessary to elucidate the optimal indications and timing of reconstruction in this patient population.

Table 1. Patient and Tumor Characteristics

	Primary Reconstruction (N=26)	Staged Reconstruction (N=55)	P-value
Age, mean ± SD (in years)	57 ± 17	61 ± 15	0.279
Male, n (%)	12 (46.2%)	38 (69.1%)	0.055
BMI, mean ± SD	31.9 ± 9.6	29.9 ± 7.3	0.789
Smoker, n (%)	11 (42.3%)	28 (50.9%)	
Comorbidities, n (%)			
Diabetes	7 (26.9%)	14 (25.5%)	0.791
CAD	2 (7.7%)	10 (18.2%)	0.323
PVD	2 (7.7%)	6 (10.9%)	1.000
Lymphedema	2 (7.7%)	3 (5.5%)	0.654
ASA score, mean ± SD	3.0 ± 0.7	3.0 ± 0.6	0.618
Laboratory, mean ± SD			
HgbA1C	6.9 ± 1.3	8.3 ± 1.9	0.143
Albumin	3.7 ± 0.9	3.9 ± 0.9	0.115
Perioperative Radiation, n (%)			0.003
Neoadjuvant	8 (30.8%)	10 (18.2%)	
Adjuvant	7 (26.9%)	8 (14.5%)	
Both Neoadjuvant and Adjuvant	3 (11.5%)	0 (0%)	
None	8 (30.8%)	37 (67.3%)	
Total radiation dose, mean ± SD	60 ± 32	51 ± 10	0.300
Perioperative Chemotherapy, n (%)			0.041
Neoadjuvant	1 (3.8%)	0 (0%)	
Adjuvant	4 (15.4%)	4 (7.3%)	
Both Neoadjuvant and Adjuvant	3 (11.5%)	0 (0%)	
None	18 (69.2%)	51 (92.7%)	
Histology, n (%)			0.029
UPS	4 (15.4%)	20 (36.4%)	
Liposarcoma	8 (30.8%)	9 (16.4%)	
Leiomyosarcoma	2 (7.7%)	11 (20%)	
Myxofibrosarcoma	3 (11.5%)	6 (10.9%)	
Clear Cell Sarcoma	1 (3.8%)	3 (5.5%)	
Dermatofibrosarcoma Protuberans	1 (3.8%)	2 (3.6%)	
Synovial Sarcoma	2 (7.7%)	0 (0%)	
Angiosarcoma	2 (7.7%)	0 (0%)	
Fibromyxoid sarcoma	1 (3.8%)	1 (1.8%)	
Extraskeletal myxoid chondrosarcoma	0 (0%)	2 (21.8%)	
Rhabdomyosarcoma	1 (3.8%)	0 (0%)	
Fibrosarcoma	0 (0%)	1 (1.8%)	
PNET soft tissue sarcoma	1 (3.8%)	0 (0%)	
Grade, n (%)			0.660
1	4 (15.4%)	10 (18.2%)	
2	9 (34.6%)	17 (30.9%)	
3	13 (50%)	24 (43.6%)	
N/A	0 (0%)	4 (7.3%)	
Depth, n (%)			0.091
Superficial to fascia	7 (26.9%)	27 (49.1%)	
Deep to fascia	19 (73.1%)	28 (50.9%)	
Size (cm2)	74 ± 70	89 ± 200	0.118
Location, n (%)			0.153
LE, other	9 (34.6%)	28 (50.9%)	
LE, inguinal	6 (23.1%)	4 (7.3%)	
LE, popliteal	1 (3.8%)	4 (7.3%)	
UE, other	2 (7.7%)	11 (20%)	
UE, axilla	2 (7.7%)	1 (1.8%)	
UE, antecubital fossa	0 (0%)	0 (0%)	
Pelvis	1 (3.8%)	2 (3.6%)	
Trunk	2 (7.7%)	2 (3.6%)	
Chest wall	3 (11.5%)	3 (5.5%)	

Table 2. Surgical Characteristics and Clinical Outcomes

	Primary Reconstruction (N=26)	Staged Reconstruction (N=55)	P-value
Excision Type, *n (%)*			0.035
Primary excision	18 (69.2%)	23 (41.8%)	
Re-excision post incomplete excision	4 (15.4%)	24 (43.6%)	
Re-excision post local recurrence	4 (15.4%)	8 (15.5%)	
Margin status after initial excision, n (%)			<0.001
Negative	24 (92.3%)	51 (90.9%)	
Positive, no re-excision performed	2 (7.7%)	0 (0%)	
Positive, re-excision performed	0 (0%)	4 (7.3%)	
Defect size, mean ± SD (cm2)	337±393	260±272	0.582
SICU stay			
No of patients, n (%)	15 (57.7%)	12 (21.8%)	0.006
Length of SICU stay*, mean ± SD (days)	2.7±1.7	2.3±1.3	0.718
Length of initial hospital stay, mean ± SD (days)	10.2±10.5	8.9±10.3	0.236
Time to recon procedure, mean ± SD (days)	NA	17 ± 15	NA
Type of ST recon procedure, n (%)			0.002
STSG	5 (19.2%)	31 (56.4%)	
Flap	21 (80.8%)	24 (43.6%)	
Type of Flap, n (%)			0.078
Pedicle muscle flap	18 (86%)	16 (67%)	
Latissimus dorsi	4 (19%)	4 (17%)	
Rectus abdominis	5 (24%)	3 (13%)	
Gastrocnemius	4 (19%)	3 (13%)	
Gluteus	0 (0%)	2 (8%)	
Rectus femoris	2 (10%)	0 (0%)	
Pectoralis major	2 (10%)	0 (0%)	
Radial forearm	0 (0%)	1 (4%)	
Vastus lateralis	1 (5%)	0 (0%)	
Gastroepiploic	0 (0%)	1 (4%)	
Hemisoleus	0 (0%)	1 (4%)	
Fasciocutaneous perforator	0 (0%)	1 (4%)	
Free Flap	2 (10%)	8 (33%)	
Latissimus dorsi	4 (15.4%)	10 (18.2%)	
TRAM	9 (34.6%)	17 (30.9%)	
ALT	13 (50%)	24 (43.6%)	
Radial forearm	0 (0%)	4 (7.3%)	
Combined Pedicle and Free Flap	1 (5%)	0 (0%)	
Pedicle Gastrocnemius + Free VRAM	1 (100%)	0 (0%)	
Number of Surgeries, mean ± SD			
Total number	2.5±2.4	3.9±2.1	0.002
Pre-ST Recon Procedure	NA	1.9±1.2	NA
Post-ST Recon Procedure	1.5±2.4	1.0±1.4	0.823
Total Anesthesia Time, mean ± SD (hours)	12.0 ±6.2	13.5±8.9	0.901
Wound Complications, n (%)			
Any	15 (57.7%)	25 (45.5%)	0.347
More than one complication	6 (23.1%)	5 (9.1%)	0.161
Total Flap/STSG Loss	0 (0%)	0 (0%)	NA
Partial Flap/STSG Dehiscence	4 (15.4%)	6 (10.9%)	0.719
Delayed Wound Healing	1 (3.8%)	3 (5.5%)	0.615
Infection	9 (34.6%)	14 (25.5%)	0.602
Superficial Infection	3 (11.5%)	7 (12.7%)	0.595
Deep Infection	6 (23.1%)	7 (12.7%)	0.193
Hematoma/seroma	4 (15.4%)	2 (3.6%)	0.080
Lymphedema	3 (11.5%)	4 (7.3%)	0.675
Cosmetic	0 (0%)	1 (1.8%)	1.000
Mean number of wound complications	0.81±0.80	0.56±0.71	0.174
Readmission for wound complication	12 (46.2%)	16 (29.1%)	0.143
Timing of First Wound Complication after ST Recon Procedure, mean ± SD (days)**	70±79	68±102	0.978
Intervention after Wound Complication, n (%)*			1.000
Antibiotics alone	2 (7.7%)	3 (12.5%)	
Wound care	4 (15.4%)	6 (25.0%)	
Surgery	9 (34.6%)	16 (29.1%)	
Wound Status, ††n (%)			
Healed at 3 month Follow Up	12 (46.2%)	29 (52.7%)	0.635
Healed at Final Follow Up	22 (84.6%)	46 (83.6%)	1.000
Local Recurrence, n (%)	2 (7.7%)	4 (7.3%)	1.000
Metastasis after reconstruction†, n (%)	5 (19.2%)	11 (20%)	0.755
Metastasis at Presentation	6 (23.1%)	2 (3.6%)	0.012
Death, n (%)	7 (26.9%)	15 (27.3%)	1.000
Follow Up, mean ± SD(months)	27±22	43±37	0.087

*For those with a SICU stay. **For those with wound complications. †Among patients without mets at presentation. ††One patient died before three months.

Poster 431 3025438

SURGICAL ADJUVANT THERAPY USING ACRIDINE ORANGE AFTER INTRA-LESIONAL OR MARGINAL RESECTION IN PATIENTS WITH HIGH-GRADE SOFT TISSUE SARCOMA. A PILOT STUDY.

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Objective: Adequate surgical margins inhibit local tumor recurrence in high-grade soft tissue sarcomas (STSs). However, if tumors are in close contact with major nerves, vessels, bones, or joints, patients can develop serious dysfunction of the affected limb after wide resection, which might involve the sacrifice of some or all those structures. Based on basic research studies, we have established acridine orange (AO) therapy, including photodynamic surgery (PDS), photodynamic therapy (PDT), and radiodynamic therapy (RDT) after marginal or intra-lesional tumor resection, with the aim of reducing local recurrence and maintaining limb function in patients with STSs. Now, we investigated the long-term clinical efficacy of this new AO therapy modality on the inhibition of local recurrence after marginal or intra-lesional tumor resection in high-grade STSs.

Methods: Our study consisted of 48 patients with STSs who received AO therapy after marginal or intra-lesional resection. The median and mean follow-up durations were 76 and 78 months, respectively. we performed intra-lesional or marginal tumor resection to avoid any damage to intact muscles, bones, joints, major nerves, and vessels in close contact with the tumor, resulting in good limb function after surgery. In the next procedure involving PDS, microscopic curettage with an ultrasonic surgical knife was immediately followed with a fluorescence surgical microscope equipped with a high-power xenon lamp and special interference and resorption filters for AO. We sprayed a 1-μg/ml solution of AO (Sigma Aldrich Co, St Louis, MO, USA) into the surgical field. Repeated fluorescence-guided curettage using the ultrasonic knife was then performed by excitation with blue light from a xenon lamp using an interference filter (450–490 nm), and the remaining tumor fragments, which had selectively taken up AO, emitted a green fluorescence that was visible under a fluorescence microscope fitted with a yellow resorption filter (>520 nm). This PDS procedure was repeated until AO fluorescence could not be elicited. PDT sequentially followed PDS. For AO-PDT, an unfiltered full-light beam from a xenon lamp was applied to the tumor curettage area for 10 minutes using a surgical microscope after administration of AO solution.
The final step of RDT was performed as follows. After a closure of the surgical wound, single-session radiotherapy with 5 Gy was immediately administered to the surgical field in the RT room in 25 patients who agreed to undergo RDT

Results: There were 25 men and 23 women, with a mean age of 46 years. The average tumor size at surgery was 8.5 cm. The tumors were histologically classified as synovial sarcomas (n=9), undifferentiated pleomorphic sarcomas (UPSs) (n=8), rhabdomyosarcomas (n=6), liposarcomas (n=5; myxoid type n=4, pleomorphic type n=1), leiomyosarcomas (n=4), myxofibrosarcomas (n=4), malignant peripheral nerve sheath tumors (n=4), and others (n=8). All tumors were high-grade sarcomas categorized as grade 2 (n=16) or 3 (n=32) according to the criteria of the FNCLCC grading system. At the last follow-up, 11 patients developed local recurrence. The 5- and 10-year local recurrence-free rates were 78.9% and 73.3%, respectively. In Cox hazard univariate analysis, the patients with large tumor sizes had worse local control (p=0.002). Female patients had significantly better local control (p=0.048). In multivariate analysis, tumor size remained significant. None of the patients developed systemic or local complications. All patients recovered activities of daily life before AO therapy.

Conclusion: We believe that AO therapy was safe and effective for local control. Tumor size is an important factor for the indication of AO therapy. We also suggest that if the tumor can be resected without serious dysfunction of the affected limb after wide resection, AO therapy should not be indicated because tumor resection with wide surgical margin is the standard treatment for good local control.

Poster 432 3029939

LONG-TERM OUTCOME IN PATIENTS WITH COMPLICATED NON-METASTATIC RETROPERITONEAL SOFT TISSUE SARCOMAS REQUIRING UNPLANNED EMERGENCY SURGERY

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Objective: Either during preoperative treatment or as inaugural event, some patients with retroperitoneal soft tissue sarcoma (RPS) develop life-threatening complications related to their tumor requiring an emergency surgery, whose survival impact is still unknown.

Methods: All consecutive patients who underwent an unplanned emergency surgery for a non-metastatic RPS in our tertiary care center between 1994 and 2016 were retrospectively analyzed.

Results: 22 patients were identified (median age of 51, range: 27 – 74). Median tumor size was 19cm (range: 7 – 50). Emergency Surgery was done in 15 patients for a first tumor resection, in 6 patients for a re-intervention after inappropriate previous surgery, and in 1 patient for a loco-regional recurrence after wide surgery. Reasons for unplanned emergency surgery were rapid tumor progression under chemotherapy and/or radiotherapy (n=7), bowel occlusion (n=6), uncontrollable sepsis (n=3), intraluminal digestive bleeding (n=1), haemoperitoneum due to the tumor rupture (n=4), ureteral obstruction (n=1). Unplanned emergency surgery was complete (R0/R1) in 19 patients and macroscopically incomplete in 3 patients. 3 patients experienced severe postoperative complications (Dindo/Clavien 3-4) and 3 patients died postoperatively (1 pulmonary embolism, 1 pneumonia and 1 ruptured septic iliac aneurysm). The most frequent histological types were malignant adipocytic tumors (n=9) and smooth muscle tumors (n=9). After a median follow-up of 22 months (range 2-61 months), 3 patients developed distant metastasis during the follow-up after a median delay of 6 moths (range 4-25 months) and 9 patients developed loco-regional recurrence or peritoneal sarcomatosis after a median delay of 13 months (range 1-36 months). 7 patients are still alive and disease free after a median delay of 66 months (range 57-133 months).

Conclusion: Unplanned emergency surgery for a life-threatening complication related to their RPS is associated with a high morbi-mortality and a poor prognosis. Nevertheless, some patients experience long remission and aggressive surgical treatment of these situations is advisable.

Poster 433 3037277

BENEFIT OF SURGICAL TREATMENT FOR PULMONARY METASTASIS IN SOFT TISSUE SARCOMA PATIENTS

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Objective: Soft tissue sarcomas (STSs) are rare heterogeneous malignancies of mesenchymal origin. The lungs are the primary sites of distant spread with over 50 % of patients developing metastatic lesions, and surgical treatment of pulmonary metastasis in STS patients has been reported to result in long-term survival. The purposes of this study were to describe factors associated with survival in a series of STS patients, and to reveal the benefit of surgical treatment of metastatic lung lesions for the prognosis of the patients.

Methods: We retrospectively reviewed 91 STS patients with pulmonary metastasis, who were treated in our institutions between January 2000 and December 2015. Uni- and multivariate analyses were used to identify factors associated with clinical outcomes, and post-metastasis survival was estimated using Kaplan-Meier survivorship curves and Cox-regression hazard models.

Results: This study included 61 men and 30 women, with a median age of 59.8 years at a diagnosis of primary lesion (range 15-88), and of 60.3 years at a diagnosis of pulmonary metastasis (range 15-89). The histologic results of the primary tumor were: 22 leiomyosarcomas, 19 UPS/MFHs, 13 synovial sarcomas, 9 liposarcomas, 7 MPNSTs, 6 myxofibrosarcomas, 4 extraskeletal Ewing/PNETs, 11 other tumors. Metastasis in other sites developed in 35 patients (38.5%), including 15 bone, 7 lymph node, 6 liver, 6 skin/soft tissue, etc. For lung lesions, 32 patients (35.2%) underwent surgical treatment, and

chemotherapy was used in 44 patients (48.4%). One-, three- and five-year post-metastasis survival in all 91 patients were 60.3%, 30.0%, and 21.3%, respectively. The survival in 32 patients with surgical treatment for pulmonary metastasis were 96.6%, 65.3% and 60.2%, and were significantly better than in 59 patients without the surgery (43.8%, 10.0%, 0%) (p<0.0001). Univariate analyses revealed that surgery for pulmonary metastasis (p<0.0001), surgery for primary lesion (p=0.0002), metastasis-free interval (p=0.047), number of metastatic nodules in lung (p=0.0003), bilateral involvement (p=0.003), had a significant correlation with the prognosis of the patients. Among the factors, surgery for pulmonary metastasis was the only independent factor, significantly associated with an improved post-metastasis survival in a multivariate analysis (HR: 6.027, 95%CI: 2.842-12.770) (p<0.0001). In the current study, site or depth of the primary tumor, size of the primary tumor, local recurrence of the primary tumor, metastasis in other sites, chemo- or radio-therapy for pulmonary metastasis did not influence the prognosis of the patients.

Conclusion: The treatment for pulmonary mestastasis in STS patients is still complex, and should be considered individually to each patient. In the current study, we retrospectively reviewed the factors associated with post-metastasis survival in STS patients with pulmonary metastasis. A multivariate analysis using the Cox regression hazard models identified that *surgical treatment for pulmonary metastasis* is the most important independent prognostic factor, and seems to prolong a post-metastasis survival in the STS patients with pulmonary metastasis. Although we should carefully weigh the risks and the benefits of the patients, surgical treatment for pulmonary metastasis could be a means of achieving long-time survival.

Poster 434 3038338

ALGORITHMS FOR THE SURGICAL MANAGEMENT OF SOFT TISSUE TUMOURS OF THE ABDOMINAL WALL: RETROSPECTIVE SINGLE CENTRE STUDY ON 120 PATIENTS

Isabelle Sourrouille[1]*; Cecilia Ceribelli*[1]*; Sara Baleri*[1]*; Olivier Mir*[2]*; Matthieu Faron*[1]*; Julien Adam*[3]*; Sarah N. Dumont*[2]*; Axel Le Cesne*[2]*; Philippe Terrier*[3]*; Charles Honoré*[1]

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Objective: The aim of this study was to report our experience in managing soft tissue tumours of the abdominal wall (STTAW).

Methods: Data included all consecutive patient with STTAW treated in our centre from 2001 to 2017. Initial treatment strategy was based on malignancy: benign tumours (BT) were scheduled for surgery on in case of severe symptoms, malignant tumours (MT) and intermediate tumours (IT) were systematically scheduled for surgery, and desmoid tumours (DT) were treated according to their potential for evolution.

Results: 120 patients were identified (median age 37 years, IQR [32-45]). Percutaneous biopsies were systematic prior to any treatment and revealed 3 BT, 41 MT, 6 IT and 70 DT. For DT, an initial “wait & see” approach was scheduled in 53 patients (76%), a medical treatment in 11 (16%) (because of rapid growth or severe symptoms) and an upfront surgery in 6 patients (8%, all before 1999). , excluding the 6 upfront surgery, 12 patients with DT (17%) eventually required surgery for tumour progression after medical treatment. In the entire series (including DT), 69 patients (58%) were eventually operated on. Median tumour size was 40mm [13-104]. 26 patients had preoperative treatment (chemotherapy (n=24), radiotherapy (n=3). Every patient underwent full thickness *en bloc* abdominal wall resection. Skin could be spared in 16 patients. Resection involved the inguinal ligament in 8, periosteal resection in 3, and thoracic wall in 2. 44 patients (64%) underwent reconstruction (prosthetic mesh in 33, reconstructive flap in 8, and both in 3); the remaining patients underwent either direct wound closure (n=17), two steps closure (n=6) or controlled healing (n=1). We observed no postoperative death, but 7 patients (10%) had severe postoperative complication (Clavien≥3), mainly due to reconstruction (4 mesh infections among which 2 had to be removed, 1 flap necrosis). Among 6 patients who had to be reoperated on, 1 had a prosthetic mesh (no initial reconstruction) and 2 had a reconstructive flap (initial reconstruction by mesh, and by mesh and flap). 13 patients had postoperative radiotherapy (no chemotherapy). 54 resections were classified R0 (78%). In patients who underwent surgery, disease-free survival (DFS) was unreached and 5-years DFS was 80% [69-92]. For MT, median overall survival (OS) was unreached and 5-years OS was 91% [81-100]. 5 patients experienced local recurrences, 2 with DT (no treatment after recurrence), 3 MT with previous inappropriate surgery.

Conclusion: Management of STTAW is complex and surgically challenging**.** Surgery requires reconstruction in 2/3 cases and a good collaboration among surgical specialities within the team.

Poster 435 3042592

FLUORESCENCE-GUIDED LYMPH VESSEL SEALING TO PREVENT LYMPHOCELE AFTER SARCOMA RESECTION

Jens Jakob[2]*; Andreas Gerken*[1]*; Ioannis Karampinis*[1]*; Peter Hohenberger*[1]
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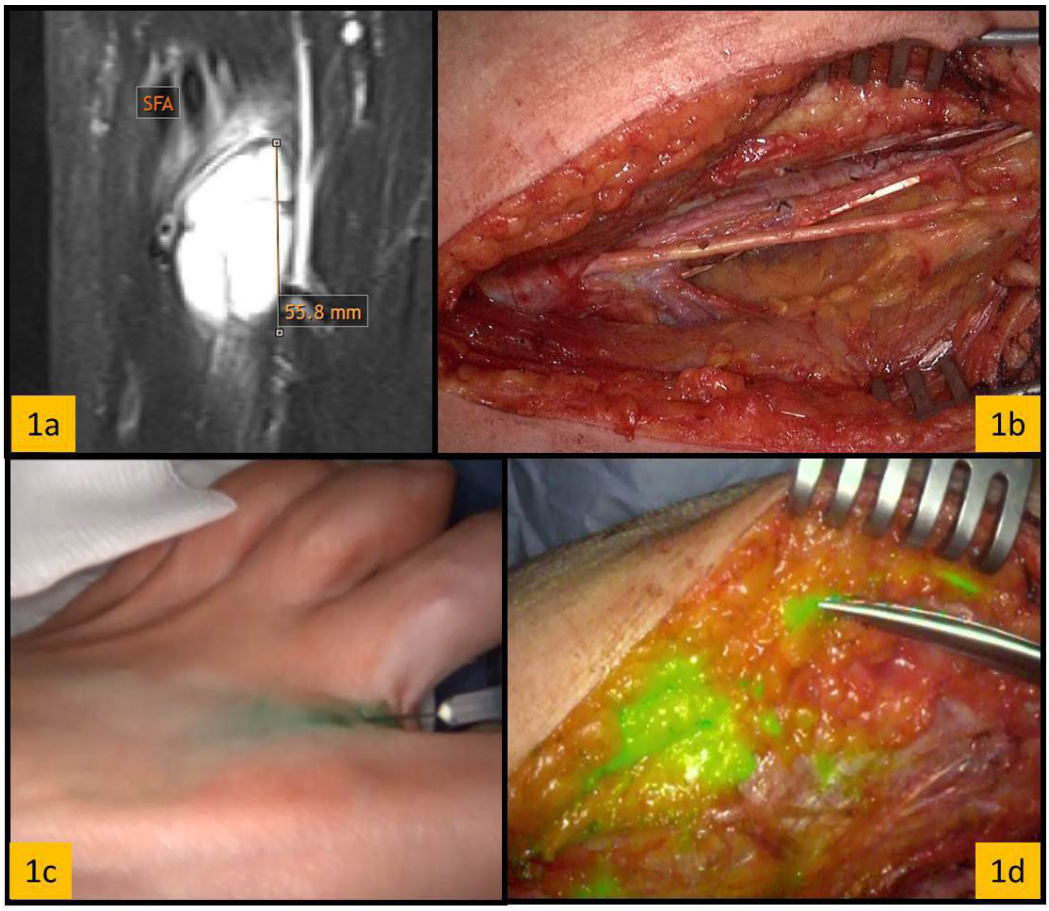
Objective: Postoperative wound infection and break down are a major challenge in the multimodal treatment setting of extremity soft tissue sarcoma. Transection of lymph vessels without sufficient lymph vessel sealing may contribute to postoperative lymphorrea and wound healing disorders. After intracutenous injection, indocyanine-green dyes are transported proximally by lymphatics. Intraoperative imaging may enable targeted sealing of transsected lymph vessels in order to prevent lymphorrhea and postoperative wound healing disorders.

Methods: Indocyanine dye was injected intracutaneously distal of the tumor immediately before tumor resection. Sarcoma resection was then performed according to standard protocols. Near-infrared imaging was applied throughout the procedure to perform and fluorescence- guided lymph vessel sealing.

Results: Fluorescence-guided lymph vessel sealing was performed in two consecutive patients undergoing resection of a lower limb soft tissue sarcoma. No adverse events occurred following fluorescence dye injection. Both patients were discharged free of wound complications.

Conclusion: Fluorescence-guided lymph vessel sealing may be a promising new technique for preventing lymphocele and wound healing disorders after soft tissue sarcoma resection. Prospective trials are required to demonstrate the efficacy of selective lymph vessel sealing in the context of tumor resections.



MRI (1a) and intraoperative situs (1b) of a myxoid tumor of the m. vastus medialis in a sixty year old lady. Resection was performed after intracutaneous injection of 1ml of a solution of 2.5mg/ml indocyanine green (1c). Throughout the operation, fluorescence imaging was used perform fluorescence guided lymph vessel sealing by suture or sealing devices (1d).

Poster 436 3028381

TUMOR NECROSIS FOLLOWING NEOADJUVANT CHEMOTHERAPY FOR SYNOVIAL SARCOMA: A REPORT FROM CHILDREN'S ONCOLOGY GROUP STUDY ARST0332

Rajkumar Venkatramani[1]*; Douglas Hawkins*[2]*; David Parham*[3]*; Jennifer Black*[4]*; Andrea Hayes-Jordan*[5]*; Suzanne Wolden*[6]*; Stephen Skapek*[7]*; Yueh-Yun Chi*[8]*; Jing Tian*[9]*; Sheri Spunt*[10]

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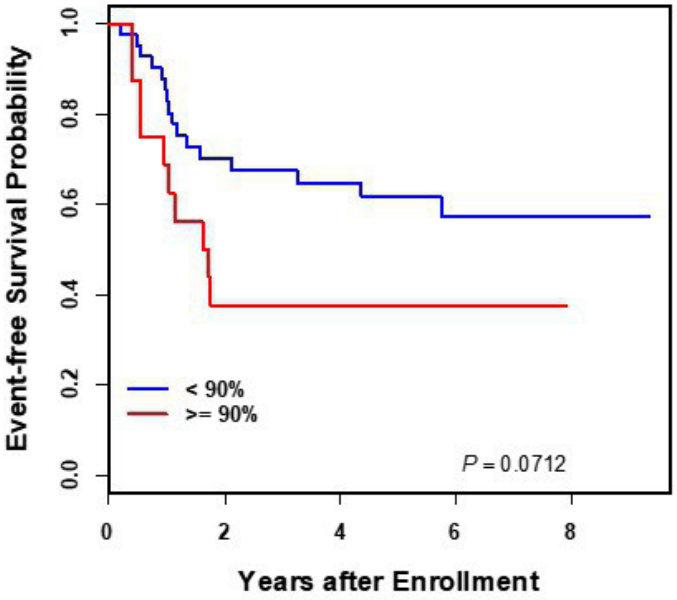
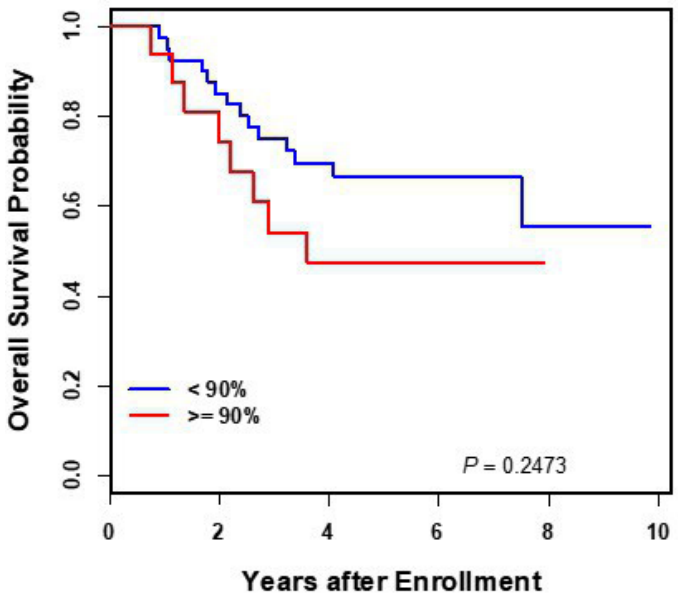
Objective: Synovial sarcoma (SS) is the second most common malignant soft tissue sarcoma in children. COG ARST0332 evaluated a risk-based treatment strategy for young soft tissue sarcoma patients designed to limit therapy for low-risk disease and to test neoadjuvant chemoradiotherapy for unresected high risk disease. While tumor necrosis following neoadjuvant chemotherapy has been shown to predict outcome in other sarcomas, it has not been studied in SS.

Methods: Newly diagnosed SS patients < 30 years old were assigned to 4 treatment arms based on risk features: those with unresected tumors at diagnosis received neoadjuvant ifosfamide/doxorubicin chemotherapy and 45 Gy RT, followed by surgery and RT boost based on margins). Resection specimens were centrally reviewed: good response (GR) ≥ 90% necrosis; poor response (PR) < 90% tumor necrosis. One patient with disease progression prior to resection was classified as PR.

Results: Of the 149 SS patients enrolled, 129 were eligible and evaluable, of whom 69 patients received neoadjuvant chemotherapy. The pathology from 57 tumors were centrally reviewed after definitive resection: 42 PR (74%), 16 GR (26%). The 4-year event free survival (EFS) for PR and GR patients were 64.7% (95% CI: 48.7%, 80.8%) and 37.5% (95% CI: 11.5%, 63.5%) respectively (p=0.07). The 4-year overall survival (OS) for PR and GR patients were 69.6% (95% CI: 54.5%, 84.6%) and 47.4% (95% CI: 21.9%, 72.9%) respectively (p=0.25).

Conclusion: Patients with GR had worse outcomes following neoadjuvant chemoradiotherapy than those with PR. Further analysis is underway to investigate the reasons for this surprising finding.





Poster 437 3012136

COMBINATION PREOPERAIVE CHEMOTHERAPY AND SURGERY FOR LOCALIZED SYNOVIAL SARCOMA: RETROSPECTIVE ANALYSIS OF 117 PATIENTS AT A SINGLE INSTITUTE FOR 26 YEARS.

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Objective: Synovial sarcoma (SS) is a rare cancer of the soft tissue. While the standard treatment is wide resection for resectable disease with acceptable functional outcomes, some reports and clinical trial suggest effectiveness of pre- or postoperative chemotherapy for soft tissue sarcomas (STSs). However, these studies were designed to examine the benefit of pre- or postoperative chemotherapy for mixed histologies of STSs. The role of pre- or postoperative chemotherapy for SS is still not clear. We explore the efficacy of the preoperative chemotherapy combined with surgery for localized synovial sarcoma in our institute.

Methods: This study included patients who were diagnosed with localized synovial sarcoma at the National Cancer Center Hospital between March 1991 and December 2017 and whose charts were accessible. We exclude patients who did not undergo surgery and received preoperative radiation treatment. The ratio of R0 resection with or without preoperative chemotherapy, Overall Survival (OS), Relapse Free Survival (PFS), and prognostic factors were analyzed.

Results: We identified 125 patients with localized SSs. Of 125 patients, 4 did not undergo surgery: only 1 did not achieve a response to marginally unresectable disease, and 3 had unresectable disease of the heart. Of 121 patients with curative intent surgery, 4 preoperative radiotherapy were excluded from our analyses. The characteristics of 117 patients were as follows: 62 males (53%), 55 females (47%), median age was 37.8 years old(5-74 years old), median tumor size was 5.5cm (1.0cm-17cm), and median follow-up time was 4.0 years (1.0-18.9 years). For 117 patients, the 5-year OS and 5-year RFS were 77.0 and 56.9%. Median OS and RFS were 14.2 years and 6.8years. The factors that affect prognosis were tumor size (<5cm vs >5cm : 5year OS:86.9% vs 71.1% p=0.04), histologic grade (2 vs 3 : 5year OS:85.9% vs 71.8% p=0.025) and primary site (Extremities vs trunk and head and neck : 5year OS:89.7% vs 62.9% p=0.0018). Seventy-nine patients had preoperative chemotherapy and 38 had surgery without preoperative chemotherapy. The most common chemotherapy regimen was Doxorubicin and Ifosdamide (AI) (22 patients). Other chemotherapeutic regimens were Ifosfamide and Etoposide(IE) (4 patients); Ifosfamide alternating with Vincristin, Doxorubicin, Cyclophosphamide (VDC) (4 patients); Ifosfamide alternating with Doxorubicin, Cyclophosphamide (AC) (2 patients); AI alternating with etoposide, cisplatin(VP); IE alternating with Doxorubicin, Cisplatin (AP); VDC alternating with IE in combination with carboplatin(ICE); Gemcitabine, Docetaxel and High dose Ifosfamide. One patient received arterial injection chemotherapy of AP.
Seventeen patients (44.7%) had partial response, 19 patients (50.0%) had stable disease and 2 patients (5.3%) were not evaluated: 5.3%. Patients who had preoperative AI achieved response rate of 50% (11 of 22 patients).

Median tumor size of surgical treatment alone was smaller (4.5cm vs 8.5cm) than patients with preoperative chemotherapy. There was no significant difference in the R0- resection rate between patients without preoperative chemotherapy and with preoperative chemotherapy (86% vs 90%: p=0.771).

Conclusion: Our retrospective study showed that preoperative chemotherapy achieved relatively good response (44.7% for all regimen and 50% for AI). These results suggest that preoperative chemotherapy could be a good option for patients need tumor shrinkage before surgery to achieve R0 resection or to preserve functional outcomes after surgery. Our study provides evidence of clinical utility of preoperative chemotherapy for SS, but further investigated is needed to confirm our findings.

Poster 438 3009765

PAZOPANIB IN ADVANCED SYNOVIAL SARCOMA: THE GUSTAVE ROUSSY EXPERIENCE

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Objective: Synovial sarcoma is a rare malignancy usually considered as sensitive to chemotherapy based on anthracyclins and ifosfamide. However, therapeutic options remain limited in the metastatic setting and the prognosis of advanced synovial sarcoma remains dismal. Since approval of pazopanib in advanced soft tissue sarcomas in 2012, very few data were reported on the activity of pazopanib in a homogeneous group of patients with advanced synovial sarcoma.

Methods: We retrospectively reviewed all patients treated with pazopanib for advanced synovial sarcoma in our institution. The histological diagnosis was systematically confirmed by a referral pathologist within the French Sarcoma Group. Patient characteristics, pathologic, treatment and follow-up data were obtained from medical records. Radiological response was assessed by CT-scan according to Response Evaluation Criteria In Solid Tumors 1.1. Adverse events were graded according to the Common Terminology Criteria for Adverse Events of the National Cancer Institute 4.03. The aim of this study was to evaluate the activity of pazopanib in advanced synovial sarcoma.

Results: From December 2006 to April 2018, 16 patients with advanced synovial sarcoma of extremities (10 patients), trunk (5 patients) or head and neck region (1 patient) were treated with pazopanib at 400 mg (3 patients), 600mg (6 patients) or 800 mg (7 patients) daily dose. Median age was 40 years old (range: 24-69). Patients received a median of 2 prior lines of doxorubicin-based chemotherapy in all but one case. Five (31%) patients received pazopanib in 2nd line therapy and 11 (69%) in subsequent lines. Before treatment, 15 (94%) patients had distant metastases (lung in 94% of patients, bone in 25%, associated with local recurrence in 20%) and 1 patient (6%) had unresectable local recurrence with no distant metastase. A clinical benefit was observed in 14 (87.5%) patients: 7 (43.7%) experienced a partial response and 7 (43.7%) a stable disease. Two patients progressed rapidly during treatment. Two patients definitively interrupted pazopanib due to grade 3 sepsis or hemoptysia. The dose was reduced for two patients due to diarrhea and hematuria. On April 2018, 6 patients were still on treatment. The median progression free survival was 6.5 months (1-17+). After a median follow-up of 8.5 months, the median overall survival was not reached.

Conclusion: Pazopanib showed significant clinical activity in advanced synovial sarcomas along with manageable toxicity profile. We observed a prolonged progression free survival compared with other histological subtypes of soft tissue sarcomas. These results need to be confirmed in prospective trials dedicated to this histological subtype of soft tissue sarcomas.

Poster 439 3028032

SYNERGISM OF P53 ACTIVATORS WITH BCL-2 INHIBITORS IN SYNOVIAL SARCOMA

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Objective: The tumor suppressor p53 plays a key role in the control of cell growth and apoptosis.The Bcl-2 protein is able to block p53-mediated apoptosis, and an inverse relationship has been found between expression of wild-type p53 and Bcl-2 in some tumors. However, synovial sarcoma usually expresses both wild type p53 and high levels of Bcl-2, with a net anti-apoptotic phenotype. In this study, we combined a p53 activator RG7388 (idasanutlin) with the Bcl-2 inhibitor ABT199 (venetoclax) to investigate if and how p53 activation and Bcl-2 inhibition might synergistically induce apoptosis in synovial sarcoma cells.

Methods: Three p53 intact (SYO-1, HS-SY-II-5933, MoJo) and one p53 mutant (Yamato-SS) human synovial sarcoma cell line were maintained in RPMI-1640 medium with 10% fetal bovine serum. *TP53* mutation status was assessed using the MSKCC IMPACT panel sequencing. Pharmacologic compounds were purchased from Selleck Chemicals (Houston, TX, USA). Cell viability was assessed in the cell lines as compared with the vehicle condition (0.1% DMSO) at 72 hours

post treatment using MTS reagent (Promega, Madison, WI, USA). Synergy was assessed by isobole plots at multiple concentrations.

Results: We first investigated p53 and Bcl-2 expression in the synovial sarcoma cell line models. The p53 protein is present, albeit at low levels, in all synovial sarcoma cell lines except Yamato-SS, which carries a *TP53* R273C mutation leading to overexpression of a mutant dominant negative form of p53 protein. SYO-1 and HS-SY-II express high levels of Bcl-2 protein but Yamato-SS and MoJo cells have much lower levels. Next, we tested cell whether there is synergism between RG7388 and ABT-199 in these synovial sarcoma cell lines. In SYO-1 and HS-SY-II cells, this combination reduced cell vitality significantly greater than either agent alone. On the other hand, there was no significant synergism in Yamato-SS or Mojo cells. Isobolograms showed that the p53 activator and Bcl-2 inhibitor drugs synergize in SYO-1 and HS-SY-II, but not in Yamato-SS or in MoJo cells. In SYO-1 cells, the combination of RG7388 and ABT-199 markedly increases the cleavage of poly (ADP-ribose) polymerase-1 (PARP-1), a marker of apoptosis. Wild-type p53 and its target gene PUMA were up-regulated by RG7388 treatment, but Bcl-2 was not affected.

Conclusion: Combining p53-activating drugs with Bcl-2 inhibitors has a synergistic effect on synovial sarcoma cells that have wild-type p53 and high Bcl-2 expression – the most common phenotype in human primary synovial sarcoma tumors.

Table MSKCC IMPACT panel sequencing

Cell line	SS type	Fusion Type	MSK-IMPACT 341 gene panel results (COSMIC gene alterations only)
SYO-1	Biphasic	SYT-SSX2	CTNNB1 G34L
Yamato-SS	Biphasic	SYT-SSX1	TP53 R273C, PIK3CA H1047R, TERT promoter; amplified CCND1, FGF cluster, KIT, PDGFRA, MET
MoJo	Monophasic	SYT-SSX1	NRAS Q61R
HS-SY-II	Monophasic	SYT-SSX1	MDM2 amplification

Poster 440 3041594

SURVIVAL PREDICTION MODEL OF SYNOVIAL SARCOMA USING ARTIFICIAL NEURAL NETWORKS WITH THE SEER DATABASE

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Objective: To develop an accurate survival prediction model for a specific disease, well controlled prospective studies are often necessary. However for rare diseases such as synovial sarcoma, it is very difficult to collect a number of cases to make up sufficient patient cohorts for the study. For this reason, there have been several efforts to analyze massive retrospective data as alternatives. Recently the machine learning (ML) has been proven to have advantage of analyzing such vast complex data in various fields. In this study, we developed a survival prediction model for synovial sarcoma using recurrent neural network ML algorithm with the Surveillance, Epidemiology, and End Results (SEER) database.

Methods: Risk Estimate Distance Survival Neural Network (RED_SNN) was used for modeling with the SEER database. To evaluate the accuracy of this prediction model, receiver operating characteristic curves (ROCs) are drawn and areas under the curves (AUCs) are calculated at each time windows. The concordance index (c-index) was found to verify further reliability of the model.

Results: A total of 1537 cases from the SEER database were used for training and internal validation. These cases were then separated into training (80%, n=1230) and test sets (20%, n=307). By using 5-fold cross validation, the training data were randomly classified as training and internal validation. After training and internal validation, this model was evaluated with external validation data from multiple institutions of Korea (n=238). The c-index was 0.880 and the mean AUC of the 5 different time windows was 0.88 (standard deviation 0.0051).

Conclusion: The survival model developed using artificial neural network with the SEER database showed great accuracy for predicting survivorship of patients with synovial sarcoma.

Poster 441 3035485

DOES CSF1 OVER-EXPRESSION OR REARRANGEMENT INFLUENCE BIOLOGICAL BEHAVIOUR IN TENOSYNOVIAL GIANT CELL TUMOURS OF THE KNEE?

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Objective: Localized- and diffuse-type tenosynovial giant cell tumours (TGCT) are regarded different clinical and radiological TGCT types. However, genetically and histopathologically they seem indistinguishable. In both types, over-expression of Colony Stimulating Factor1 (*CSF1*), due to genomic rearrangements, is believed to be the driver mechanism in tumour formation, resulting in an admixture of neoplastic and reactive cells, coined as landscape effect. We aimed to correlate *CSF1* expression and *CSF1* rearrangement with the biological behaviour of different TGCT-characteristics (e.g. localized-/diffuse-type and clinical outcome (recurrence)).

Methods: Along a continuum of extremes, therapy naïve knee TGCT patients with >3 year follow-up were carefully selected: nine localized- (two recurrent disease) and 16 diffuse- (nine recurrences), mean age 43 (range 6-71) years, 56% female. Four control cases of synovitis were included. In selected regions with high expected tumour load, *CSF1* expression (mRNA In Situ Hybridization (ISH)) and rearrangement of the *CSF1* locus (*CSF1* locus specific split-apart Fluorescence In Situ Hybridization (FISH) probes) were evaluated, using digital correlative microscopy. Besides detection of the typical translocation, DNA FISH was evaluated to detect inversion by a proven chromosome 1 inversion index case. *CSF1* rearrangement was considered positive in samples containing >2 split signals /100 nuclei.

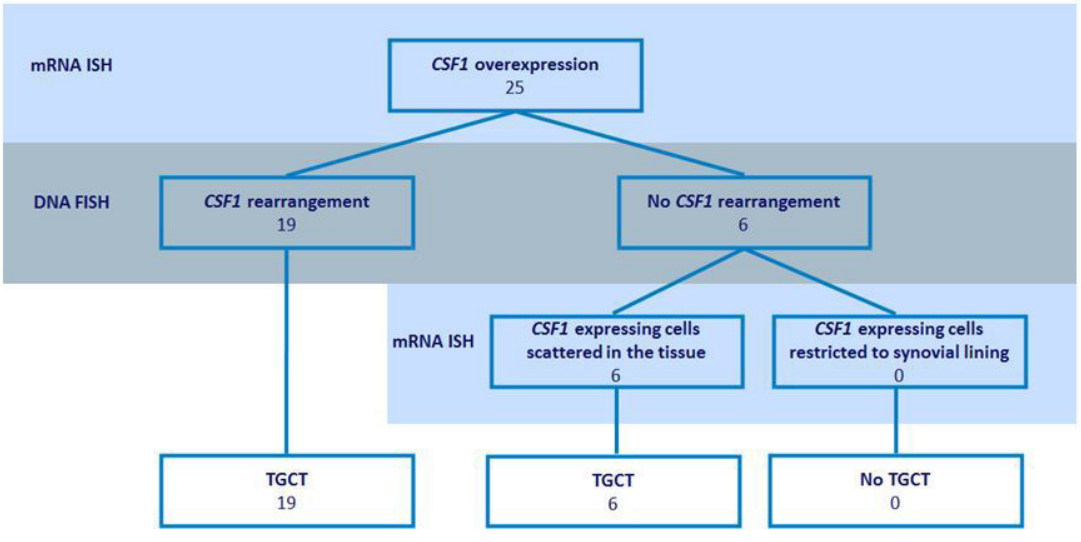
Results: The *CSF1* probe set was suited for detection of chromosome inversion. Irrespective of TGCT subtype, all cases showed *CSF1* expression and in 76% *CSF1*-gene rearrangement was detected. Quantification of *CSF1* expressing cells was not informative, due to the extensive intra tumour heterogeneity. Of the four synovitis cases, two also showed *CSF1* expression, without *CSF1* gene rearrangement. No correlation between *CSF1* expression or rearrangement with clinical subtype and local recurrence was detected. Both localized- and diffuse-type TGCT cases showed a scattered distribution in the tissue of *CSF1* expressing cells.

Table: Proportion of cases with *CSF1* mRNA expression and *CSF1* gene rearrangement

	N	*CSF1* over-expression	*CSF1* gene rearrangement
Localized	7	7 (100%)	5 (78%)
Localized recurrence	2	2 (100%)	2 (100%)
Diffuse	7	7 (100%)	6 (86%)
Diffuse recurrence	9	9 (100%)	6 (67%)
Synovitis	4	2 (50%)	0 (0%)

Localized: Localized-TGCT; Diffuse: Diffuse-TGCT

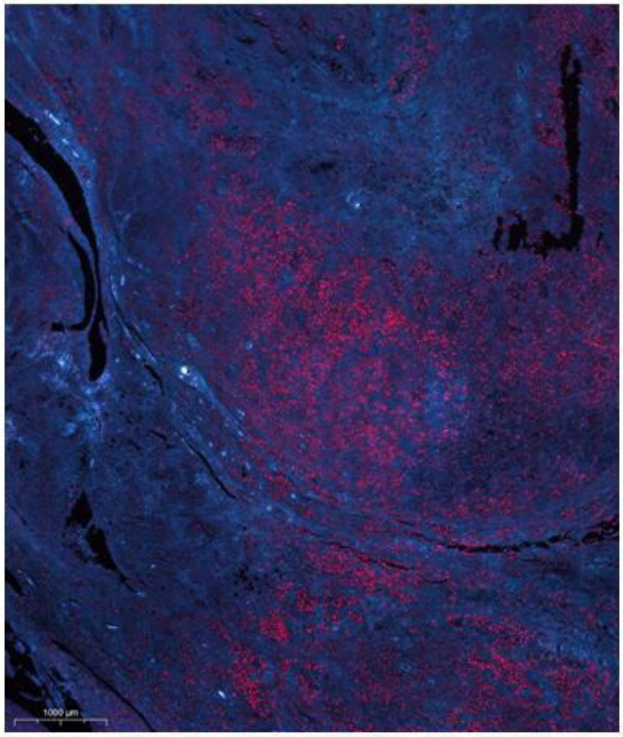
Figure: TGCT proposed workflow



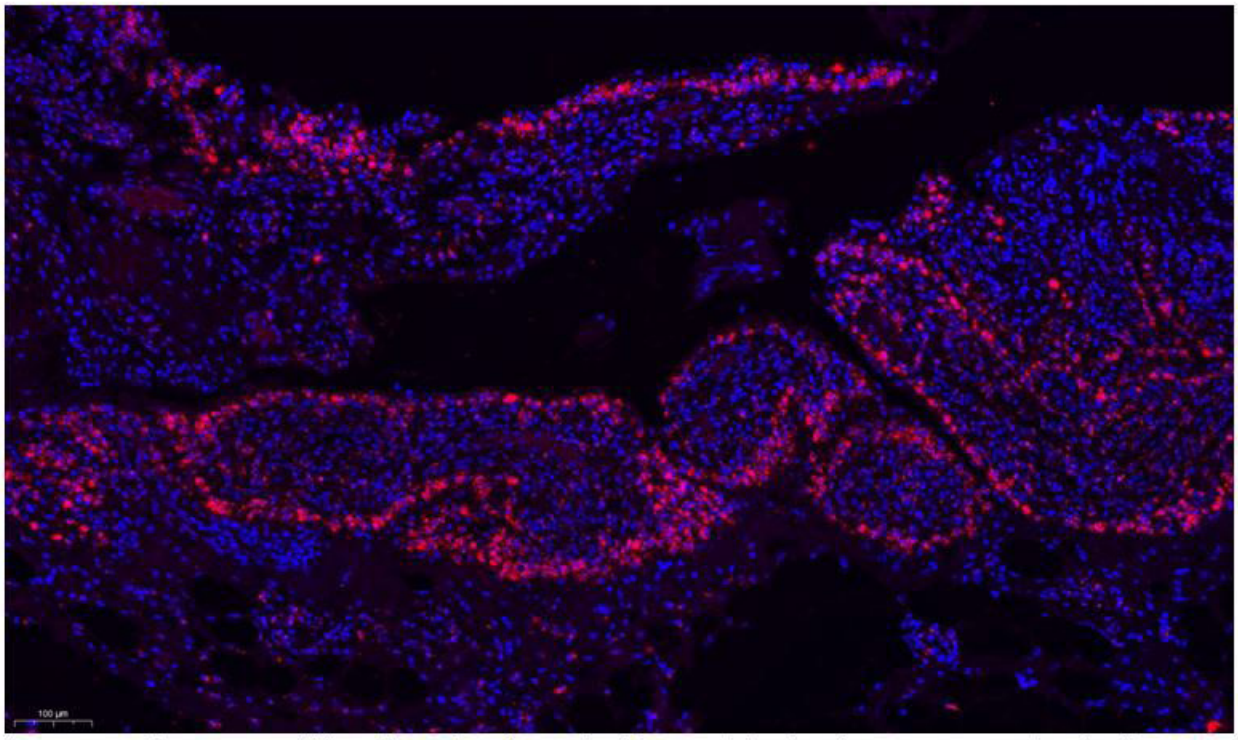
Numbers present TGCT cases

CSF1, Colony Stimulating Factor1; mRNA ISH, mRNA In Situ Hybridization; DNA FISH, DNA Fluorescence In Situ Hybridisation

Conclusion: In diagnosing TGCT, *CSF1* mRNA ISH in combination with *CSF1* split-apart FISH; using digital correlative microscopy, is an auxiliary diagnostic tool to identify rarely occurring neoplastic cells. This combined approach allowed us to detect *CSF1*-gene rearrangement in 76% of the TGCT cases. Neither *CSF1* expression nor presence of *CSF1* rearrangement could be associated with the difference in biological behaviour of TGCT.



61-year-old male patient (L3496), with extensive recurrent diffuse-TGCT. mRNA ISH shows a scattered distribution of CSF1 expression cells (red). CSF1 expression negative cells are blue after DAPI staining.



mRNA ISH of a 45 year old female patient (L5620) with synovitis, showing *CSF1* expression (red) restricted to cells localised in the synovial lining.

Poster 442 3042843

SURGERY IN TENOSYNOVIAL GIANT CELL TUMORS IMPROVES PATIENT REPORTED QUALITY OF LIFE AND JOINT FUNCTION

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Objective: Tenosynovial giant cell tumors (TGCT, also known as pigmented villonodular synovitis), is a rare proliferative joint disease, mostly affecting young adults. They often cause significant morbidity due to local recurrences necessitating multiple surgeries. The aim of this study was to evaluate patient-reported quality of life and joint function in TGCT patients before and after surgical treatment.

Methods: This prospective cohort study, in two Dutch referral centers, assessed patient-reported outcome measures (SF-36, VAS and WOMAC) in 359 consecutive patients with localized- and diffuse-type TGCT of large joints (682 questionnaires). Patients with recurrent disease, conservative treatment and without available measures prior to recurrence were excluded. Collected data was analyzed at specified time categories pre- (baseline) and/or postoperatively up to 5 years.

Results: One-Hundred-and-eight localized- and 98 diffuse-type eligible TGCT patients were analyzed. **Median age at diagnosis of localized- and diffuse-type was 41 (IQR 29-49) and 37 (IQR 27-47) years, respectively. Depending on SF-36 subscale and TGCT subtype, SF-36 analyses showed significantly and clinically relevant lower preoperative- and direct postoperative scores compared with general population means. After 6 months follow up** these scores improved to general population means and continued fairly stable the following years. Figures 1a and b. Median pain (VAS) scores, **for both-subtypes, showed no clinical relevant difference pre- or postoperatively. Pain experience differed tremendously between patients and over time.** M**ean function (WOMAC) scores, for both TGCT subtypes, showed no clinical relevant differences (effect size < MCID 20) pre- versus postoperatively.** However, in diffuse-type patients WOMAC pain and physical function scores showed a trend of improvement **preoperative versus** postoperative.

Conclusion: We presented the largest study on the patient-perspective, quality of life and joint function in patients with TGCT. Three to six months after surgery quality of life recovered to general population means. Joint function improvement showed a similar trend, without confirmation of clinical relevance. Surgery showed no influence on mean pain experience. In the emergence of systemic therapy, these results confirm the importance of surgery as the treatment for TGCT.

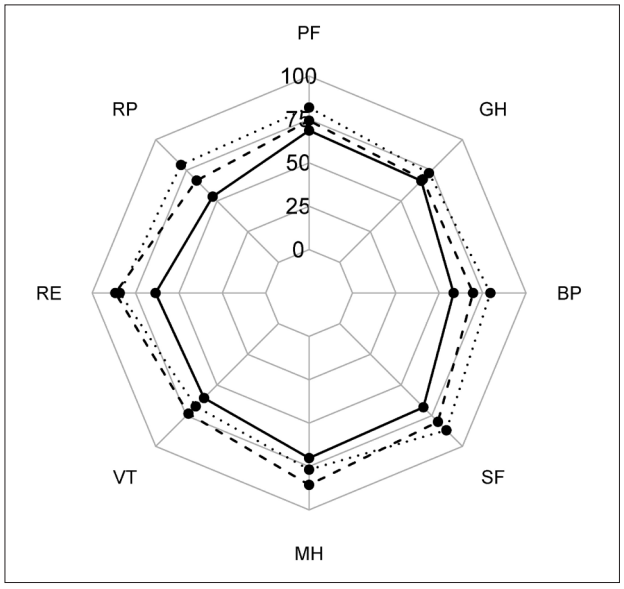

Figure 1a. SF-36 scores of localized-type, therapy-naïve, TGCT patients; preoperatively (continues line) and 6 months postoperatively (----) compared with general population means(…..). Physical functioning (PF), Social functioning (SF), Role limitations due to physical problems (RP), Role limitations due to emotional problems (RE), General mental health (MH), Vitality (VT), Bodily pain (BP) and General health (GH).

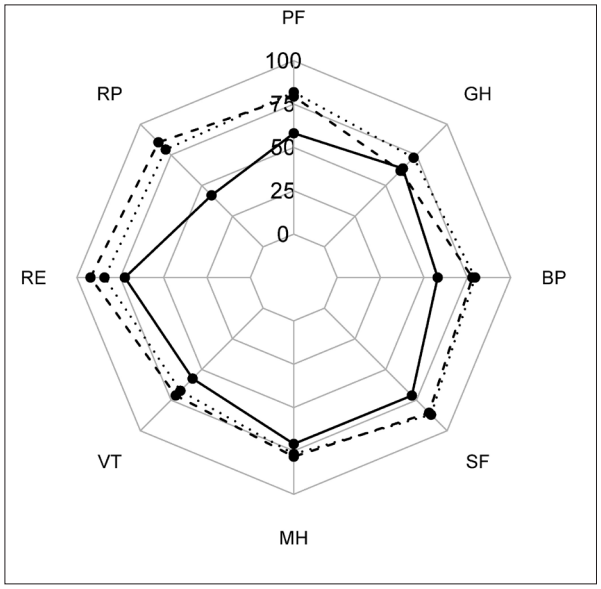

Figure 1b. SF-36 scores of diffuse-type, therapy-naïve, TGCT patients; preoperatively (continues line) and 6 months postoperatively (----) compared to general population means(…..). Physical functioning (PF), Social functioning (SF), Role limitations due to physical problems (RP), Role limitations due to emotional problems (RE), General mental health (MH), Vitality (VT), Bodily pain (BP) and General health (GH).

Poster 443 3028098

CHEMOTHERAPY IN THE TREATMENT OF UNDIFFERENTIATED HIGH GRADE PLEOMORPHIC SARCOMA (UPS) OF BONE

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Objective: UPS of bone is a rare bone sarcoma subtype accounting for <2% of all primary bone malignancies. While treatment is often based upon osteosarcoma-like regimens, the optimal treatment and prognostic significance of pathologic treatment response is not defined. We sought to evaluate outcomes for this rare sarcoma subtype and identify active chemotherapy regimens.

Methods: Patients were identified by retrospective review of the institutional pathology database. Patients were excluded if the final pathology at resection was re-classified to osteosarcoma, chondrosarcoma, or another bone-sarcoma subtype or if clinical characteristics were consistent with soft tissue sarcoma involving bone. 38 patients with UPS of bone received chemotherapy for either primary or recurrent/metastatic disease between 1993-2017. The Kaplan-Meier method was used to estimate rates of both overall survival (OS) and relapse-free survival (RFS). Log-rank tests were used to assess for significance of differences between groups.

Results: 38 patients received chemotherapy for UPS of bone. Median age at diagnosis was 53 yrs (range, 19-83). The majority (n=32, 84%) presented with localized disease. Median OS for localized disease was 5.2 years as compared to 1.7 years for metastatic disease. 32 patients (29 localized, 3 metastatic) received neoadjuvant chemotherapy and resection. 15 patients received chemotherapy for recurrent/metastatic disease. The most common neoadjuvant regimens were doxorubicin/cisplatin (AP, n=16), doxorubicin/ifosfamide (AI, n= 6), or a combination of multiple regimens (n=6). Adjuvant therapy was varied. Pathologic tumor necrosis was variable (range 10-99%). Only 8 patients exhibited >90% necrosis, and this did not correlate with favorable outcomes. Amongst patients with localized disease, preoperative AP chemotherapy was associated with improved OS (median OS: not reached; 5-year OS: 75%) as compared with all other regimens (median OS: 1.6 years; 5-year OS: 30%) (Log-rank *p=0.02*). Objective RECIST-type responses were uncommon in either the neoadjuvant (3/32, 9%) or recurrent/metastatic setting (3/15, 20%). Responses were seen with AP, AI, high-dose methotrexate (HD MTX), and gemcitabine/docetaxel (GT).

Conclusion: Osteosarcoma-like regimens show limited activity in the treatment of UPS of bone. In addition, the prognostic significance of pathologic treatment response could not be defined in this cohort. In the absence of clinical trials, AP should be considered for initial neoadjuvant therapy.

Poster 444 3042645

HIGH-RISK UNDIFFERENTIATED PLEOMORPHIC SARCOMA (UPS) TREATED WITH PERIOPERATIVE CHEMOTHERAPY: A SECONDARY ANALYSIS OF A ISG-GEIS RANDOMISED CLINICAL TRIAL (RCT) COMPARING 3 VERSUS 5 CHEMOTHERAPY CYCLES FOR HIGH-RISK SOFT TISSUE SARCOMA (STS)

Sandro Pasquali[1]*; Chiara Colombo*[1]*; Sara Pizzamiglio*[1]*; Paolo Verderio*[1]*; Dario Callegaro*[1]*; Silvia Stacchiotti*[1]*; Javier Martín-Broto*[2]*; Antonio Lopez-Pousasup*[3]*; Stefano Ferrari*[4]*; Andres Povedasup*[5]*; Antonino De Paoli*[6]*; Vittorio Quagliuolosup*[7]*; Josefina Cruz*[8]*; Alessandro Comandone*[9]*; Tiziana Venesio*[10]*; Rita De Sanctissup*[7]*; Elena Palassini*[1]*; Antonio Llomboart-Bosch*[11]*; Angelo P. Dei Tos*[12]*; Paolo Casali*[1]*; Piero Picci*[4]*; Alessandro Gronchi*[1]

[1]Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy; [2]Hospital Universitario Virgen del Rocio, Sevilla, Spain; [3]Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; [4]Istituto Ortopedico Rizzoli, Bologna, Italy; [5]Valencian Oncologic Institute, Valencia, Spain; [6]Centro di Riferimento Oncologico, Aviano, Italy; [7]Humanitas Cancer Center, Milano, Italy; [8]University of Canarias Hospital, La Laguna, Spain; [9]Presidio Sanitario Gradenigo, Spain, Italy; [10]IRCCS Fondazione Piemontese per la Ricerca sul Cancro, Candiolo, Italy; [11]Medical School of Valencia, Valencia, Spain; [12]Treviso General Hospital, Treviso, Italy

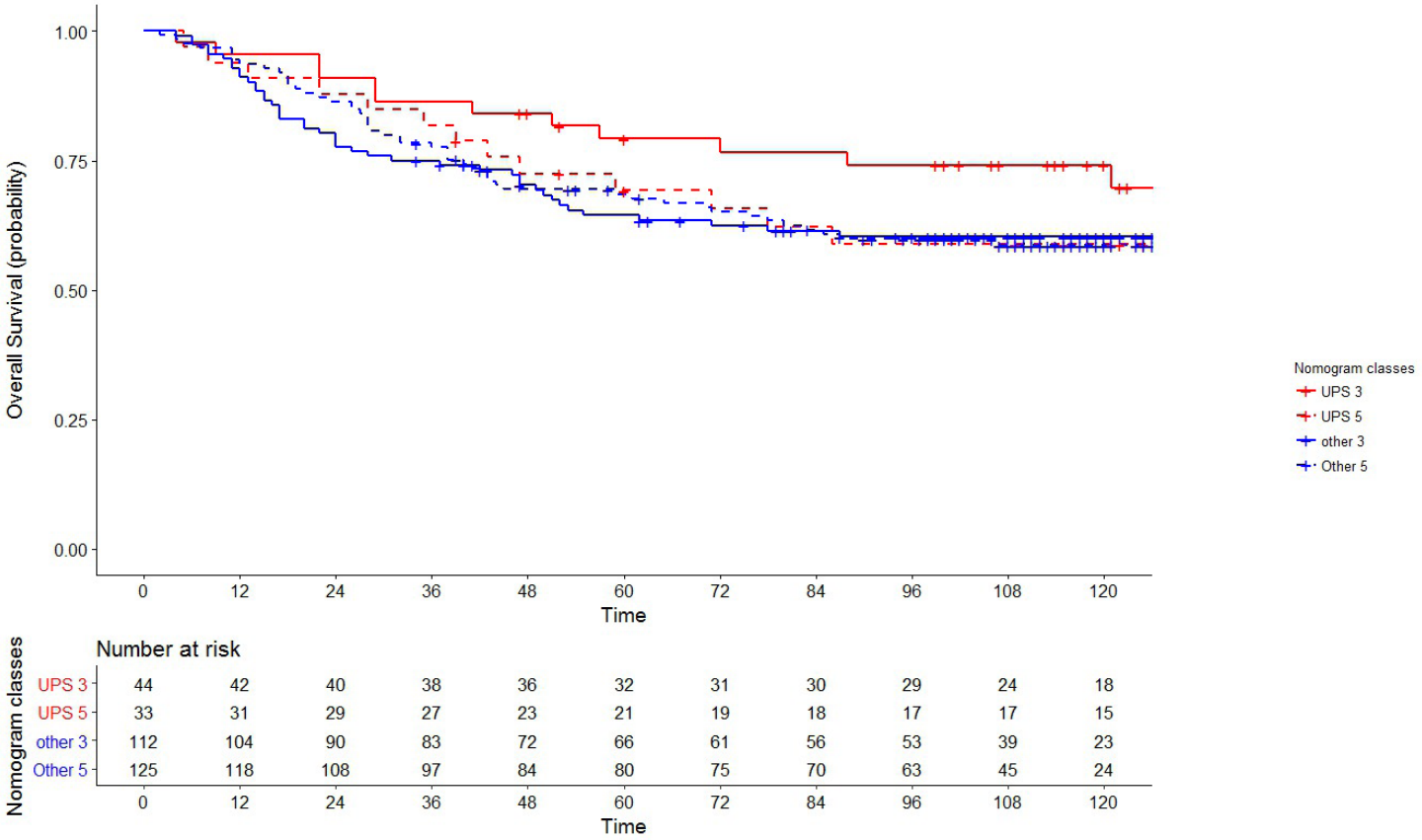
Objective: UPS accounts for approximatively one in five patients with high-risk STS of extremity and trunk wall. In a RCT which compared 3 vs 5 cycles of preoperative epirubicin plus ifosfamide chemotherapy for high-risk localized STS, the subgroup of patients with UPS had a better overall survival (OS) compared to the other high-risk STS subgroups. We tested whether the non-inferiority of 3 vs 5 perioperative chemotherapy cycles is maintained also in the subgroup of patients

affected by primary UPS.

Methods: This study retrospectively analysed data from patients with high-risk UPS enrolled in a ISG-GEIS RCT which compared 3 preoperative cycles of epirubicin 120 mg/m2 plus ifosfamide 9 g/m2 (Arm A) and the same 3 cycles of preoperative CT followed by 2 further cycles of post-operative CT (Arm B) in a population of patients affected by high risk STS (ie ≥5cm in longest diameter, high malignancy grade according to FNCLCC, deeply seated relative to the investing fascia) in an extremity or trunk wall enrolled between 2002 and 2007. Radiotherapy could be delivered either preoperatively or postoperatively. Non-inferiority of the primary end-point, OS, was assessed by the confidence interval of the hazard ratio (HR; Arm A/Arm B) derived from Cox model. Radiological tumour response was assessed by RECIST and Choi criteria.

Results: A total of 160 and 161 patients were allocated to Arm A and B, respectively. At the median study follow-up of 117 months (IQR 103-135 months), 10-year OS was 61% for the entire group of patients, 64% in Arm A and 59% in Arm B (HR 0.92, 95% confidence interval [CI] :0.68–1.23), respectively, demonstrating the non-inferiority of 3 compared to 5 cycles of preoperative chemotherapy. The study enrolled 77 patients with UPS (Arm A, N = 44; Arm B, N = 33). Median tumour size was 10cm (range 5-30) and median patient age was 57 years (range 18-71). 13 patient deaths were observed for each study arm in patients with UPS (39.3% and 29.6% in Arm A and B, respectively). 10-year OS was 0.74 (95%CI 0.58-0.85), 0.59 (95%CI 0.40-0.74), 0.60 (0.50-0.69), and 0.60 (0.49-0.67) in patients with UPS in Arm A, UPS in Arm B, STS other than UPS in Arm A, and STS other than UPS in Arm B, respectively (log-rank test, P=0.56, Figure 1). Further analysis for tumour response will be presented.

Conclusion: This secondary analysis of this ISG-GEIS study comparing 3 vs 5 perioperative cycles of epirubicin plus ifosfamide was consistent with the study results and confirmed the non inferiority of 3 courses of full-dose epirubicin plus ifosfamide compared with 5 cycles even in UPS, the histological subtype with the best OS in the study.



Overall survival (OS) of patients with undifferentiated pleomorphic sarcoma (UPS) and other soft tissue sarcoma histology treated with 3 preoperative or 3 preoperative followed by 2 postoperative cycles of epirubicin and ifosfamide.

PO 001 3042134

SARCOMA OF THE HEAD AND NECK. A RETROSPECTIVE STUDY OVER 30 YEARS, FROM A SINGLE INSTITUTION

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Objective: Head and neck soft tissue sarcoma (STSNH) is a rare malignant disease, which accounts for approx. 10% of all sarcomas. Furthermore, it comprises a heterogeneous group of subtypes. The rarity and heterogeneity makes standardization of treatment difficult.
The aim of the study is to retrospectively cover patients treated in a single institution over a period of 30 years, in terms of clinical presentation, subtype-distribution, treatment modalities, outcome and demography of the patients, to define prognostic factors of sarcomas of the head and neck, to contribute to future definition of- and managing guidelines.

Methods: A retrospective review of all patients treated for STSHN in Western Denmark 1979-2013, extracted from the Aarhus Sarcoma Registry (ASR) (accounting for approx. 50% of all patient diagnosed with sarcoma in Denmark), validated from medical records, and from the pathological registry in the years 2000-2013. Primary endpoints are overall survival (OS) and relapse free survival (RFS). The 5-year OS and RFS are reported using Kaplan-Meyer estimates and compared using log-rank test. Crude and adjusted analysis will be performed by Cox' proportional hazard model.

Results: A total of 260 patients are included in this study with 212 patients having STS and 48 bone sarcoma. The 5 year overall survival was 54(95%CI: 47-61%) and 70(95%CI: 54-81%) for STS and bone sarcoma respectively. At the time of analysis 150 patients had died. A total for 81 patients relapsed after complete response of the primary treatment. The median time to recurrent disease was 3.4 year. Analysis of prognostic factors and characteristics of head and neck sarcoma is under preparation and will be presented at the CTOS meeting.

Conclusion: The results will hopefully help define characteristics of STSHN, presumably helpful to define and manage disease as well as defining prognostic outcome for this rare malignant disease.

PO 002 3042401

SMALL ROUND BLUE CELL TUMOR WITH FUS-NFATC2 FUSION, A CASE REPORT

Maribel Deus Lacambra[1], Herbert Loong[2], Chit Chow[1], Shekhar Madhukar Kumta[3], Kwok Chuen Wong[3], Wing Hung Ng[4], Wang Kei Chiu[3], Teresa Tse[2], Shin Loong Cina Tong[4], Ka Fai To[1]
[1]Department of Anatomical and Cellular Pathology, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong; [2]Department of Clinical Oncology, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong; [3]Department of Orthopedic and Traumatology, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong; [4]Department of Imaging and Interventional Radiology, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong

Objective: With the advent of molecular diagnosis, rare cases of translocation-associated sarcomas have been identified. NFATC2 is a transcription factor that mainly functions in T-cell differentiation and immune response. It does not belong to the E26 transformation-specific (ETS) family which usually fuses with the EWSR1 or rarely the FUS gene in Ewing sarcoma. Rare Ewing-like sarcomas with fusion of EWSR1 to non-ETS family have been reported, such as the EWSR1-NFATC2. Recently, FUS gene fusion with NFATC2 has been described in few cases.

Methods: We describe a 41 y/o male who complained of thigh swelling for three months. Radiographic examination showed a 9.0 cm mass at the left femur. Clinical, radiological, histopathologic, and molecular data were analyzed.

Results: A biopsy of the mass showed small round blue cell tumor with similar morphology to Ewing's and Ewing-like sarcomas. Immunohistochemistry stains were positive for SATB2 and negative for CD99. Cyclin D1 was not expressed and INI-1 was preserved. CDK4 and MDM2 were negative. Epithelial markers (AE1/AE3, EMA), hematolymphoid markers (LCA, CD3, CD20, tdT, myeloperoxidase), muscle markers (SMA, desmin, myogenin), and melanocytic markers (S100, HMB45, and MITF) were all negative. The proliferative index measured by Ki-67 was about 30-40%. Flourescence in-situ hybridization

for EWSR1 break apart was negative. RNA-seq using Illumina RNA Pan Cancer kit showed fusion of exon 6 of the FUS gene with exon 3 of the NFATC2 gene. The fusion transcript was further validated by digital RT-PCR. Vincristine-doxorubicin-cyclophosphamide (VAC) chemotherapy, alternating with ifosfamide-etoposide (IE) was administered, which is the standard treatment regimen for Ewing's sarcoma. The patient recently completed two cycles of neoadjuvant chemotherapy VAC and with clinical response and symptomatic relief.

Conclusion: Molecular analysis is now an integral part in diagnosing sarcomas, particularly in resolving frequent diagnostic dilemmas. FUS-NFATC2 is a novel gene fusion, harboring drug-resistant gene properties distinct from the recently reported EWSR1-NFATC2 tumors. There are only three cases described in the literature, belonging to the same age group and all occurring in the femur. However, no clinical data was further reported. In our case, the patient was initially responsive for Ewing's sarcoma regimen pending radiological confirmation. Further details on pathological response and treatment outcome will be presented.

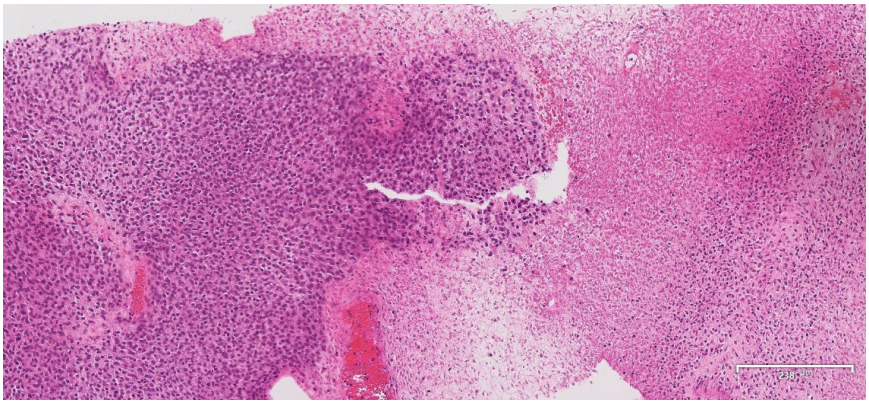

Figure 1: proliferation of small round blue cells with necrosis.

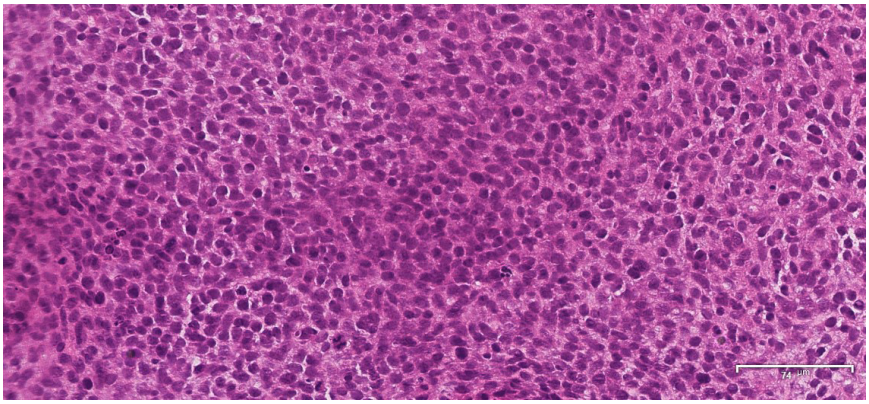

Figure 2: small round blue cells with brisk mitotic activity.

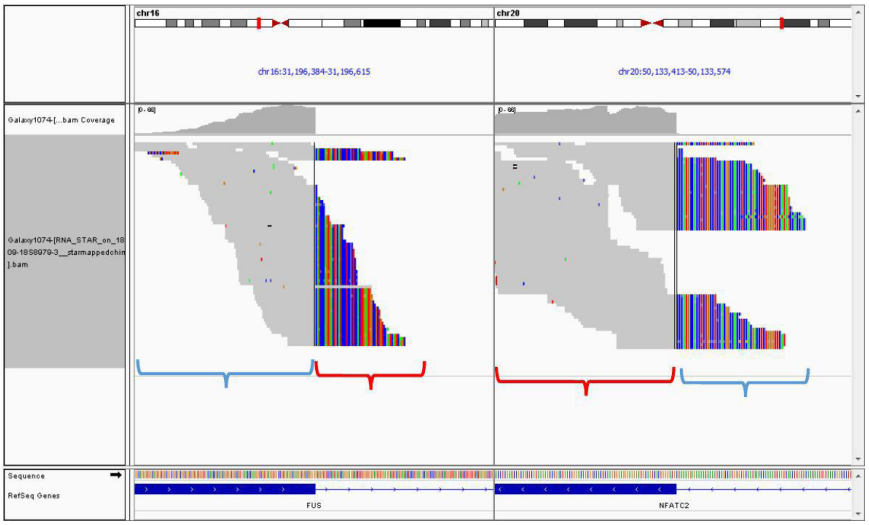

Figure 3: The break-points at exon 6 of FUS gene and exon 3 of NFATC2 gene were reviewed on IGV. The split reads mapped to the RNA junctions were shown. The fusion junction was supported by 37 split reads.

PO 003 3042872

SCHWANNOMA OF THE PORTA HEPATIS: A CASE SERIES AND TIPS FOR SURGICAL MANAGEMENT

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Objective: Schwannomas are benign and uncommon lesions arising from the nerve sheaths of peripheral nerves which may occur in virtually any part of the body (except the olfactory and optic nerves), especially in neck, head, upper and lower extremities. Schwannoma of the porta hepatis is an extremely rare finding, but it is possible because of the networks of sympathetic and parasympathetic nerve fibers present on hepatic-duodenal ligament, and into vascular and biliary walls.

Methods: We report three cases of schwannoma located in the porta hepatis operated in our Center.

Results: Case 1
In 2003, a 30 years old women, affected by Recklinghausen's syndrome, was admitted to our hospital claiming right quadrant pain. Abdominal US, CT scan, and MRI were performed: a solid mass about 5 cm of diameter, behind the pancreas, near the celiac trunk was found. FDG PET resulted negative. A US guided biopsy was performed with a diagnosis of ganglioneuroma. The patient underwent explorative laparotomy: since the lesion was cleavable from vascular structures (celiac trunk, hepatic artery, superior mesenteric artery and vein) and from the superior margin of the pancreas, the lesion could be easily resected. Histology on the specimen revealed a schwannoma of the hepatic-duodenal ligament. At present, the patient is still alive with no evidence of relapse.

Case 2
In 2014, a 74 years old man presented to our hospital because of right quadrant pain, especially after food intake. Abdominal CT-scan and MRI showed a 17-cm mass in the porta hepatis. Due to high suspicion of mesenchymal tumour of the hepato-duodenal ligament, the patient underwent surgery, without a preoperative biopsy. The mass was cleavable from structures of the hepatic hilum, from the duodenum, and the pancreas, and an en-bloc resection was performed. S-100 protein was positive in tumor cells and the histopathological diagnosis of the resected specimen revealed a schwannoma. At present, the patient is still alive and disease free.

Case 3
In 2018, a 68 years old woman was admitted to our hospital on 2018 with a history of jaundice (total bilirubin 10 mg/dl, direct bilirubin 6.2 mg/dl) and upper quadrant pain. Abdominal CT-scan and MRI showed a mass of 5 cm located in the porta hepatis. The lesion showed an increased uptake of glucose at FDG-PET. EUS with biopsy was performed with diagnosis of mesenchymal neoplasia with spindle cells. At time of surgery, the common bile duct was completely involved by the neoplasia, while hepatic artery and portal vein were cleavable. Tumor removal required a biliary duct resection with hepatico-jejunal anastomosis. At the specimen exam, S-100 protein was positive in tumor cells and schwannoma arising from the common bile duct wall was diagnosed. Postoperative course was regular and after 4 months the patient completely recovered and shows no sign of relapse.

Conclusion: Schwannoma of porta hepatis is a rare entity. More common and fearsome neoplasia such as cholangiocarcinoma or gastrointestinal stromal tumor (GIST) should be considered at first as differential diagnoses. Malignant transformation of schwannomas is rare and overall prognosis is favorable.With these premises, if schwannoma of the porta hepatis is suspected, a preoperative biopsy is recommended; considering the rarity of the disease, the experience of the pathologist together with a multidisciplinary approach, are fundamental in defining the strategy of treatment.Due to the high anatomical variability of the arising structure of the porta hepatis, surgery for schwannoma in this peculiar district could involve different structures of the hepatic hilum and could require challenging high risk vascular or biliary resection and reconstruction. Therefore, a conservative approach is recommended and should be pursued whenever it is possible, considering surgery in symptomatic patients.

PO 004 3042836

CONTINUED CLINICAL RESPONSE TO HIGH DOSE MTX IN MULTIPLY RELAPSED, HEAVILY PRETREATED OSTEOSARCOMA CASE

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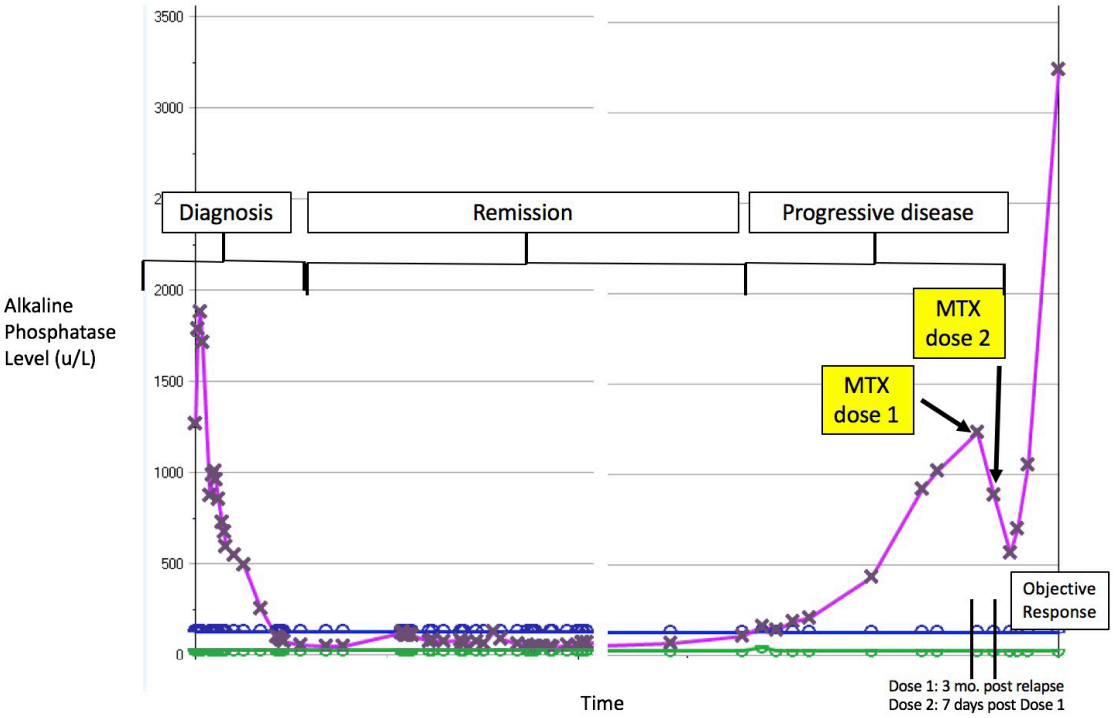
Objective: Methotrexate (MTX), an anti-folate antineoplastic agent, has been used since 1986 as a standard of care to treat osteosarcoma (OST). Relapsed OST cases have limited systemic treatments no standard second or third line therapies. In general practioners try one of a handful of agents (interferon, doxorubicin, cis-platinuum, MTX, ifosfamide, etoposide, gemcitabine and taxotere) that have shown efficacy in OST and avoid repeating previous agents. However in a multiply relapsed patient retreatment with an agent know to have previously worked, when other options have been exhausted may be reasonable. For example intra-arterial cis-platinum has been successful used as retreatment in several cases (Cancer.1990 66(4):801-5.) and a review by St. Jude found that some patients responded to re-exposure to previous drugs in OST, usually doxorubicin. We report a case of multiply recurrent, progressive OST, retreated with two doses of HD-MTX with a demonstrable clinical and palliative objective response.

Methods: We reviewed PubMed and Google Scholar using keywords: “osteosarcoma,” “retreatment,” “methotrexate.” The search was limited to the English language.

Results: There found no reported cases of response or non-response to HDMTX re-exposure for relapsed OST found. Case Report: At the time of diagnosis, our patient was a 17-year-old female with metastatic osteosarcoma to the lungs and bone. At presentation she had pain at sites metastasis and palpable tumors in her bones. The presenting alkaline phosphatase level of 1880 u/L. The patient was successfully treated with “MAPIE”, (HDMTX, Adriamycin, cis-platinuum, ifosfamide, etoposide) and aggressive surgical resection of primary, bone and lung tumors and achieved radiological and clinical remission with an alkaline phosphatase level of 42 u/L. Twelve months post-chemotherapy, the patient relapsed in the lungs, presenting with an alkaline phosphatase level of 162 u/L. The patient was treated with denosumab for 6 cycles but progressed and also progressed on doxorubicin and also on nivolumab. At that point the alkaline rose to over 1200. At that point, the patient requested to ‘re-try’ MTX given the rapid elimination of pain she had had with MTX in the past. After a difficult approval process, it was approved and the patient experience again eliminating of pain, dramatic decrease in the size of the bony vertebral mass and a decrease in her Alkaline phosphatase from 1248 to 889 with the first dose and from 889 to 571 after the second dose. The patient tolerated the therapy without any adverse effects. Unfortunately no further doses of MTX were approved. The patient tried experimental therapy that did not work and died 3 months later.

Conclusion: In a setting of limited or no options of treatment of relapsed osteosarcoma, retreatment of MTX is worthy of consideration. In our particular case, there was an objective response to the retreatment of MTX including alleviation of pain, decrease in size of vertebral mass, and decrease in alkaline phosphatase levels. The therapy was well tolerated. Retreating osteosarcoma was successfully explored and provides a plausible palliative treatment option for cases of relapsed, progressive OST.



Graph of Patient’s Alkaline Phosphatase Levels

PO 005 3042706

CONGENITAL PRIMITIVE NEURO-ECTODERMAL TUMOUR

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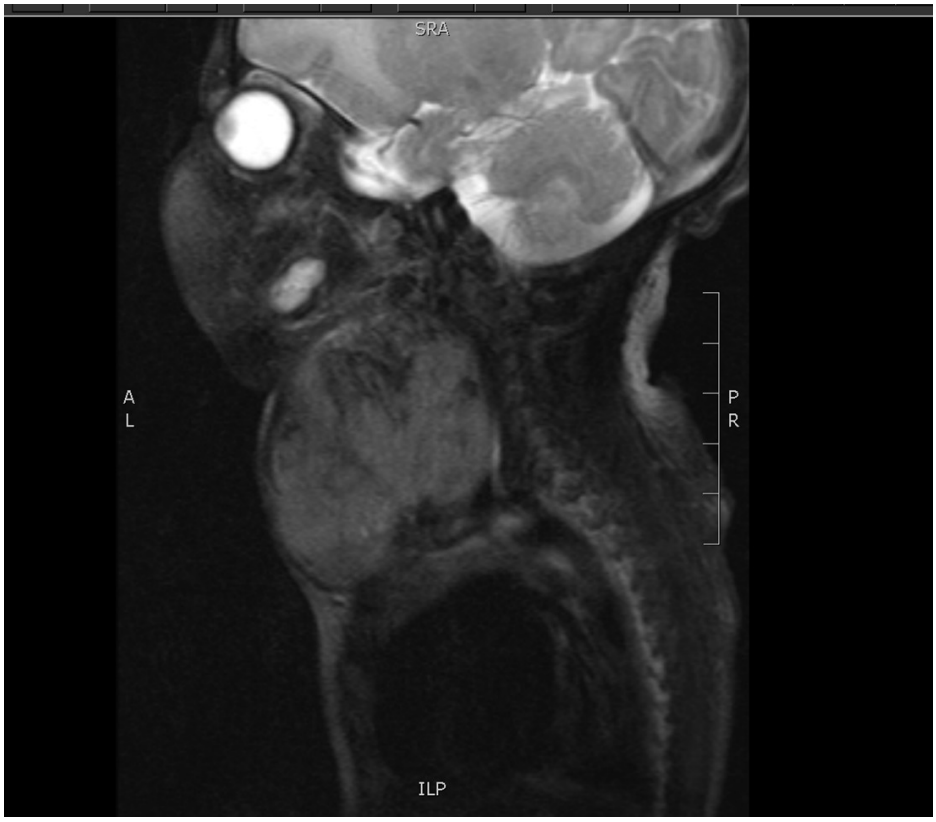
Objective: To review the management of congenital primitive neuro-ectodermal tumour (PNET)

Methods: We report the case of a male infant born at 36 weeks gestation with left sided neck swelling. Investigation of the extensive swelling identified the lesion to be a soft tissue sarcoma. Biopsy demonstrated a small round blue cell tumour with features consistent with the histological diagnosis of Ewing's sarcoma/PNET with FISH analysis confirming a chromosome translocation typical of soft tissue Ewings sarcoma/primitive neuro-ectodermal tumour (PNET) (disruption of the EWSR1 gene at 22q12.2 with a loss of the distal 3'EWSR1 segment in 70% of nuclei and no evidence of the EWSR1-FLI1 t(11;22)(q24.3;q12.2) rearrangement).
Despite concerns regarding potential toxicities and morbidity/mortality of chemotherapy in this age group, full therapeutic chemotherapy as per Children's Oncology Group AEWS1031 was commenced. Multiagent cheotherapy was given for 12 weeks, initially complicated by tumour swelling post biopsy requiring intubation and full respiratory support. Re-evaluation after 12 weeks of treatment demonstrated significant clinical and radiological response. Tumour was completely resected with good tumour response assessed by degree of necrosis and followed by further chemotherapy as per protocol to complete 12 months of therapy.

Results: Review of the literature for this rare congenital tumour presenting in the neonatal period idenitifies a lack of uniformity in management and therapy and overall significantly poor prognosis in similar cases. Many therapies were compromised due to concerns regarding the use of intensive multi-agent chemotherapy in the neonatal period with under treatment potentially contributing to the poor outcomes documented in previously reported cases. Our patient tolerated all treatments with minimal toxicities albeit significantly poor weight gain despite enteral support. Global development was not impacted. The patient completed all planned therapy and is well in follow-up in continued complete clinical and radiological remission.

Conclusion: The use of granulcyte colony stimulating factor combined with mandated full doses of chemotherapeutic agents, results in an excellent response in congenital primitive neuro-ectodermal tumour presenting as a life-threatening lesion in the neonatal period.



MRI tumour at birth

PO 006 2996611

DEVELOPMENT OF HIGH-GRADE OSTEOSARCOMA IN A PATIENT WITH RECURRENT GIANT CELL TUMOR OF THE ISCHIUM WHILE RECEIVING TREATMENT WITH DENOSUMAB

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Objective: Malignant transformation of giant cell tumor of bone (GCTB) without radiotherapy exposure is exceptionally rare, occurring in less than 1% of GCTBs. The safety and efficacy of denosumab in patients with GCTB was recently reported.

Methods: We herein report a case of a benign recurrent GCTB with an H3F3A mutation (fig.1) that underwent secondary malignant transformation during treatment with denosumab.

Results: A 29-year-old woman underwent curettage of a GCTB of the left ischium in 2005. Ten years after the first surgery, the GCTB recurred locally. We started treatment with denosumab. During the first 5 months of treatment, we observed a demarcated area of osteosclerosis in the recurrent lesion, and the patient's clinical condition improved. At 6 months, however, the patient developed pain, and a rapidly growing mass was detected by computed tomography. An incisional biopsy was performed. Histologic analysis showed a high-grade osteosarcoma (fig. 2a,b). The patient developed lung metastases and died soon after beginning chemotherapy.

Conclusion: The mechanism of sarcomatous transformation of GCTB during denosumab therapy is unclear. These findings suggest that the scientific community should be aware of the possible malignant transformation of GCTB during denosumab treatment.

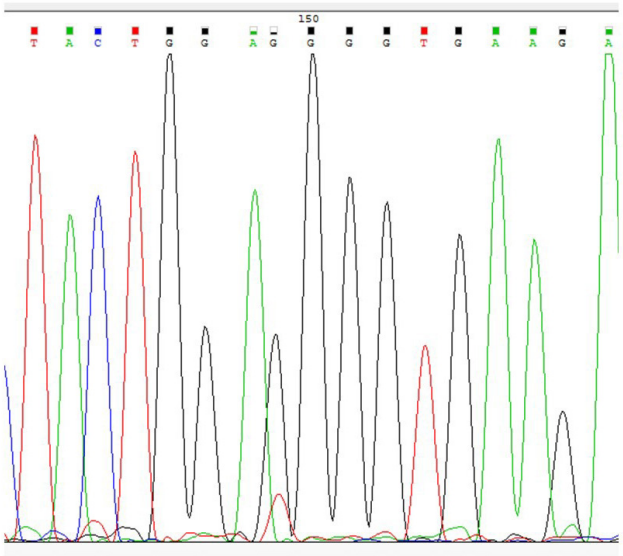

Fig.1 Direct sequencing for the presence of H3F3A in the coding region between codons 1 and 42a showed a p.Gly35Trp (p.G35W; NP_002 098.1) mutation.

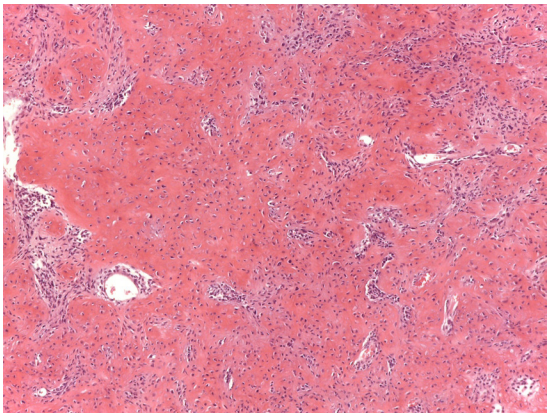

Fig. 2 After denosumab treatment, two different areas were evident in the incisional biopsy specimen. (a) In particular, areas of giant cell tumor of bone with morphological features after denosumab treatment consisted of the disappearance of osteoclast-like giant cells (×100 magnification)

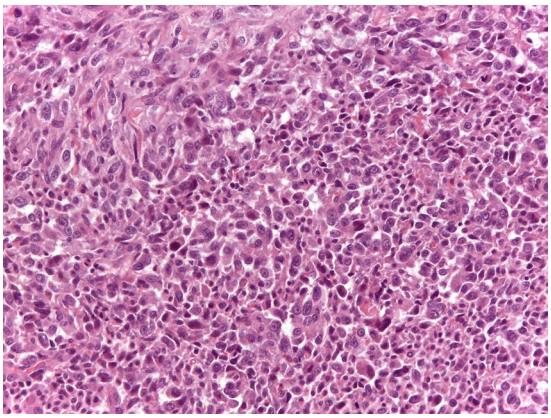

Fig. 2 and (b) variable production of abundant fibrillary extracellular osteoid-like matrix with areas of high-grade fibroblastic and osteoblastic osteosarcoma (×200magnification).

PO 007 3015919

STEVEN'S JOHNSON SYNDROME AFTER USING SORAFENIB FOR RECURRENT SOFT TISSUE SARCOMA

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Objective: Sorafenib is a vascular endothelial growth factor (VEGF) receptor inhibitorthat targets certain cancers including soft tissue sarcomas and is FDA approved for renal cell carcinoma (RCC) and hepatocellular carcinoma (HCC). It is being clinically tested in refractory sarcoma and now being tried in pediatric cases of recurrent sarcoma (Kim et al, 2015) (Maki et al., 2009).

Sorafenib can cause serious adverse effects including skin toxicity, Steven's Johnson Syndrome (SJS) and/or toxic epidermal necrolysis (TEN) (NIH, 2018). SJS differs from palmar-plantar erythrodysesthesia (hand-foot syndrome) is clinically different due to the cutaneous involvement and the mucosa. It has been reported that SJS is fatal in 10% of cases (NIH, 2018). We report the first case of life-threatening Steven's Johnson Syndrome (SJS) induced by Sorafenib of a pediatric patient with recurrent sarcoma. The goal of this study is to increase the awareness of a rare yet life threatening adverse effect to a promising treatment for recurrent sarcoma in the pediatric oncology population.

Methods: A literature review was conducted through PubMed and Google Scholar using the following keywords: "sorafenib-induced, steven's johnson syndrome, pediatric, oncology, and sarcoma." The search was limited to the English language.

Results: Of the 138 results listed, 3 cases of Steven's Johnson Syndrome induced by sorafenib were reported. The first case was a 67-yr old male with metastatic renal cell carcinoma who was treated with sorafenib 800mg q day and presented SJS symptoms of oral mucositis, epistaxis, genital erosion, etc. (Ikeda et al, 2013). Pt was given 14 days of oral prednisolone and SJS resolved (Ikeda et al, 2013). The second case was a 47-yr female with hepatocellular carcinoma with metastases to the adrenal glands was given 400 mg of sorafenib BID and developed ulceration/lesions on lips and oral membranes and full-body plaques. Pt was treated with oral prednisolone 15 mg q day and rashes resolved in 1 week. The last case reported sorafenib-induced SJS, but did not include further details (Faye, Bondon-Guitton, Olivier-Abbal & Monrastruc, 2013).
While the search found 3 cases of sorafenib-induced SJS, none were similar to our case of an 18-year old male with a 3rdrecurrence of undifferentiated low-grade sarcoma that failed to respond with the standard treatment protocol. Due to the absence of a standard therapy for relapsed soft tissue sarcoma, Sorafenib, a multikinase inhibitor, was incorporated into the treatment plan. Subsequently, the patent developed sorafenib-induced SJS and presented with full-body desquamation, erythema, etc. Hospitalization was required for 5 days along with a course of steroids to resolve the case of SJS.

Conclusion: There have been only 3 cases of sorafenib-induced Steven's Johnson Syndrome in the adult patient population with either metastatic renal cell carcinoma or hepatocellular carcinoma and no published cases of sorafenib-induced SJS in a pediatric patient with sarcoma. This occurrence must be further studied and monitored to increase awareness of this life-threatening complication to a medication potentially utilized in refractory and recurrent sarcoma cases.

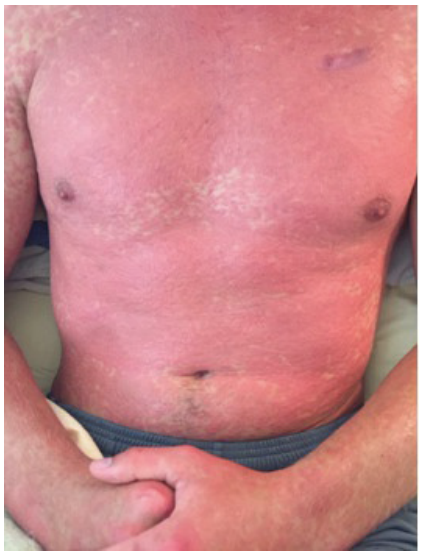

Figure 1

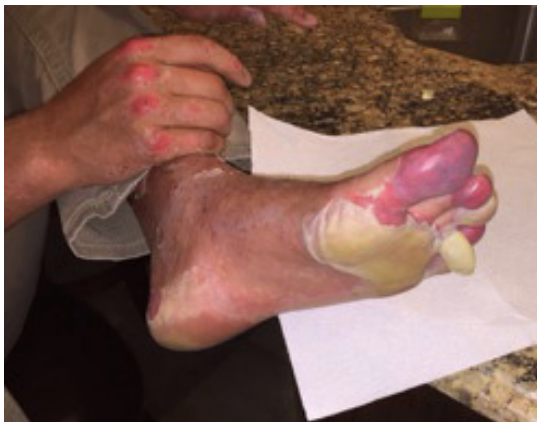

Figure 2

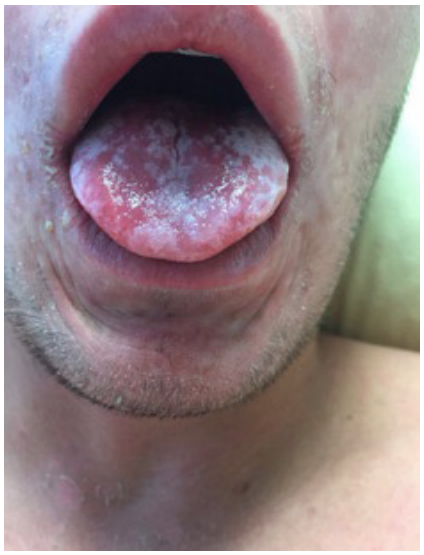

Figure 3

PO 008 3030520

A RARE CASE OF MALIGNANT PERIVASCULAR EPITHELIOID TUMOR IN THE LUMBAR SPINE

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Objective: Perivascular epithelioid cell tumor (PEComa) is a rare mesenchymal tumor of varying malignant potential. It has been described to arise from the lung and visceral organs, but PEComas of the bone are exceedingly rare. We herein report a case of malignant PEComa in the lumbar spine and subsequent detection of multiple lung metastases.

Methods: A 45-year-old woman presented with 3 years history of progressive low back pain. Plain radiographs revealed an increasing radiolucency in the L5 vertebral body. An MRI demonstrated destruction of the L5 vertebra with irregular signal changes. With a tentative diagnosis of spinal tumor, a thorough workup was performed to find a possible primary tumor that could result in metastasis, but none was found. A transpedicular biopsy was performed, which yielded a diagnosis of malignant mesenchymal tumor. Total en bloc spondylectomy was performed after preoperative transcatheter arterial embolization. A final diagnosis was malignant PEComa. Two months after the surgery, we confirmed a recurring mass on the right side of the L5 vertebral area on MRI. Because further surgery would not be able to totally resect the tumor, we selected carbon-ion radiotherapy (70.4 GyE / 16 sessions) for the recurrent lesion. One year later, CT scan demonstrated multiple lung lesions, so we performed excision of lung metastases. The patient has no local recurrence and distant metastasis now.

Results: PEComas are mesenchymal tumors composed of distinctive, so-called perivascular epitheloid cells, which were first described by Bonetti in 1992. Clear criteria for malignancy have not been elaborated in this very rare tumor entity until now. Confirmation of the diagnosis includes immunohistochemical studies that should show dual melanomyocytic differentiation. Surgery seems to be the only approach for aggressive cases. Therefore, we performed a wide excision of primary lesion and pulmonary metastasectomy.

Conclusion: We herein report a rare case of malignant PEComa involving the lumbar spine. It is therefore important to be aware of the pathologic features of this rare tumor entity.

PO 009 3040943

CHANGES IN EXPRESSION LEVELS OF CIRCULATING ANGIOGENESIS-RELATED GENES AS POTENTIAL PREDICTIVE BIOMARKER OF REGORAFENIB RESPONSE IN GASTROINTESTINAL STROMAL TUMOR (GIST) PATIENTS

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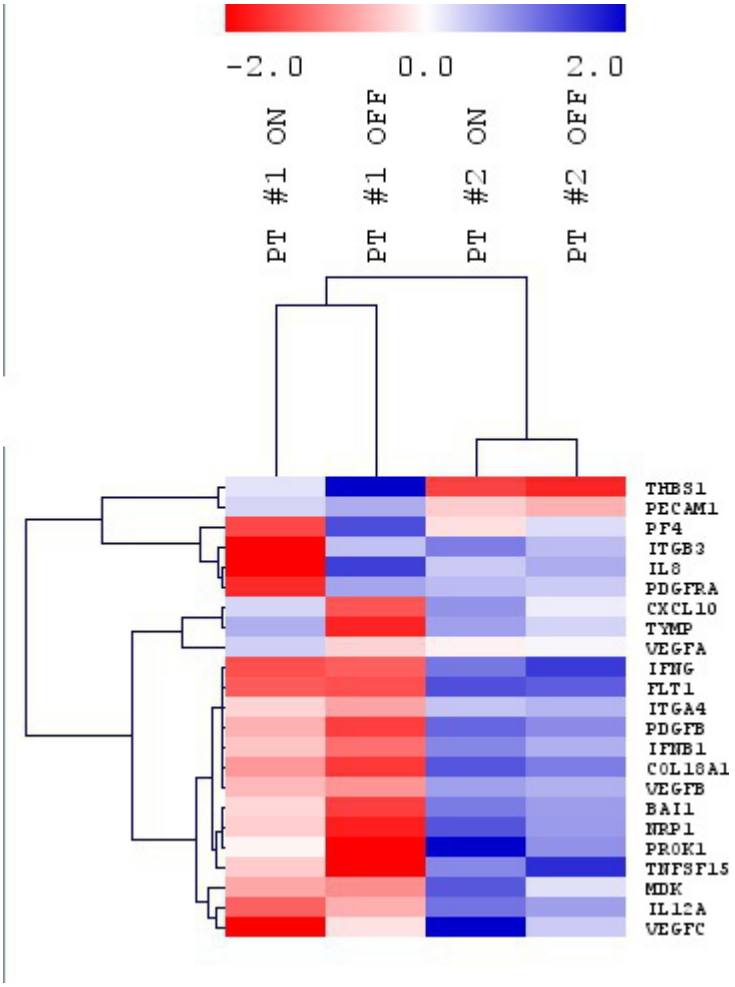
Objective: Regorafenib (REG) is an oral multi-kinase inhibitor (TKI) that potently inhibits the activity of multiple protein kinases, mostly including those involved in the regulation of tumour angiogenesis, vessel stabilization and lymphatic vessel formation, such as VEGFR-1, VEGFR-2, VEGFR-3, TIE2, and PDGFRB.
It represents the standard third-line therapy in GIST patients after imatinib and sunitinib failure, administered at the recommended dose and schedule of 160 mg daily for the first 3 weeks of a 4-weeks cycle.
Plasmatic levels of VEGF-pathway biomarkers (VEGF-A, VEGF-C, sVEGFR-2, sVEGFR-3), interleukin (IL)-8 and stromal cell-derived factor (SDF)-1α (SDF-1α) were suggested as predictors of clinical efficacy of sunitinib in metastatic renal cell carcinoma (mRCC) and advanced pancreatic neuroendocrine tumours (pNET). Data on the association between circulating biomarkers and TKIs clinical efficacy in GIST patients are still lack.
Thus, we evaluated the gene expression profile of circulating angiongesis-related genes in metastatic GIST patients during the REG treatment course.

Methods: Nearl 10 ml peripheral blood (PB) of two adult advanced GIST patients (pt) under REG were collected at two different time-points of REG cycle: one during the treatment-period ON and the other one during the treatment-period OFF. Peripheral blood mononuclear cells (PBMC) were isolated by density gradient centrifugation using Histopaque 1077 (Sigma). The mononuclear cells were washed twice with RPMI Medium 1640 (Invitrogen), centrifuged at 1500 rpm for 8 min, then stored at −80°C until needed. RNA was extracted from isolated PBMC using TRIZOL reagent (Invitrogen) according to manufacturer's instructions. RNA was retrotrascribed to cDNA using MasterMix Vilo IV (Invitrogen). To evaluate the expression of a set of gene involved in the angiogenesis pathway, each sample (ON e OFF) was run in a TaqMan® Human Angiogenesis array which evaluate a total of 93 different genes and 3 endogenous controls. The data were analyzed according to the ΔCt method.

Results: The gene expression levels of selected angiogenesis-related genes in pt#1 was profoundly different depending on the REG treatment window. In particular, the expression of IL8, PF4, ITGB3, PDGFRA, and VEGFC was higher during the treatment-period ON, while the expression of VEGFA, TYMP, PROTK and TNFSF15 was higher during the treatment-period OFF. On the contrary, in pt#2 no variations in angiogenesis-related gene expression levels depending on REG treatment windows were observed (Fig 1). Interestingly, correlating these data with patients' disease status at the time of PB collection, we could observe pt #1 had a responding disease, whereas pt#2 had a progressing disease.

Conclusion: These preliminary data may suggest that REG treatment response seems to correlate with changes in expression levels of circulating angiogenesis-related genes. Further studies in an enlarge cohort of GIST patients treated with REG are mandatory to prove this early hypothesis.



Heatmap showes the expression levels of the most deregulated genes in phase ON and Off in Pt#1 (responding to REG) compared to Pt2 (not responding to REG) who does not show any alteration during the on or off windows.

PO 010 3041808

CONCOMITANT BONE REGENERATION TO RESTORE BONE STOCK DURING REVISION DISTAL FEMUR REPLACEMENTAFTER LARGE TUMOR RESECTION

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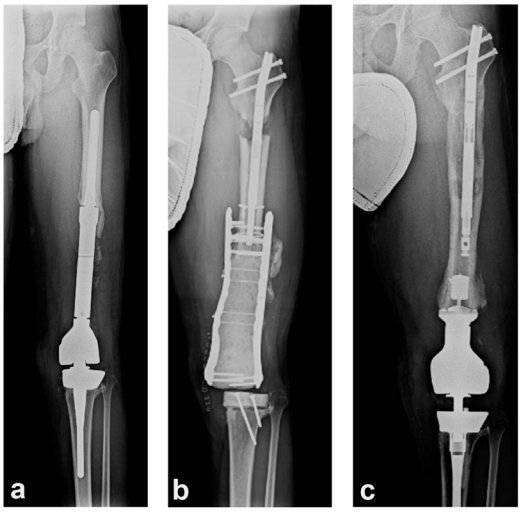
Objective: Loss of bone stock is a common problem in revision arthroplasty. Restoration of bone using distraction osteogenesis with an intramedullary nail may be appropriate for lengthening bone proximal to distal femur implants. In this case series, we describe the successful use of distraction osteogenesis via an internal device to address bone loss after a large osseous resection and revision endoprosthetic reconstruction. A combination of lengthening and bone transport were performed to restore bone stock. A multi-stage revision strategy was employed: removal of existing hardware, treatment of infection if present, lengthening of proximal femur with a temporary antibiotic spacer in the distal femur, and re-implantation

of a definitive distal femur replacement after bone stock had been restored. A magnetically actuated internal lengthening intramedullary nail was utilized to perform the proximal femur osteoplasty.

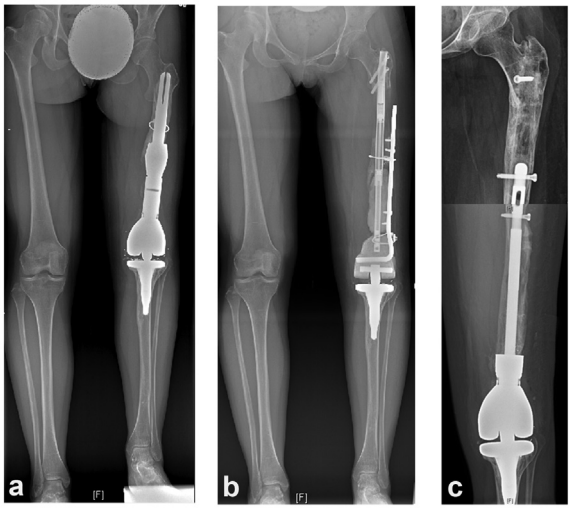
Methods: 1. A 19-year-old male with high-grade osteogenic sarcoma of the left distal femur underwent resection with negative margins and reconstruction with a distal femur replacement. He developed a periprosthetic joint infection and underwent revision surgery 2 weeks postoperatively. Eight months after completing chemotherapy, the patient developed a recurrent periprosthetic joint infection and underwent multi-stage revision arthroplasty to eradicate the infection, during which time the internal lengthening was performed restoring 13cm of bone stock. After that, a standard distal femur arthroplasty was performed without further infection. The patient went on to excellent function until he succumbed to metastatic disease. 2. A 9-year-old female with high grade osteogenic sarcoma of the left distal femur underwent chemotherapy and wide resection with negative margins and reconstruction with distal femur replacement. She had 3 revision surgeries due to failure of that implant, resulting in a distal femur replacement with 10.5 cm of leg length discrepancy. At the age of 18, internal distraction osteogenesis was performed of the proximal femur to achieve a lengthening of 8 cm to equalize limb lengths with additional restoration of bone stock of 6 cm for a total regeneration of 14 cm. After completing the lengthening, a distal femur arthroplasty and quadricepsplasty was performed without further infection and good range of motion and return of function. 3. A 31-year-old male with low grade osteogenic sarcoma of the left distal femur underwent wide resection with negative margins and reconstruction with a standard distal femur replacement. He had numerous complications and underwent 4 revision surgeries. He did well for 8 years until he developed loosening of the cemented implant due to chronic infection. He underwent staged revision arthroplasty, during which time distraction osteogenesis was performed to achieve a restoration of bone stock of 6 cm and lengthening of 4 cm. The infection could not be eradicated and an above the knee amputation was performed. The lengthened femoral bone was retained and has remodeled allowing full weight bearing on the end of this residual limb.

Results: The conversion to a definitive weight bearing distal femur replacement was obtained in two patients; one patient required an above the knee amputation for chronic osteomyelitis which could not be controlled. In this patient, the infection could be eradicated from the lengthened bone, the regenerate bone served to provide length to the amputation stump and fully remodeled to provide full weight bearing and prosthetic use.

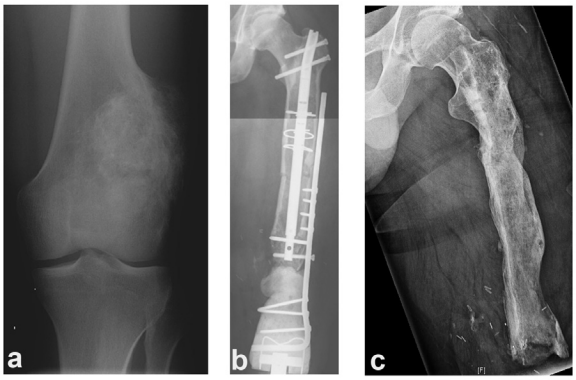
Conclusion: Our report highlights the use of distraction osteogenesis for revision distal femur replacement to restore bone stock in 3 patients. In one of the 2 cases for which revision was required because of infection, the patient ultimately required an amputation. All three patients achieved successful bone regeneration, leading to good functional outcomes without recurrence of infection or local recurrence of osteogenic sarcoma.



a. After reconstruction with a press-fit distal femur replacement
b. After removal of the existing distal femur replacement and insertion of an internal lengthening nail and a distal femur articulating cement spacer
c. After removal of the antibiotic spacer and implantation of a distal femur replacement



a. Before limb lengthening surgery: Patient had a distal femur replacement with 10.5 cm of ipsilateral leg length discrepancy
b. After limb lengthening surgery
c. After distal femur arthroplasty



a. Before surgery
b. During limb lengthening
c. After amputation

PO 011 3042210

EPIDEMIOLOGY, MANAGEMENT, OUTCOMES AND LESSONS LEARNT FROM THE TREATMENT OF FOOT SARCOMAS – MULTI INSTITUTIONAL RETROSPECTIVE ARMS STUDY FROM INDIA (ARMS– AIIMS, RGCI, MAX STUDY)

Arun Garg[6], Akshay Tiwari[2], Manish Pruthi[3], Adarsh Barwad[1], Ekta Dhamija[4], Aditi Aggarwal[8], Rambha Pandey[5], Naresh Gundu[6], Ankur Varshney[6], Venkatesan Sampath Kumar[7], Shah Alam Khan[7], Sameer Rastogi[6]
[1]Pathology, AIIMS, Delhi, India; [2]Musculoskeletal Surgical Oncology, Max Institute of Cancer Care, Saket, Delhi, India; [3]Musculoskeletal Oncology, Rajiv Gandhi Cancer Institute & Research Centre, Delhi, India; [4]Radiology, All India Institute of Medical Sciences, Delhi, India; [5]Radiation Oncology, All India Institute of Medical Sciences, Delhi, India; [6]Medical Oncology, All India Institute of Medical Sciences, Delhi, India; [7]Orthopedics, All India Institute of Medical Sciences, Delhi, India; [8]Radiation Oncology, Maulana Azad Medical College, Delhi, India

Objective: In view of sparse data on foot sarcomas treated on contemporary therapies in english literature we conducted this study on the clinical profile, treatment pattern, response and prognosis of patients with foot sarcomas presenting at the three hospitals with oncology superspecialty services in New Delhi, India, for sarcoma patients. This is the first and largest multicentric study from a developing country on foot sarcomas spanning over last 3 years.

Methods: This was a multi-institutional retrospective analysis with data collected from April 2015 to May 2018. All histologically proven cases of foot sarcoma presenting to these three cancer centers were enrolled in the study. All statistical analysis was done by SPSS version 23. Survival curves were analyzed by Kaplan Meir test and univariate analysis was done by Log Rank test.

Results: There were total of twenty patients **(n=20)** with median age of 22 years (11-66 years) and male preponderance with 70% (14/20) male patients. Median time to presentation was 5 months. Out of 20 patients, 16(80%) were soft tissue and 4 (20%) were osseous sarcomas (metatarsal =2, calcaneum =2). Histologically, Synovial sarcoma (n=10,50%) was the most common type followed by Ewing's sarcoma (n=7,35%) followed by others (extra skeletal myxoid chondrosarcoma, malignant peripheral nerve sheath tumor and dermatofibrosarcoma protuberans- fibrosarcomatous variant). On Imaging, median size was 7 cm (4 to 13 cm). Majority of them were non metastatic (n=13) (65%). Fifteen (75%) patients underwent definitive surgery; 7 underwent wide local excision and 8 underwent below knee amputation. Out of 7 patients who underwent wide local excision; 2 patients had positive margin and 1 developed gangrene due to post-operative wound complication leading to below knee amputation. Majority of the patients required radiotherapy: definitive radiotherapy in 8, post-operative radiotherapy in 7 and palliative radiotherapy in 2. 10 out of 20 patients received chemotherapy: received Ifosfamide/Adriamycin combination chemotherapy in 4, alternating cycles of Vincristine/Adriamycin/Cyclophosphamide and Ifosfamide/Etoposide in 3; and palliative chemotherapy including either Vincristine/Adriamycin/ Cyclophosphamide or Single agent Ifosfamide in 3. All the patients who relapsed had local recurrence (100%) with or without systemic recurrence. Out of 20 patients; two mortalities occurred and 4 events happened in terms of progressive disease. Demise of two patients was recorded due to progressive disease (1) and chemotoxicity (1). With a median follow up of 11 months, overall survival was 83%. On univariate analysis by Log rank test, it was found that progression free survival (PFS) was significantly higher in non-metastatic patients as compared to metastatic patients (not reached versus 16 months in metastatic patients) (p=0.036).

Conclusion: Due to limited literature on soft tissue sarcomas, the treatment protocol is not unified. Our study highlighted that majority of foot sarcomas are either synovial or Ewing's with poor surgical & functional outcome which we attribute to large size, late presentation and difficult or intricate anatomy which limits function preserving surgery. Hence, it needs multidisciplinary management for these patients in order to achieve better outcome.

PO 012 3042646

CLINICAL OUTCOME WITH TRABECTEDIN THERAPY IN ADVANCED SOFT TISSUE SARCOMAS: CLINICAL PRACTICE DATA FROM A SINGLE INSTITUTION

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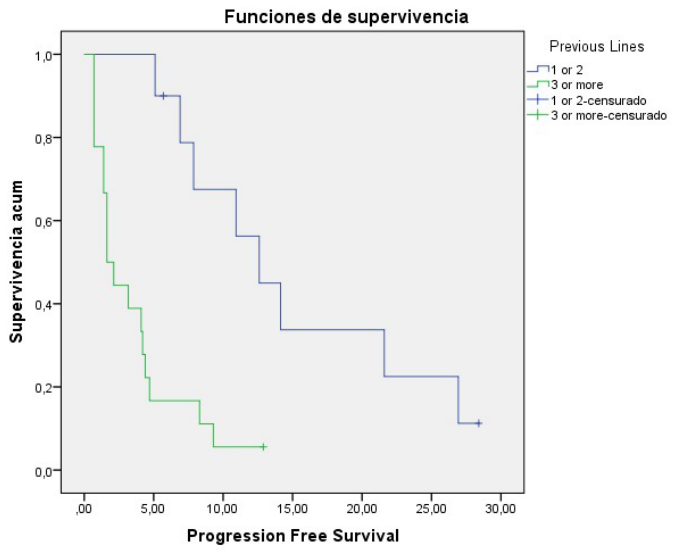
Objective: Soft tissue sarcomas are a group of rare and heterogeneous tumors. In the last 10 years some new drugs are emerging, and due to their nature, there is a lack of consensus of the optimal sequence of these drugs. The aim of this study is to describe potential prognostic factors in patients with advanced soft tissue sarcoma (STS) treated with Trabectedin (Trb).

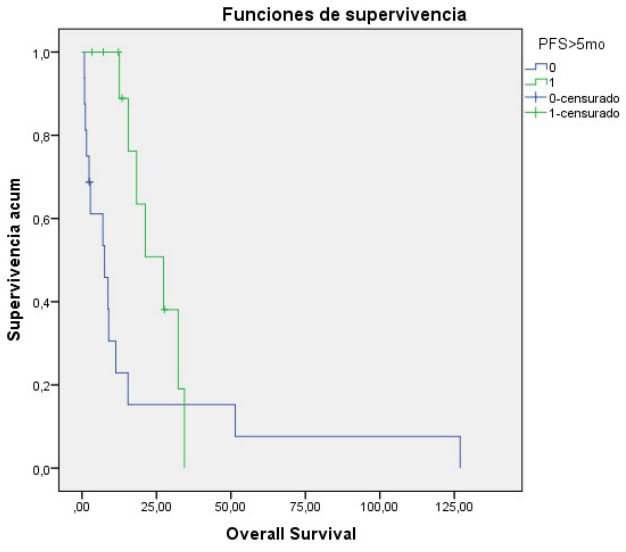
Methods: Observational, descriptive and retrospective study carried out in a tertiary health center (Hospital Universitario Central de Asturias), attending 1 million habitants. 28 patients were included with metastatic STS treated with Trb in the last 15 years. Data were collected anonymously from the medical records. Classical parameters such as histology, primary location, grade and line of treatment were included. Survival analysis was performed by Kaplan-Meier method and compared by log-rank test.

Results: The histology distribution was leiomyosarcoma (LMS) 39.3% (11), liposarcoma (LPS) and pleomorphic sarcoma 14,3% (4) each, synovial sarcomas 10.7% (3) and the remaining 21.4% (6) for other histotypes, which corresponds to 64.3% of L-sarcomas and translocation-related sarcomas. High grade was observed in 71.4% (20). Primary tumors were retroperitoneal 35.7% (10), extremity 25% (7), uterine 25% (7) and 14.3% (4) thoracic. Median time from metastatic disease to Trb start was 21.95 months (mo) (CI95% 17.97-29.13). Trb was prescribed in 3rd line or earlier in 35.7% (10) of the cases. Median progression-free survival (PFS) was 4.4 mo (CI95% 3.1-5.7). Primary sarcomas of the extremity had a better PFS 5.1 vs 4.5mo in uterine and retroperitoneal sarcomas and 1.63 in those arising in the thorax, with no statistical significance (SS). L-sarcomas and translocation-related sarcomas presented better survival 5.1 vs 2.0mo in other histologies (no SS). When Trb was prescribed in 3rd line or earlier median PFS was 12.6mo vs. 1.63mo later (p<0.0001). A correlation was also found between time from metastatic disease to Trb start and PFS (p=0.02). Median overall survival (OS) was 15.47mo (CI95% 9.78-21.15), and no SS were observed by histology, grade, primary tumor or previous lines to Trb. However, those patients who achieved a PFS>5mo presented better OS 27.37 compared to 7.6mo in those with lower PFS (p=0.04).

Conclusion: In this series, the sooner the treatment with trabectedin, the better disease control was observed. Clinical benefit of at least 5mo was associated with an improvement in OS. A better outcome was observed in those with so-called L-Sarcomas (LMS and LPS), but there was also found benefit in other histologies, as described in previous studies. This study reinforces the importance of histology tailored therapy to maximize the benefit by choosing the best sequence.



Progression free survival by previous lines received



Overall survival by clinical benefit with trabectedin

PO 013 3042730

THE CONTRIBUTION OF MOLECULAR BIOLOGY IN SARCOMA DIAGNOSIS AND MANAGEMENT

Stefania Kokkali[1], Jose Duran Moreno[3], Georgios Koukoulis[2], Anastasia Constantinidou[4], Anna Koumarianou[7], Ilias Athanasiadis[8], Anastasios Kyriazoglou[12], Nektarios Koufopoulos[6], Dionisios Papachristou[9], George Agrogiannis[10], Evagelia Skarpidi[11], Elpida Magou[1], Ioannis Boukovinas[5]

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Objective: In January 2018 a multi-disciplinary meeting of specialists (medical oncologists, orthopedic surgeons, pathologists, radiation oncologists) dealing with sarcoma took place in Athens, which served as the first meeting of the Greek-Cypriot sarcoma group. During the meeting a research protocol was proposed and accepted, aiming at studying the role of molecular and cytogenetic techniques in sarcoma diagnosis and management in the two countries. Given the rarity and great heterogeneity of sarcomas, there is a certain degree of complexity within sarcomas diagnosis and classification. Approximately 40% of sarcomas exhibit a specific genetic alteration, such as chromosomal translocations involving transcription factors and gene mutations. Some retrospective data, as well as the French GENSARC study, support the role of molecular methods as a valuable tool for histotype diagnosis refinement, leading to some therapeutic modifications (Italiano et al 2016, Neuville et al 2013). However, there is a lack of prospective data on the exact contribution of these techniques in sarcoma management.

Methods: Our protocol will include every new sarcoma case in Greece and Cyprus for an initial one-year pilot period (09/2018-09/2019). Approximately 10 centers (comprehensive cancer centers, university hospitals and private clinics) in Greece and Cyprus will participate in the study.
Inclusion criteria are histological diagnosis of sarcoma, available material for molecular methods and at least one histotype associated with a known genetic aberration in the differential diagnosis. Clinical (treatment modalities, outcome) and histological data (initial diagnosis based on morphology and immunohistochemistry and final diagnosis) will be prospectively collected. RT-PCR and FISH will be used for genetic aberrations analysis. All samples will be sent to one of the 4 expert laboratories to perform analysis.

Results: The incidence of genetic aberrations in sarcoma patients will be calculated. In addition, we plan to assess the rate of initial diagnosis modification and the rate of treatment plan modification, after the results of the molecular/cytogenetic methods.

Conclusion: The results of the study will shed some more light on the contribution of molecular biology in sarcoma diagnosis and management. It is expected that the quality of care in sarcoma patients will be improved through the study. Molecular techniques are not widely known yet and, in some cases, financial issues do not allow their realization in Greece.

PO 014 3042834

ADOLESCENT AND YOUNG ADULT SARCOMA PATIENTS CHOOSE GNRH AGONISTS FOR FERTILITY PRESERVATION

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Objective: Female adolescent and young adult (FAYA) patients diagnosed with sarcoma are faced with difficult decisions regarding fertility. Infertility caused by chemotherapy is a significant cause significant psychosocial distress and can have a negative impact on survivors' interpersonal relationships, including reduced likelihood of marriage and greater likelihood of divorce (Janson et al., 2009). Education regarding infertility and pursuit of fertility preservation (FP) has been associated with improved quality of life and less regret in survivors (Letourneau et al., 2012). Unfortunately, FAYAs with sarcoma do not always receive counseling regarding their infertility risk and FP options. (Letourneau et al., 2012; Loi et al., 2010; Oosterhuis, et al., 2008; Schover, et al., 2002). Options for FP in FAYA patients include gonadotropin release hormone agonists (GnRH-a) and cryopreservation. Cryopreservation requires ovarian stimulation and can take 2–6 weeks, delaying

initiation of cancer treatment. (Levine et al., 2010). GnRH-a treatment temporarily suppresses ovarian function and reduces gonadotoxicity during chemotherapy. (Blumenfeld Z, et al., 2008; Munster PN, et al, 2012). Importantly, GnRH-a therapy does not require delay, is non-invasive, has fewer side effects, and is significantly lower in costs than cryopreservation. At our institution the standard practice is to refer all FAYA sarcoma patients to a fertility specialist for detailed discussion of available options. Here, our focus was to explore whether, after this consultation, patients and families chose to undergo GnRH-a therapy.

Methods: Query of the electronic health record system was performed to identify female patients with sarcoma treated by the pediatric oncology service at Rush University Medical Center in Chicago IL, between 2008 and 2018. Chart review was performed and data collected. We reviewed 19 cases of post-pubertal FAYA sarcoma patients who were offered GnRH-a therapy with the goal of preserving future fertility to determine the frequency with which such patients chose to pursue GnRH-a therapy.

Results: Nineteen patient cases were identified. Of these 19 patients 13 (68%) were between 12-19yo, the remaining patients were older than 19. All patients provided informed consent for their treatment. Seventeen out of 19 (89.5%) of FAYA patients (13 of whom were between 12-19yo) chose to undergo GnRH-a therapy before and/or during adjuvant chemotherapy between 2008-2018.

Conclusion: When provided information on FP options, a majority of post-pubertal FAYA sarcoma patients, 89.5%, opted to undergo GnRH-a treatment. Despite being informed of the experimental nature of GnRH-a therapy, unproven efficacy, unknown chemotherapy interactions, lack of clear consensus or established best practices, inability to guarantee fertility and uncertain insurance coverage, most patients still chose this therapy. Moreover, the potential psychosocial effects of offering FP cannot be overstated. The forward-looking nature of FP therapy can have powerful effects of the mindset of newly diagnosed sarcoma patients and their families. From our data it is clear mere chance of FP is extremely important to this cohort and the notion that the patient's future fertility is being so seriously considered by the medical team may provide patients hope and confidence that they have a future to which they may look forward.

PO 015 3015723

RECONSTRUCTION WITH MODULUS STEM AFTER PROXIMAL FEMORAL TUMOR RESECTION: 9 CASES

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Objective: Reconstruction of massive bone defects after wide resection of bone tumors occurring in the proximal femur has been performed using tumor megaprosthesis. However, the megaprosthesis does not allow precise adjustment of the size of femoral head, neck length, or neck shaft angle, unlike conventional total hip arthroplasty (THA). We present a case of the Modulus stem used for reconstruction after resection of a proximal femur tumor.

Methods: 9 patients who underwent resection of the proximal femoral tumor were assessed: sixe patients with bone metastases from carcinomas (liver, kidney, lung, breast and colorectal) and two with myeloma. Another patient underwent second-look revision of tumor megaprosthesis due to an infection implanted six years ago after wide resection of leiomyosarcoma arising beneath the femoral head. All patients underwent reconstruction surgery using the Modulus stem.

Results: All patients obtained walking ability with fully weight bearing within one week after surgery, and no complications, such as dislocation or hip pain, were seen within a median follow-up of 12 months.

Conclusion: The Modulus stem is generally used for a revision surgery after THA involving massive bone defects. Broad size variation of the stem and femoral head of this system enables more appropriate selection of the femoral head and neck with precise adjustment during the reconstruction procedure. In addition, favorable early fixation is possible due to its design. Although only short-term follow-up was conducted, we believe that use of the Modulus stem would be an alternative approach to reconstruction after resection of proximal femur tumor, especially in metastatic disease.

PO 016 3041846

TREATMENT OF MASSIVE DEFECTS AFTER RESECTION OF ADAMANTINOMA WITH DISTRACTION OSTEOGENESIS

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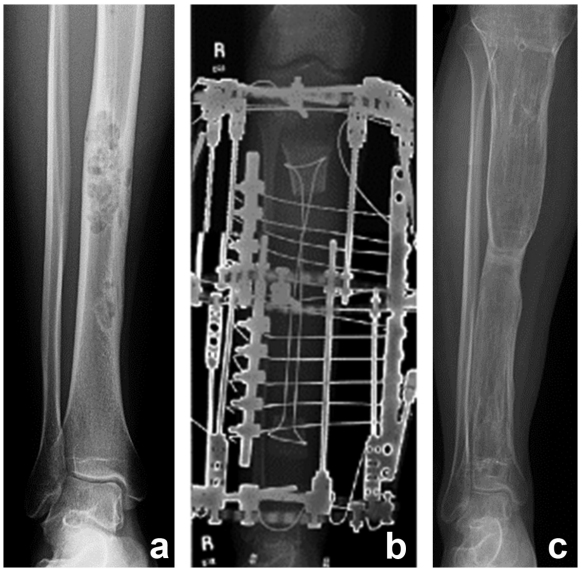
Objective: Adamantinoma, osteofibrous dysplasia (OFD) and OFD-like adamantinoma are complex and confusing amalgam of rare diseases. Typically, adamantinoma involves large portions of the tibia requiring large resections leading to complex reconstructions. There are several reconstructive options to bridge bone defects: allografts, vascularized or nonvascularized autologous fibula grafts, intercalary prostheses, or distraction osteogenesis. Distraction osteogenesis can be used to bridge massive bone defects and has the advantage of yielding structural, viable, physiologically productive and durable bone. Techniques of bone regeneration utilizing internal or external methods are used to manage bone defects in trauma, infection and congenital deformities, and less commonly used for oncological osseous defects. We present two cases of patients diagnosed with adamantinoma in a background of osteofibrous dysplasia treated with distraction osteogenesis via an external fixator and double level cable bone transport. We propose that this is a safe and effective surgical treatment for massive bone defects.

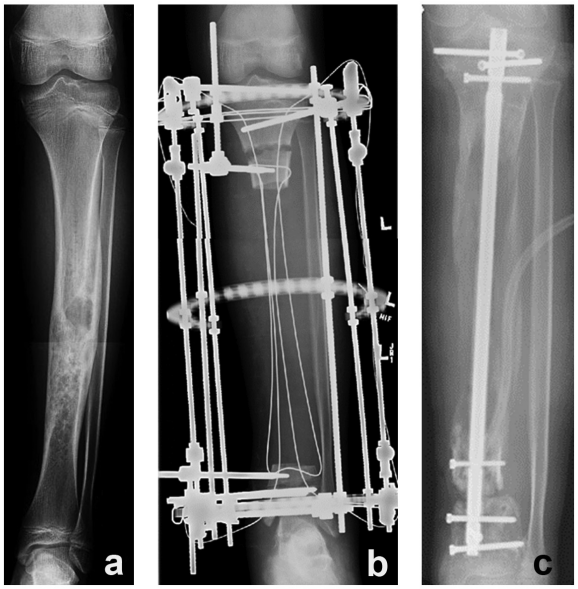
Methods: In both cases wide resection of the adamantinomas was performed to provide R0 surgical margins, followed by double level bone transport using external fixation with cables via trifocal distraction osteogenesis to reconstruct the defect. Bone transport occurred at a total rate of 2 mm per day: 1mm proximally and 1mm distally. Full weight-bearing and ambulation were encouraged immediately and throughout the recovery. In the first case the patient utilized the external fixator until full osseous consolidation. In the second case the patient was converted to internal fixation after completion of the bone transport.

Results: The first patient presented with classic adamantinoma of his right tibia at the age of 17. The lesion was treated with a wide resection of the tibia, leaving a 23.5 cm bone defect. The transport was completed in 20 weeks and the frame was removed after 49 weeks, yielding an external fixation index (EFI) of 0.47 months/cm. Six weeks after frame removal, the patient developed a non-displaced fracture at the junction of the transported bone and regenerate bone. The patient was treated conservatively with a walking boot. Nine months after frame removal the patient has returned to full activity without restriction achieving excellent bone quality and full range of motion. The MSTS score at recent follow up was 30 at 21 months after index surgery. The second patient presented at age 5 with osteofibrous dysplasia of the left tibia. The patient was followed routinely with imaging when at age 14 he reported new pain correlating with radiographic changes on MRI leading to a biopsy consistent with OFD-like adamantinoma. The patient underwent a wide resection of the tibia, leaving a 25 cm defect. The transport was completed after 28 weeks, and the external fixator was removed after 34 weeks, converting to internal fixation with an antibiotic coated intramedullary nail, yielding an EFI of 0.31 months/cm. The initial post-operative course was complicated by premature consolidation of the regenerate leading to loss of fixation of the distal fragment and infection requiring subsequent debridement surgeries, negative pressure wound therapy, and loss of 2 cm of regenerate length. The patient required a subsequent surgery with an internal lengthening nail to achieve full 25cm of regenerate. The MSTS score at recent follow up was 25 at 9 months after index surgery.

Conclusion: Despite several typical obstacles and complications of prolonged external fixation, both patients have excellent results with an average MSTS score of 27.5. The average EFI of 0.39 months/cm, compared to average EFI of 1 month/cm for typical DO reconstructions, supports the hypothesis that double level DO with cable transport is an effective surgical reconstructive option in these massive defects offering an excellent option for sustainable limb reconstruction.



A. First patient at the age of 17, x-ray before surgery
B. X-ray one month after resection and reconstruction surgery
C. X-ray at the most recent follow-up visit, two years after resection and reconstruction surgery



A. Second patient at the age of 14, X-ray before surgery
B. X-ray one month after resection and reconstruction surgery
C. X-ray 10 months after resection and reconstruction surgery

PO 017 3028743

ACTIVITY OF THE CDK 4/6 INHIBITOR RIBOCICLIB IN DESMOID TUMOR. CASE REPORT OF A PATIENT WITH MULTIFOCAL DESMOID TUMORS TREATED WITH A COMBINATION OF RIBOCICLIB, GOSERELIN AND LETROZOLE

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Objective: Desmoid tumors are rare mesechymal neoplasms associated to famial adenomatous polyposis (FAP) in approximately 10% of patients. For FAP patients desmoid tumors present an important cause of mortality. Patients with progressive inoperable tumors may benefit from systemic treatment including hormonal therapy. The typical β-catenin accumulation has been associated with cyclin D1 overexpression in desmoid tumors. Our aim was to investigate the activity of cyclin-dependent kinase 4/6 inhibitor ribociclib, goserelin and letrozole in a desmoid tumor patient.

Methods: A female patient with famial adenomatous polyposis and multiple progressing desmoid tumors was treated with ribociclib, letrozole, and goserelin. The response was recorded according to RECIST 1.0 and 1.1. criteria.

Results: Ribociclib combined with goserelin and letrozole led to symptomatic relief and a 10-month stabilization of multiple desmoid tumors. The best response according to RECIST 1.0 criteria was stable disease with maximal size reduction of 18%. After discontinuation of the therapy the patient was diagnosed with promyelocytic leukemia.

Conclusion: According to our experience, ribociclib should be further investigated in desmoid tumors.

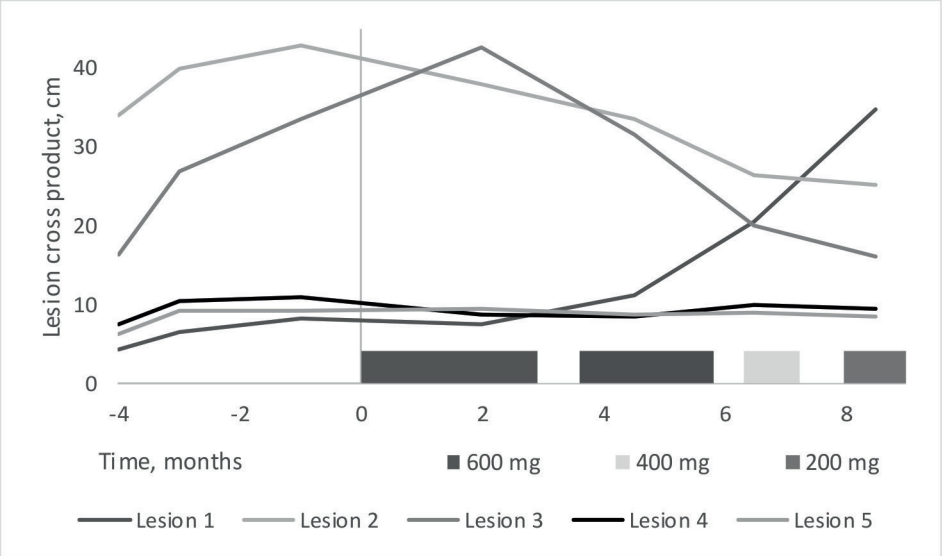

Figure 1. Ribociclib dose and the cross product of desmoid tumor diameters before and after initiation of the medication.

PO 018 3041739

IS CRYOSURGERY REALLY NECESSARY FOR INTRALESIONAL RESECTION OF LOW-GRADE CHONDROSARCOMA?

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Objective: Low-grade chondrosarcoma of long bone can be successfully treated with intralesional resection with various types of adjuvant therapy. Although cryosurgery is one of the most common adjuvant treatments, the effect on oncological outcome still remains unclear. We analyzed the outcome of treatment of low-grade chondrosarcoma using intralesional resection with or without cryosurgery.

Methods: Eleven patients of low-grade chondrosarcoma of long bone treated with intralesional resection between 1999 and 2012 were analyzed. Indication for surgical treatment included the radiographic appearance consistent with low-grade chondrosarcoma with evidence of aggressive behaviors such as pain, progressive enlargement and endosteal erosion, and/or the histological diagnosis of the biopsy. The tumor was removed by complete curettage and mechanical burring. Additional cryosurgery (direct pouring liquid nitrogen) was performed in 7 patients until 2000. Since then 4 patients were treated with intralesional resection alone.All 11 patients treated with intralesional resection showed no local recurrence and no distant metastasis with average follow-up of 146 (69-216) months (162 months for cryosurgery and 117 months for non-cryosurgery). 3 patients treated with cryosurgery showed postoperative complication including 2 fractures, 2 infections and 1 radial nerve palsy. One fracture required surgical fixation, and 2 infections were treated with surgical debridement. One radial nerve palsy recovered conservatively within 4 months postoperatively. Patient treated without cryosurgery showed no major surgical complication. MSTS score of 1 patient with pathological fracture followed by deep infection was 22/30 and all other patients demonstrated 30/30 at final follow-up.

Results: All 11 patients treated with intralesional resection showed no local recurrence and no distant metastasis with average follow-up of 146 (69-216) months (162 months for cryosurgery and 117 months for non-cryosurgery). 3 patients treated with cryosurgery showed postoperative complication including 2 fractures, 2 infections and 1 radial nerve palsy. One fracture required surgical fixation, and 2 infections were treated with surgical debridement. One radial nerve palsy recovered conservatively within 4 months postoperatively. Patient treated without cryosurgery showed no major surgical complication. MSTS score of 1 patient with pathological fracture followed by deep infection was 22/30 and all other patients demonstrated 30/30 at final follow-up.

Conclusion: Previous papers demonstrated that the use of adjuvant cryotherapy might cause increased fracture rates, which ranged from 1% to 30%. Two postoperative fracture (29%) occurred after cryosurgery, and 2 infections and 1 nerve palsy were also identified postoperatively. Due to high rate of complications, we abandoned adjuvant cryosurgery. Extensive intralesional resection alone resulted also in good local control. Although other adjuvant therapies besides cryosurgery are widely acceptable in the treatment of low-grade chondrosarcoma, recent reports demonstrate that intralesional resection alone can provide good oncological outcomes with minimum complication.

PO 019 3042710

ANGIOFIBROMA OF SOFT TISSUE

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Objective: Angiofibroma of soft tissue (AFST) is a benign fibrovascular tumor reported in 2012. It is usually characterized by a painless tumor that arises in the limbs and has a clear boundary. Histopathologically, it consists of spindle-shaped cells that irregularly grow with fibrovascular stroma abundant, poor atypia of nucleus and little mitotic figures. We report two cases of angiofibroma of soft tissue.

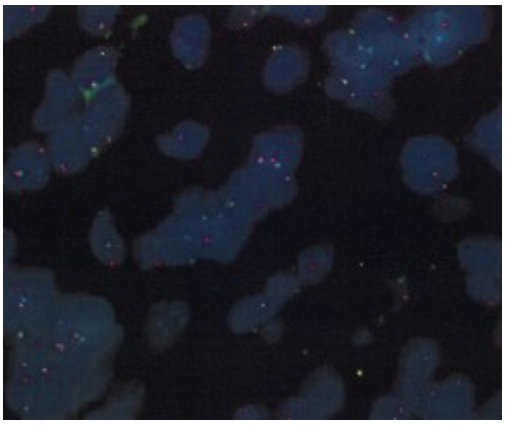
Methods: Since we experienced two cases of AFST, we investigated the medical record retrospectively, examined the clinical course, MRI and histopathological findings, and presence of fusion genes (AHRR-NCOA2).

Results:
Case 1: A 69-year-old man. In December 2012, he notices the mass of the right popliteal region. MRI was performed by a nearby hospital and a malignant soft tissue tumor was suspected and introduced to our hospital. There was no local

tenderness and a tumor with a mobility of about 50 mm in diameter was observed. In MRI, the tumor was multilocular and lobulated, showing a low signal in the T1 weighted image, a nonuniform high signal in the T2 weighted image, and was contrasted with Gd. Based on the above MRI findings, a malignant soft tissue tumor containing mucous components was suspected. A biopsy was performed in May 2014, and the diagnosis of AFST was made histopathologically. Because of cardiovascular disease complications, it is currently under observation.

Case 2: 52-year-old man. In 2012, he notices the tumor of the right brachial region. Because it increased slowly, we visited nearby hospital in August 2017. Malignant soft tissue tumor was suspected and introduced to our hospital. A tumor of about 10 cm in diameter was found in the right upper arm, and a marked thermal sensation was noted in the right brachial region. The tumor showed a low signal in the T1-weighted image of MRI and a high signal in the T2-weighted image. Increased abnormal blood vessels were found inside and around the tumor. Immediate biopsy was performed and diagnosed as histologically AFST. Fusion gene of AHRR and NCOA2 by chromosome translocation (5; 8) (p15: q13) could be confirmed (Fig.1).Tumor resection was performed in October 2017, and it is currently under observation.

Conclusion: AFST reported by Fletcher and colleagues in 2012 as a benign soft tumor with fibroblast-like spindle cells and abundant vascular components. It is a soft tissue tumor classified as various benign and malignant soft tissue tumors and recognizes a fusion gene of AHRR and NCOA2 by chromosome translocation (5; 8) (p15: q13). Even in our cases, the fusion gene could be detected. For surgical treatment of AFST, marginal resection is the principle, and wide resection like malignant soft tissue tumor is unnecessary. When histological diagnosis is difficult, fusion gene detection is useful for diagnosis.



PO 020 2991603

PROGNOSTIC VALUE OF SUVMAX MEASURED BY F-18 FDG PET/CT IN PATIENTS WITH LIPOSARCOMA

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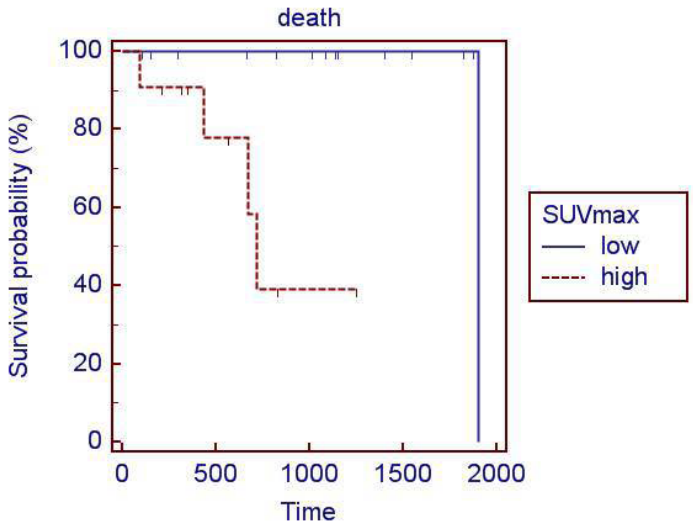
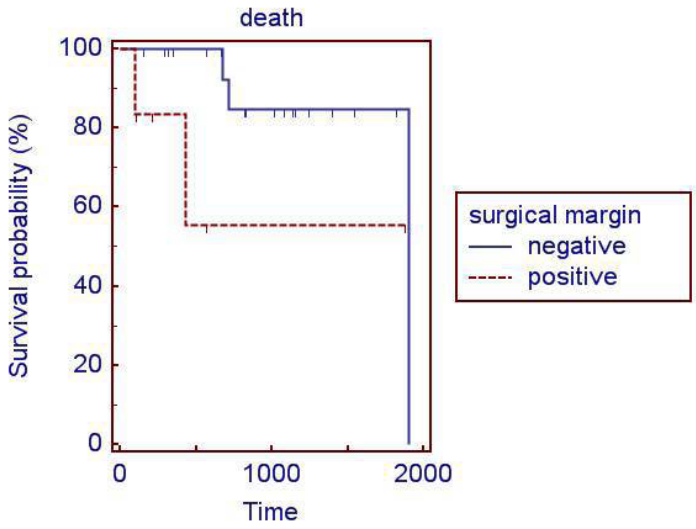
Objective: The aim of this retrospective study was to determine whether glucose metabolism assessed by F-18 FDG PET/CT provides prognostic information independent of established prognostic factors in patients with liposarcoma.

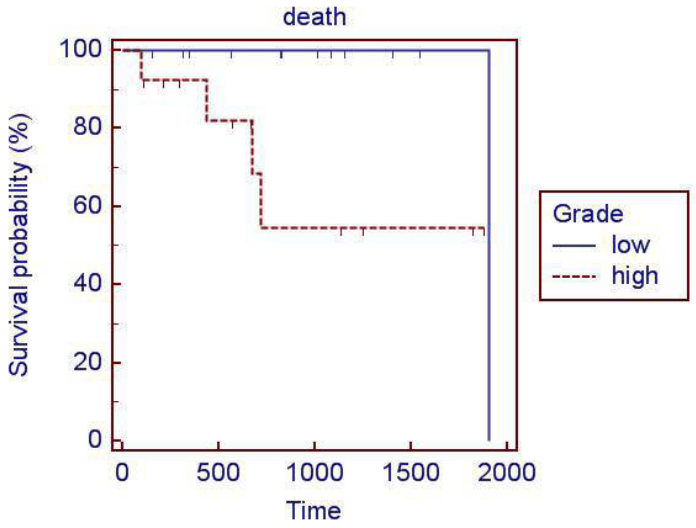
Methods: We reviewed retrospectively the medical records of 25 patients (men 17, women 8, mean age 60±12 years) with pathologic proven liposarcoma. They underwent F-18 FDG PET/CT as part of a pretreatment workup from April 2008 to December 2012. For the analysis, patients were classified by age, sex, primary site, type of histology, histologic grade, surgical margin, AJCC stage, tumor size, type of treatments and maximum standardized uptake value (SUVmax). The relationship between FDG uptake and survival was analyzed using the Kaplan-Meier with log-Rank test and Cox's proportional-hazard regression methods.

Results: Median survival for all 25 study subjects was 717 days and median SUV by PET/CT was 3.3 (range: 1-20.6). Patients with SUVmax of <!--[if gte vml 1]><v:shapetype id="_x0000_t75" coordsize="21600,21600" o:spt="75" o:preferrelative="t" path="m@4@5l@4@11@9@11@9@5xe" filled="f" stroked="f"> <v:stroke joinstyle="miter"/> <v:formulas> <v:f eqn="if lineDrawn pixelLineWidth 0"/> <v:f eqn="sum @0 1 0"/> <v:f eqn="sum 0 0 @1"/> <v:f eqn="prod @2 1 2"/> <v:f eqn="prod @3 21600 pixelWidth"/> <v:f eqn="prod @3 21600 pixelHeight"/> <v:f eqn="sum @0 0 1"/> <v:f eqn="prod @6 1 2"/> <v:f eqn="prod @7 21600 pixelWidth"/> <v:f eqn="sum @8 21600 0"/> <v:f eqn="prod @7 21600 pixelHeight"/> <v:f eqn="sum @10 21600 0"/> </v:formulas> <v:path o:extrusionok="f" gradientshapeok="t" o:connecttype="rect"/> <o:lock v:ext="edit" aspectratio="t"/> </v:shapetype><v:shape id="□□_x0020_1" o:spid="_x0000_i1025" type="#_x0000_t75" alt="≤" style='width:5.25pt;height:7.5pt;visibility:visible;mso-wrap-style:square'> <v:imagedata src="file:///C:/Users/HP/AppData/Local/Temp/OICE_16_974FA576_32C1D314_1257/msohtmlclip1/01/clip_image001.gif" o:title="≤"/> </v:shape><![endif]-->3.3 survived significantly longer than patients with SUVmax of >3.3 (Median 1901 vs. 717 days, p = 0.027). These two groups also differed significantly with regard to type of histology (p=0.006) and AJCC stage (p=0.009). Univariate analysis revealed that the patients with low SUVmax (p=0.004), low grade (p=0.028) and negative surgical margin (p=0.032) had a longer survivals.

Conclusion: Higher SUVmax on pretreatment F-18 FDG PET/CT can predict poorer survival in patients with liposarcoma.







PO 021 3030751

OUR EXPERIENCE OF SECOND LINE THERAPY FOR ADVANCED SOFT TISSUE SARCOMA

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Objective: Soft tissue sarcoma (STS) is a rare tumor. Doxorubicin and Ifosmide are currently standard option for the first-line treatment of STS. However, there is no standard therapy for second-line and palliative chemotherapy at present. Since 2012, pazopanib, trabectedin, and eribulin have been approved in Japan for the second-line or later treatment of patients with advanced STS. We investigate the effect of pazopanib and eribulin for second-line and the role of the palliative chemotherapy in advanced soft tissue sarcoma patients.

Methods: We investigated retrospectively the advanced STS patients, who received pazopanib and/or eribulin from 2000 to 2018 in our institute. Best response rate according to Response Evaluation Criteria In Solid Tumors (RECIST) criteria and severe adverse events (AEs) according to National Cancer Institute Common Terminology Criteria for Adverse Events were evaluated. We also evaluated progression-free survival and overall survival (OS).

Results: We investigated 27 patients (15 men and 12 females). Median age was 46 (range, 24-80) years, with Eastern Cooperative Oncology Group performance status of 0 - 1. Twenty one patients were treated by pazopanib and 10 were treated by eribulin. The median number of previous chemotherapy regimens was 2 (range, 1-5). Median duration of pazopanib was

3.5 month (range, 0-9). Median number of eribulin was 6 cycle (range, 1-21). According to histotype, clinical benefit (partial response + stable disease) was reported in leiomyosarcoma (n=2), dedifferentiated liposarcoma (n=1), retroperitoneal liposarcoma (n=2), myxoid liposarcoma (n=2), stromal sarcoma (n=1), high-grade undifferentiated pleomorphic sarcoma (n=4), myxofibrosarcoma (n=1), synovial sarcoma (n=1), and malignant peripheral nerve sheath tumor (n=1). Any grade AEs were noncumulative, reversible, and manageable. With a median follow-up time from advanced disease of 13 (range, 1-81) months.

Conclusion: Our experience confirms pazopanib and eribulin as an effective therapeutic option for some advanced STS and these drugs are also effective option for palliative chemotherapy.

PO 022 3033304

PROGNOSTIC FACTORS OF AGGRESSIVE FIBROMATOSIS AFTER POSTOPERATIVE RADIOTHERAPY

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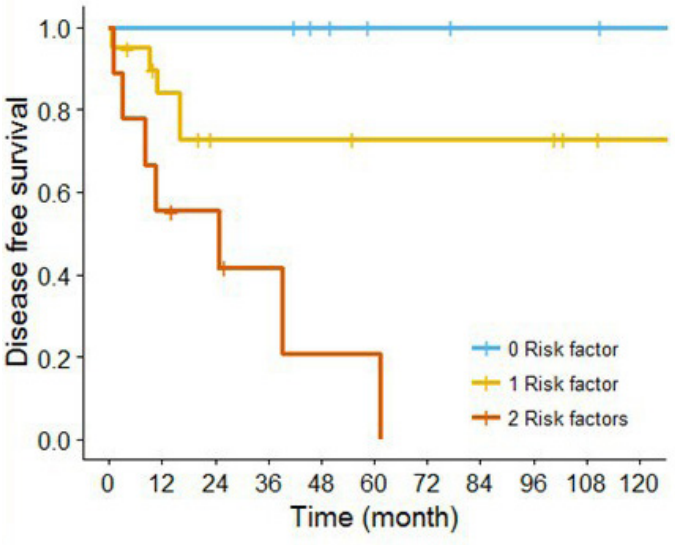
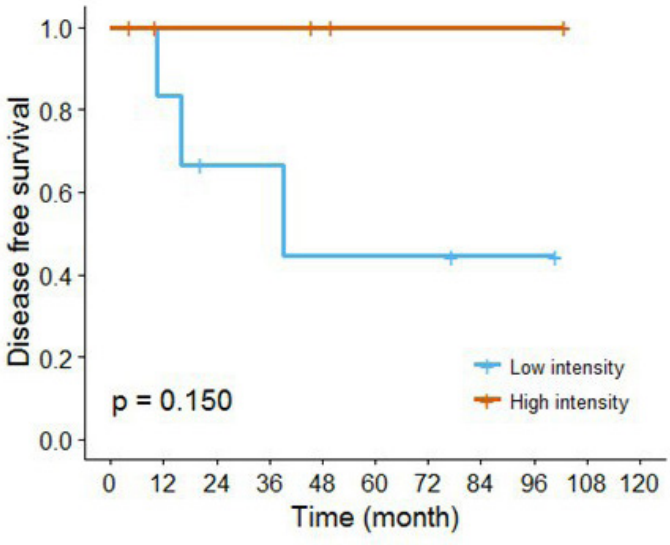
Objective: We identified the prognostic factors influencing disease-free survival (DFS) of patients with aggressive fibromatosis (AF) after postoperative radiotherapy (PORT). We also assessed the correlation between immunohistochemistry (IHC) features of β-catenin/SMA and DFS.

Methods: The records of 37 patients with biopsy-proven AF treated by PORT from 1984 to 2015 were retrospectively reviewed. Fifteen patients underwent wide excision for AF and 22 patients received debulking operation. The median total dose of PORT was 59.4 Gy. IHC of β-catenin and SMA were evaluated in available 11 patients. IHC staining intensity was graded and compared between low and high intensity. Log-rank test and Cox proportional hazard model were performed.

Results: The median follow up duration was 105.9 months. The 5-year DFS rate was 68.0%. Multivariate analysis showed that tumor size ≥10cm (HR 3.871, 95% CI 1.137-13.173, p=0.030) and interval from surgery to PORT >5 weeks (HR 10.334, 95% CI 1.308-81.655, p=0.027) were independent risk factors for AF local recurrence. Patient with 2 risk factors had significantly lower 5-year DFS than patients with no risk factor (20.8% vs. 100.0%, p=0.001). Nuclear β-catenin intensity had a tendency to inversely correlate with 5-year DFS, although it did not have statistically significance (low intensity, 44.4% vs. high intensity, 100.0%, p=0.150).

Conclusion: Postoperative radiotherapy should be performed immediately after surgery for patients with aggressive fibromatosis, especially large tumor patients. β-catenin staining intensity of IHC might correlate with local recurrence. Further investigations to validate its prognostic value are needed





PO 023 3034649

MULTIDISCIPLINARY MANAGEMENT OF A LOCALLY ADVANCED PERINEAL CELLULAR ANGIOFIBROMA INVOLVING BASE OF PENIS AND ANAL SPHINCTER MUSCLE

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Objective: Cellular angiofibromas are rare benign genital stromal tumors located in the inguinal and scrotal region in males and the vulvar and vaginal regions in females. Given the vascularity of these tumors and difficult locations, preoperative embolization if a useful adjunct when managing locally advanced tumors. We discuss the multidisciplinary management of a perineal cellular angiofibroma utilizing interventional radiology as well as urologic and surgical oncology to successfully remove a locally advanced benign tumor with minimal morbidity from a male perineum.

Methods: Patient is a 47 year old male who presented with a rapidly enlarging perineal mass. Pelvic MRI demonstrated an 8.1cm mass that extended to the bulbospongiosis muscles, involving the perineal body and partially invading the external anal sphincter muscles (Fig 1). There was significant intratumoral vascularity. Core needle biopsy demonstrated a spindle cell neoplasm consisting of a moderately cellular population of spindle cells with mild nuclear atypia. No mitotic activity nor necrosis was identified. IHC results are seen in Table 1. There were multiple medium sized vessels within the tumor. The mass was characterized as a cellular angiofibroma. Given the vascularity and the size, preoperative selective embolization of the bilateral distal pudendal arteries with 300-500micron spheres was performed (Fig 2).

Results: The patient was taken to the operating room where the mass was dissected off the base of the penis as well as the periurethral tissue without injury by Urologic Oncology. Surgical Oncology then resected the mass en-bloc with approximately 2cm of the involved anterior anal sphincter muscle (Fig 3). Primary sphincteroplasty was performed. A permanent or temporary ostomy was avoided. The perineal body was then resected and a primary closure was attained. The patent tolerated the procedure and had good urinary/sexual function as well as good sphincter control. After 3 years, there has been no evidence for recurrence.

Conclusion: Cellular angiofibromas are rare benign genital stromal tumors located in the inguinal and scrotal region in males and the vulvar and vaginal regions in females. Given the vascularity of these tumors and difficult locations, preoperative embolization if a useful adjunct when managing these tumors. It can decrease the bleeding risk and potentially decrease the size of the tumor prior to operating. These tumors are benign and should be excised locally. However, as was demonstrated here, involvement of surrounding structures may occur. The importance of making an accurate initial diagnosis can obviate the need for radical resections. While demonstrating a more locally aggressive phenotype, preoperative planning and a multidisciplinary approach allowed this tumor to be removed with minimal morbidity.

Table 1

PROTEIN:	Estrogen	Progesterone	Desmin	CD34	S100	EMA
LEVEL OF EXPRESSION:	Positive	Weak	Weak	*Vessels Only	Negative	Weak

*The findings are generally consistent with cellular angiofibroma except for the CD34 negative stromal IHC stain - which does not exclude the diagnosis

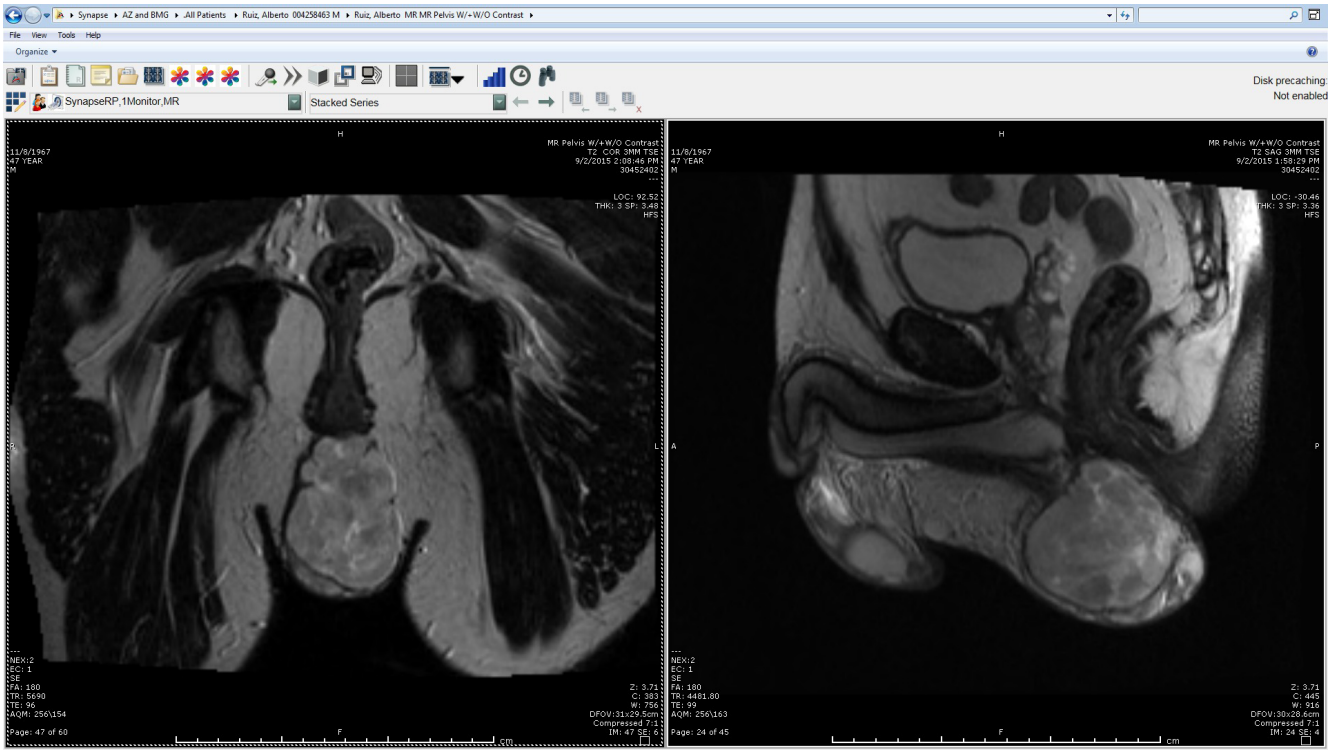

Figure 1. Pelvic MRI

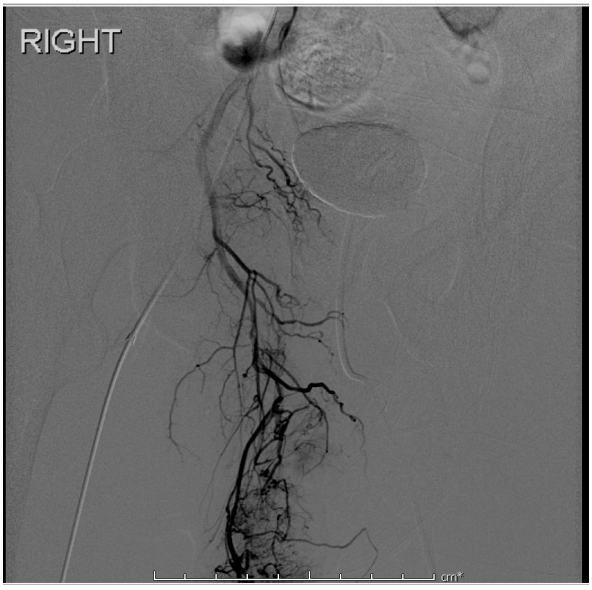

Figure 2. Internal Iliac Angiogram demonstrating vascularity of tumor

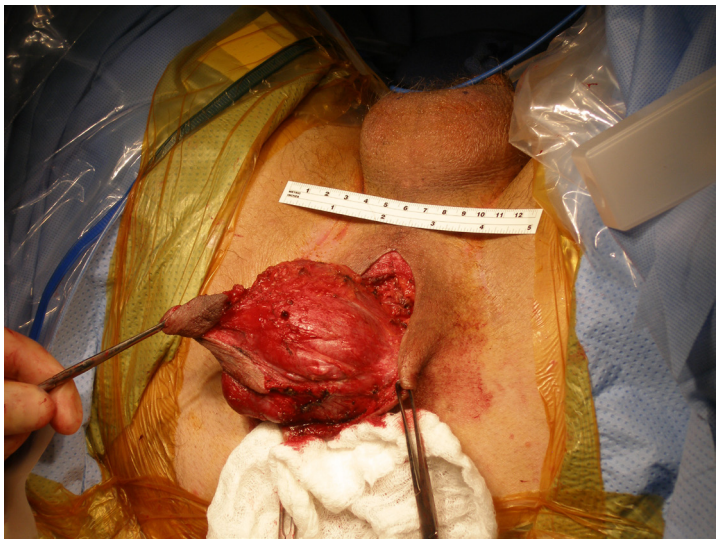

Figure 3. Cellular Angiofibroma with external anal sphincter involvement

PO 024 3035715

VERY PROLONGED RESPONSE TO TRABECTEDIN IN METASTATIC LEIOMYOSARCOMA: A CASE REPORT

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Objective: Leiomyosarcomas (LMS) are rare tumors (~1%) in adults with an extremely poor prognosis. Trabectedin (Yondelis®) has a unique mechanism of action as in addition to direct growth arrest it has selective anti-inflammatory and immunomodulatory properties.

Methods: We report the case of a patient with metastatic LMS refractory to previous treatments who obtained a prolonged disease control following the treatment with trabectedin.

Results: A 60-year-old male patient with no relevant medical history presented in August 2008 in the Hospital of Burgos (Spain) with a 13x12 cm tumefaction in the left lower extremity. In September 2008 the patient underwent a non-radical tumor surgery and following the supracondylar amputation of the extremity in November 2008 the high-grade pleomorphic LMS (T2b-14cm, N0, M0) diagnosis was confirmed. This was followed with 6 cycles of adjuvant treatment with ifosfamide/adriamycin. In July 2009, a CT scan found the multiple lung relapse. Subsequently the patient received 6 cycles of gemcitabine/docetaxel in the advanced setting and achieved a complete radiological response. During the follow-up, in October 2011, the patient experienced a slow-growing tumefaction on the left biceps. A MRI evaluation displayed a solid tumefaction (3x2.4x1.8cm) in the middle third of the left arm as well as an intramuscular involvement of the brachial biceps muscle in contact with the arm cephalic vein. The arteriography also confirmed a pathological arterial capture. Consequently, the patient underwent another R0 surgery. A post-operative adjuvant cytostatic treatment or radiotherapy boost was not performed and it was decided to continue with clinical and radiological follow-up. In June 2012, a MRI evaluation displayed another nodule of 2 cm in the left thigh root followed by a R0 metastasectomy. A CT scan done in September 2012 showed two hepatic lesions of 5cm and 2cm, and a lesion in psoas of uncertain meaning. Next, the second-line of cytostatic treatment for advanced disease with gemcitabine/docetaxel was resumed and after 16 cycles of treatment the patient achieved a complete response in one and a partial response in another hepatic lesion. The next combined CT and positron emission tomography (PET) scan showed the presence of multiple metastases of muscular involvement in the lung (right upper lobe), liver, and myocardium, left psoas, left buttock, right iliac psoas, distal middle third of the right quadriceps and right third humeral. Given multiple metastases, the asymptomatic nature of the disease, and the need of a therapeutic rest we decided to maintain an expectant approach with the therapeutic rest from January 2014-January 2015. At the end of January 2015, a CT/PET evaluation revealed an increase and the development of a new nodule in the lung, an increase of the hepatic metastases and pathological captures at muscular level and the right axillary lymph node. Given the metastatic progression of the disease, we shared with the patient the option of a 3rd-line treatment with trabectedin 1.3 mg/m^2 given as a 24-hour infusion every 3 weeks. Between January 2015 and May 2018 the patient completed a total of 36 cycles of trabectedin. The disease was stable after 5 cycles and a partial response was confirmed after 10, 13, 17, 19, 23, 29, and 34 cycle of treatment. The progression-free survival of the patient from the start of the treatment with trabectedin was 36 months, whereas the overall survival from diagnosis was 117 months. Currently, trabectedin therapy is maintained, with no signs of cumulative toxicity and with adequate clinical and analytical tolerance of the treatment.

Conclusion: Our findings suggest that trabectedin is an effective (by increasing survival and quality of life) and safe option for prolonged treatment of heavily pretreated metastatic LMS. Future clinical trials are warranted to better understand the mechanism of prolonged response to trabectedin and to identify predictive biomarkers for response to trabectedin.

PO 025 3036640

THE CLINICAL OUTCOMES OF UNDIFFERENTIATED PLEOMORPHIC SARCOMA: A SINGLE CENTER EXPERIENCE OF TWO DECADES

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Objective: Undifferentiated pleomorphic sarcoma (UPS), so-called malignant fibrous histiocytoma (MFH) previously, is the most common type of adult soft tissue sarcoma, usually occurred in old age. As the incidence of sarcoma is low itself, very little is known about the UPS, including clinical behavior, proper treatment strategies and prognosis. The mainstream of current strategy is complete surgical resection followed by adjuvant radio- or chemotherapy to reduce the risk of recurrence in localized UPS. The aim of this study was to assess the clinical course and oncologic outcome of UPS.

Methods: We retrospectively reviewed the all consecutive patients who were treated with UPS in Asan Medical Center, between January 1995 and December 2016, using the clinical database system of our institution (Asan BiomedicaL research Environment, ABLE). The patients whose stored data were incorrect or insufficient were excluded in this analysis.

Results: A total of 205 patients were included in this study with the median follow-up of 49.8 (95% CI 39.5-60.1) months. There were 121 males (59%) and 84 females (41%), and the median age of patients was 59 years at the time of diagnosis. The most frequently involved primary site was extremities (n=97, 47.3 %), followed by abdomen and pelvis (n=55, 26.8 %), thorax (n=36, 17.6 %), and head and neck (n=17, 8.3 %). Twenty one patients (10.2 %) had initially metastatic disease and the median overall survival (OS) of these patients was 17.75 (95% CI 0.0-37.2) months. Among the patients with localized disease, 176 patients underwent curative-intent surgical resection. The R0 resection rate was 65.3% and 60.8 % of patients (n=107) received adjuvant treatment; radiotherapy (n=58), chemotherapy (n=24), or both (n=25). Recurrence was observed in 72 patients (40.9%) after curative surgery, and a third of them (n=24) were local recurrence. The median relapse-free survival (RFS) was 117.4 (95% CI 57.2-177.7) months and improvement of RFS with adjuvant treatment was not observed (5-year RFS, 55.0% vs 54.8%, *P*=0.234). The estimated 5-year OS in these patients was 75.6% and the higher 5-year overall survival was observed in patients receiving adjuvant therapy (81.8% vs 65.2%, *P*=0.002). However, more than half of patients in this group (57.0% vs 33.3%, *P*=0.004) had favorable extremity sarcoma.

Conclusion: In this report, we presented clinical outcomes of UPS patients in real world setting with relatively large number patients and long term follow-up durations. The OS of metastatic UPS patients was comparable with previous studies. Of note, no significant RFS benefit was observed in localized UPS patients with adjuvant treatment following surgical resection in this study. However, these results are limited by heterogeneous patient population and its retrospective nature. Further studies are needed to comprehensively understand the course of UPS and apply the best treatment to each patient.

PO 026 3037500

PANCREATIC METASTASIS OF INTIMAL SARCOMA: A CASE REPORT AND REVIEW OF LITERATURE

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Oncologie, CHUV, Lausanne, Switzerland

Objective: Pancreatic metastasis from Soft tissue sarcoma (sts) is quite rare and a standard regiment has not been established. In this report we present a case of solitary pancreatic metastasis from intimal sarcoma and a review of literature of pancreatic metastasis of STS.

Methods: A 51 years old woman who has a history of left pneumectomy of a 11 cm intimal sarcoma in 2012 with MDM2 amplification by immunohistochemistry. She received every 3 months follow up with computed tomography. The patient was free of disease until Februar 2014 when bilateral adrenal metastasis confirmed by biopsie was diagnosed. The patient was treated with systematic chemotherapy of adriamycin/ifosfamid with partial response followed by adrenal resection. The regular follow up computed tomography in February 2016, 12 months after left adrenal metastases resection evidenced a solitary mass of the head of pancreas indicating potentially malignant lesion. An MRI evidenced a solitary mass of 3.2 cm in diameter localized at the head of pancreas. Fluorodeoxyglucose positron emission tomography (PET) showed metabolic activity only at the level of the head of pancreas, with no evidence of abnormal uptake in the whole body. The patient was asymptomatic and laboratory tests of routine biochemical parameters were within their respective normal range including CA 19-9. The case was discussed within the multidisciplinary approach and it was judged that the metastases could be completely resected without residual tissue. In march 2015 pancreaticoduodenectomy with excision of whole gallbladder and loco regional lymph nodes dissection was performed. The histopathological report confirmed the diagnostic of pancreatic metastasis of the intimal high-grade sarcoma. Since the patient undergoes diagnostic surveillance with computed tomography every 3 months and twenty four months postoperatively she is doing well with no sign of relapse.

Results: Metastases to the pancreas are rare and represent only 1-2% of pancreatic malignancies. Pancreatic metastases are usually not discovered until widespread systemic disease therefore no curative treatment is applicable. Most frequently, metastases to the pancreas originate from primary renal cell carcinoma, lung cancer, melanoma and gastrointestinal cancer. The cases of asymptomatic pancreatic metastases are rare, usually pancreatic metastases being associated with multiple localization of metastases to other organs.
An intimal sarcoma with solitary metastasis of the pancreas is an extremely rare condition, therefor a very unusual case. To our knowledge, no case has been so far presented to literature. For our patient the metastatic tumor was discovered incidentally during diagnostic surveillance. The treatment is difficult and non-standardize, as indications for pancreatic resection of metastases have not yet been clearly defined. We have chosen to do surgical excision though prognosis after such approach is not yet established because of the rarity of candidates for pancreatectomy. We do know that aggressive surgical resection of pulmonary metastases from soft-tissue sarcoma has proved a 5 year survival rate after pulmonary resection to 39%.
Wiltberger et al. prove survival benefit of the surgical treatment of pancreatic metastasis in a retrospective analysis of

676 patients who underwent pancreatic surgery between 1994-2012 at the University Hospital in Leipzig. The authors have proved good long term survival for patients undergoing resection of pancreatic metastases [8]. Few cases found in the literature, which underwent surgical resection, are listed in Table 1, showing that pancreatic metastasectomy can be associated with favorable morbidity and mortality.

Conclusion: In conclusion, pancreatic metastasis from STS are uncommon, little is known about their epidemiological aspects and biological behavior. In this context, we underlie the necessity of meticulous investigation of lesions of the hepatobiliary system when the patient has a past history of sarcoma.

PO 027 3040616

GADOLINIUM-BASED CONTRAST INCREASES DIAGNOSTIC EFFICACY FOR DETECTION OF RECURRENT SOFT TISSUE SARCOMAS

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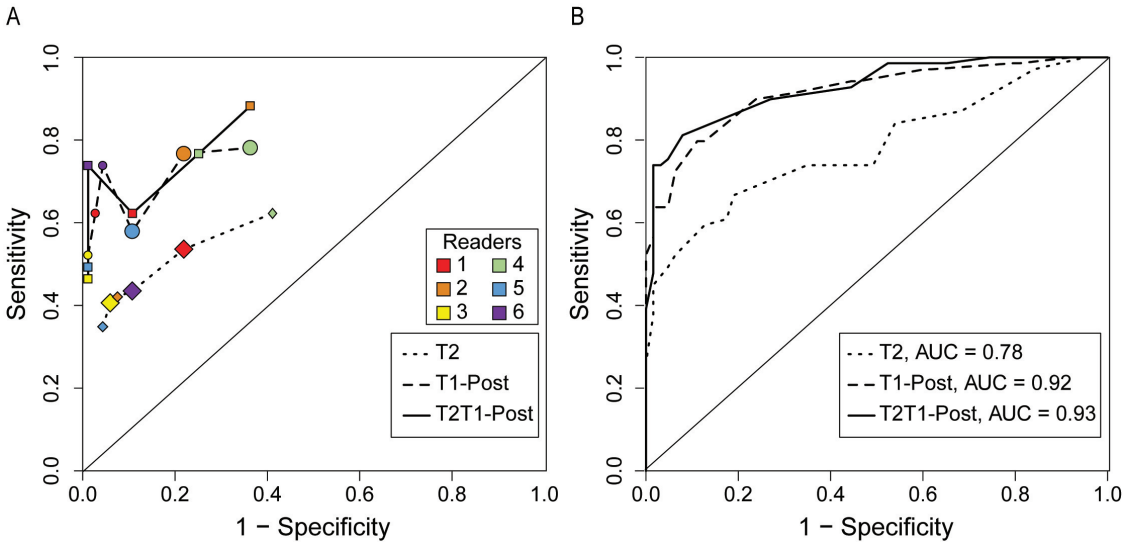
[2]Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Objective: To determine the utility of gadolinium-based contrast administration in detection of recurrent soft tissue sarcomas.

Methods: Following institutional review board approval, a retrospective search from 1/1/2009 to 12/31/2014 for patients with soft tissue sarcomas of the extremity and body wall yielded locally recurrent disease in 69 patients, with pathology serving as the reference standard. The control group consisted of cases in the same patients at a different time point without recurrent disease, but with postoperative findings (e.g., seroma, hematoma, and granulation tissue), resulting in 63 age- and gender-matched controls. Six readers from the musculoskeletal imaging section at a tertiary cancer center with a mean of 30 years of experience were blinded to the pathology results and asked to review the 132 randomized MRI studies and determine if recurrence was present on a 5-point scale (1, definitely; 2, probably; 3, indeterminate; 4; probably not; 5, definitely not). Images in the axial plane were presented to each reader in 3 different groups with a minimum of 2 weeks between each set: 1) T1 pre-contrast and T2 (T1T2), 2) T1 pre-contrast and T1-post-contrast (T1T1-Post), and 3) T1 pre-contrast, T2, and T1-post contrast (T1T2T1-Post). No consensus readings occurred. Ratings were dichotomized by grouping a score of 1-2 as positive for recurrence, and 3-5 as negative. Sensitivity and specificity were calculated using McNemar's test.

Results: Mean sensitivity was 54%, 70%, and 71% for the T1T2, T1T1-Post, and T1T2T1-Post groups, respectively. Mean specificity was 92%, 94%, and 97% for the same groups, respectively. Readers interpreting the image sets with contrast (T1T1-Post and T1T2T1-Post) had significantly higher sensitivity for detection of recurrence than when interpreting the non-contrast (T1T2) images (p = 0.001 and 0.008, respectively). There was no significant difference in sensitivity between the T1T2T1-Post and T1T1-Post (p = 0.65). There was no significant difference in specificity between the 3 groups (p> 0.05).

Conclusion: Gadolinium based intravenous contrast administration results in improved sensitivity for detection of locally recurrent soft tissue sarcomas.



PO 028 3040867

FAMILIAL CASTLEMAN'S DISEASE AS PRECURSOR TO EGFR-OVEREXPRESSED FOLLICULAR DENDRITIC CELL SARCOMA, UNRESPONSIVE TO ERLOTINIB

Benjamin Powers[1], Joshua Mammen[2], Alykhan Nagji[4], Mark Thompson[6], Da Zhang[3], Ziyan Pessetto[5], Andrew Godwin[5]
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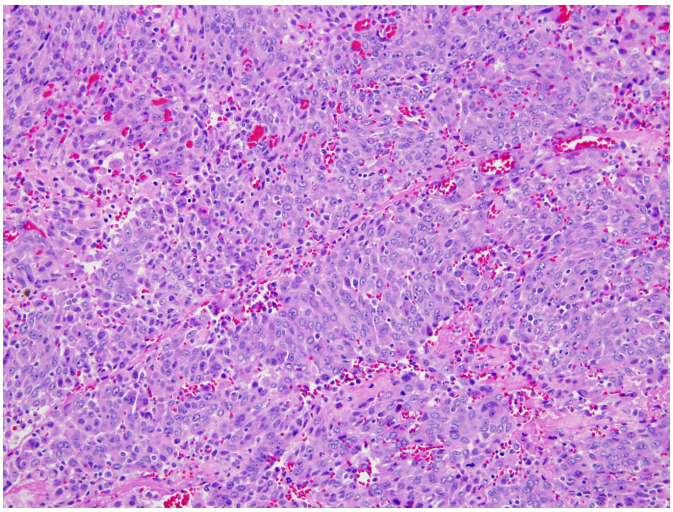
Objective: A 47 year old man noticed swelling and tenderness of right shoulder, attributing the symptoms to his construction job. It did not respond to conservative therapy, so MRI of the right shoulder was done, showing soft tissue mass (12.6 x 6.9 x 5.5 cm) deep to the trapezius, superficial to the supraspinatus, posterior to clavicle with medial portion abutting the chest wall, with 3-4 smaller masses located immediately superior to the brachial plexus and subclavian vessels without evidence of invasion, suspicious for malignant adenopathy.

Biopsy was conclusive for follicular dendritic cell sarcoma (FDCS). IHC stains showed tumor cells positive for CD21, CD35, with scattered background positivity for CD45, CD3, and CD20, negative for CD1a, pan CK, S-100, CD34, p40, desmin, and SOX-10. Ki-67 was variable, 40-80% (see histology). EBV and HHV-8 were negative. PET scan showed right supraclavicular mass, but also 1.4cm right lower lobe lung nodule, a 6cm retroperitoneal mass, a right external iliac node, and a right thigh mass.
His mother, sister, brother, maternal cousin and maternal aunt all had Castleman's disease, which can be a precursor to FDCS. His brother died due to FDCS. There is no published hereditary/familial cause of Castleman's disease, or FDCS for that matter. Sun et al showed EGFR overexpression in both disease states ("Epidermal growth factor receptor expression in follicular dendritic cells: a shared feature of follicular dendritic cell sarcoma and Castleman's disease." *Hum Pathol*. 2003 Sep;34(9):835-40) and his showed EGFR overexpression via IHC.
He was started on neoadjuvant CHOP IV q 21days. His pain worsened over 3 cycles, and CT showed no significant decrease, so surgery was pursued. Path showed R0 resection, with 85% of tumor viable. He then received adjuvant radiation (60Gy) in the R neck/axilla.
Repeat PET after radiation showed resolution of activity in R neck, but stable retroperitoneal mass, thigh, pulmonary nodule, and development of left hilar node, lateral left pleural-based lesion. Biopsy of pleural-based lesion was consistent with FDCS. Within two weeks, he started coughing and running fevers, and found to have loculated left pleural effusion needing drained.
At this point, we wanted to explore activity of erlotinib in refractory EGFR(+) follicular dendritic cell sarcoma.

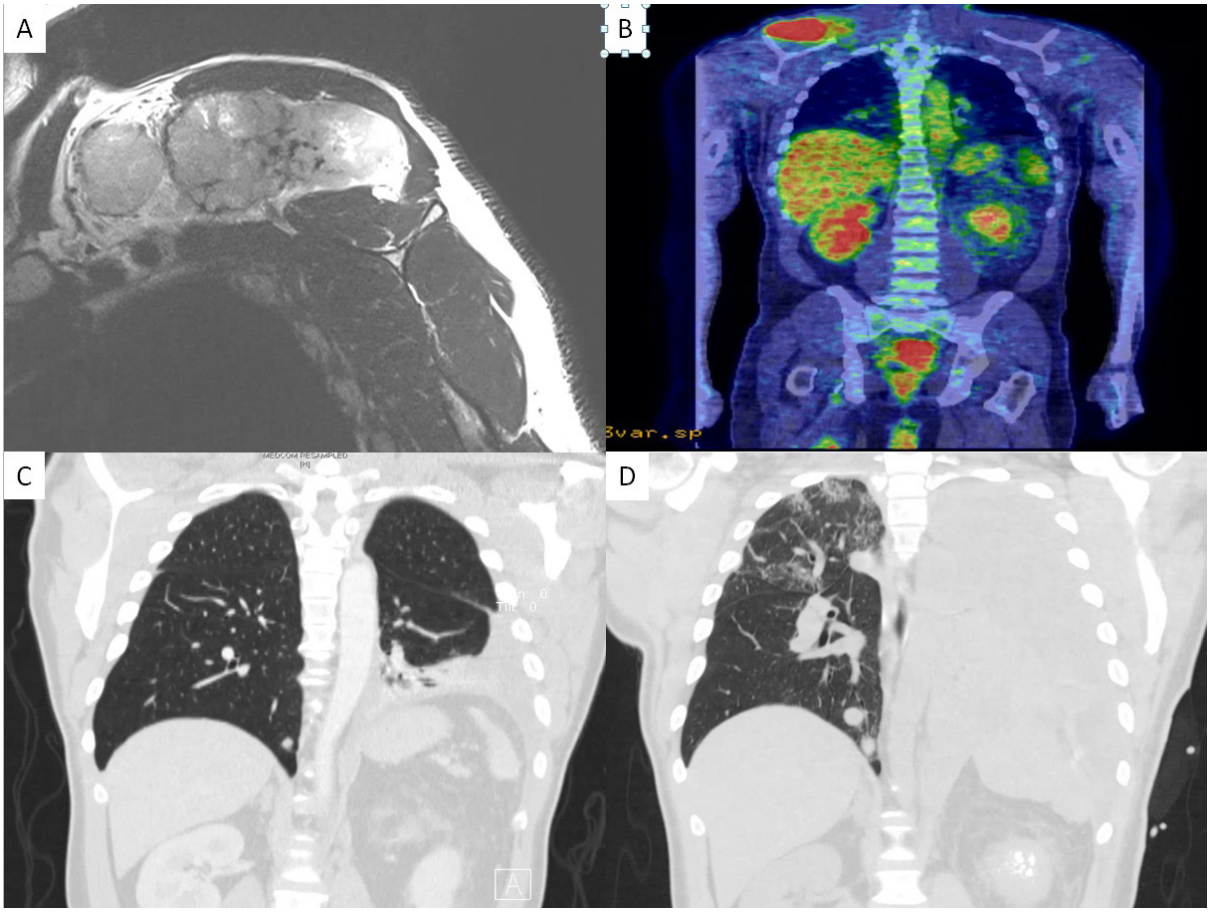
Methods: While finishing antibiotics, he started erlotinib 150mg daily as off-label use for treatment of this tumor.

Results: A week into erlotinib, he manifested acneiform-rash and skin peeling, which we hoped would signify a response. At a month, he had lost weight and appetite due to mouth sores, so drug was temporarily held. Within the week of stopping erlotinib, he started with cough, fever, shortness of air, and pain in the left lung base along his incision site, with no breath sounds on left side. CT chest showed large left pleural effusion with progression of left pleural thickening and nodularity, multiple right pulmonary metastases, large left anterior diaphragmatic mass, progression of right upper lobe volume loss and bronchiectasis related to radiation pneumonitis, and a stable partially calcified left retroperitoneal mass. 2L of red hemorrhagic fluid were expressed via thoracentesis, so he was taken emergently for thoracotomy, partial decortication and evacuation of hemothorax. Path showed recurrent FDCS of both soft tissue and pleural rind. This was tested for genetic mutations; he had an unknown variant involving exon 1 of ALK gene (p.A206V); EGFR mutation was not seen.
He underwent palliative radiation (30Gy) to left lung base, but he decided against more systemic treatment. He made the most of life for another four months before passing away at home peacefully.

Conclusion: Erlotinib did not help in this refractory case of EGFR-expressing FDCS. We have undertaken whole genome DNA sequencing on various family members both with and without Castleman's disease to determine what, if any, could be leading to this particular hereditary pattern.



Excisional biopsy from a lymph node replaced by plump spindle cells with oval nuclei, vesicular chromatin, distinct nucleoli and scattered small lymphocytes.



A. Sagittal T2 MRI showing lobulated mass in right supraclavicular area
B. Staging PET at original diagnosis, showing right shoulder mass, right lung nodule, left retroperitoneal mass, right external iliac node and right thigh mass
C. CT chest with contrast at initiation of erlotinib
D. CT chest without contrast after one month of erlotinib, showing hemothorax involving entire left lung space, progressive disease of right lung mets

PO 029 3041688

MEASURING VOLUME WHERE IT MATTERS - MRI BASED SEGMENTATION

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Objective: Utility of MRI based segmentation and volume measurement has been limited to research do to time constraints and postprocessing needs. Currently the technology exists on standard workstations. The purpose of the study was to show that even a surgeon could segment and measure volume on two sequential MRI scans using the tumor tracking modality in less than 10 minutes.

Methods: Tumor size and growth can be measured with several methods. RESIST uses maximal diameter (2 data points). Long and short axis diameters (4 data points), 3D (including Z axis- 6 data points) or volume measurements (numerous data points). The gold standard imaging for sarcomas and connective tissue tumors has long been MRI scans. Recently, an algorithm has been developed that enables segmentation and volume measurement of a tumor on MRI using various series (axial, coronal and sagittal). This is currently accessible on a commercial radiology workstation. Assessing volume in connective tissue tumors is important especially when analysing asymmetric tumors where assessing volume from diameter measurements compared to segmentation and volume measurements differ significantly. Changes in tumor size and volume become increasingly important when this is the basis for treatment decisions. This includes-
Tumor growth as an indication to treat-
In desmoid tumors the initial treatment is watchful waiting. Tumors that grow by 20% are an indication to begin chemotherapy treatment.
In a chondral tumors where biopsy does not denileate well between benign and grade I and II tumors. Change in size and pain are better indicators (Sacral and spine).
Tumor decrease in size as an indicator of response to treatment-
Bone tumors (Ewing sarcoma) with a soft tissue component are treated with neoadjuvant chemotherapy. When the soft tissue component shrinks this may aid in surgery and more chemotherapy can than be given upfront (Pelvic tumor) Soft tissue sarcomas when large in young patients are given chemotherapy. Tumor size can assessed after 2 rounds of chemo and 2 additional rounds may be given if there is stable disease, whereas chemo may be discarded in progressive disease.
Tumor stability as an indication to continue treatment-
Giant cell tumor of sacrum may be inoperable, these are treated with Denosumab for life. The dosage and treatment interval changes over the years and should depend on tumor growth and size. (Sacral GCT)

Results: A total of twenty patients with 40 MRI scans were segmented and volume was measured by 2 orthopaedic oncology surgeons in keeping with the 10 minute limitation for each patient.

Conclusion: This supports the applicability of volume measurements as a quantitative measure for clinical treatment decisions. Clinicians should be aware that they can request and expect to receive volume comparisons on their MRI radiology reports.

PO 030 3042771

FIRST CASE REPORT OF A DRAMATIC RESPONSE TO OLARATUMAB IN A PATIENT WITH MALIGNANT PHYLLODES TUMOR WITH MULTIPLE METASTASIS

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Objective: Phyllodes tumor of the breast is a fibroepithelial neoplasm, and malignant phyllodes tumor accounts for 10-30% of all phyllodes tumors. Although it can be cured with surgical resection, an inoperable case, such as local recurrence or metastasis, carries a poor prognosis with a median survival time of less than two years. Chemotherapy has been used for metastatic phyllodes tumor, but there is no clear recommended regimen due to the relatively rare incidence of the disease as well as the variety of drugs used for systemic treatment. The authors report a first case of a remarkable response to olaratumab in a patient with multiple metastatic malignant phyllodes tumor.

Methods: Case report.

Results: A 40-year-old Korean woman visited breast surgery department of Inha university hospital in December 2016

because of a 24cm sized palpable mass in her right breast. She underwent right mastectomy, and the postoperative biopsy result was malignant phyllodes tumor. In the stromal element of the tumor, approximately 12-15 mitotic figures were seen in 10 high power fields, and the composing cells showed sarcomatous stromal overgrowth pattern. The Ki-67 labeling index was 10-20%. One year after the breast surgery, on the regular follow up period, enhanced computed tomography (CT) including the chest and abdominal area was performed due to her newly-onset severe epigastric discomfort. The CT revealed a huge mass, approximately 20cm-sized, in the gastric area and multiple metastatic lesions in liver and lung. The pathologic diagnosis of the liver and gastric endoscopic biopsy was consistent with metastatic malignant phyllodes tumor. Immunohistochemically, all the tumor cells of the stroma were strongly positive for SMA and vimentin. Tumor cells were negative for desmin, iron, and cytokeratin 7. In the situation that there was no recommended standard treatment for the disease, chemotherapy consisted of olaratumab and doxorubicin to target metastatic malignant phyllodes tumor was started. After two cycles of treatment, PET-CT showed a marked decrease in tumor volume of more than 30% and FDG uptake. The patient is now receiving her fourth cycle of chemotherapy.

Conclusion: Although further trials are needed to identify the precise efficacy of this combination, olaratumab and doxorubicin, the regimen might be useful for treatment of metastatic malignant phyllodes tumor.

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