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2017 Annual Meeting

November 8 - 11, 2017

Grand Wailea Resort • Maui, Hawaii

Final Program

Stephen Lessnick, M.D., Ph.D.
2017 CTOS President

Irene Andrulis, Ph.D. & Damon Reed, M.D.
Program Co-Chairs

Maui 2017

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CTOS Annual Meeting

November 8 - 11, 2017

Maui, Hawaii

Welcome to the 22nd Connective Tissue Oncology Society meeting in Maui, Hawaii!

We are delighted to present the CTOS Annual Meeting. We have been fortunate to assemble and work with a team of CTOS members that has created the exciting program that will continue to provide the latest research findings in sarcoma. This meeting has been guided by your collective voice from last year's survey. The abstracts have been thoroughly reviewed by a pool of reviewers and session moderators who set the final agenda for the presentations.

We have worked to capture the sense that this growing organization may be able to play an even larger role for the multidisciplinary, collaborative, international sarcoma community. Special sessions on Saturday have been designed for all attendees to enable discussions towards how CTOS may continue to evolve. We would like more of your feedback and ideas. Please talk with these session leaders and share your ideas. The conference app will be used to solicit your ideas throughout the meeting.

Other highlights of this year's program include special sessions on Epithelioid Sarcoma, Trials in rare sarcomas, and New Research Technologies. Of course this year's gala event – a luau – will be spectacular, followed by dancing into the late evening continuing the CTOS tradition.

We plan to finish the meeting by coming together during the Future Multidisciplinary Collaborative Session with the goal of developing a clear vision for future CTOS meetings and roles.

We are aware that the program competes with enticing beaches and adventure right outside our doors at the beautiful Grand Wailea Resort, but we are excited by the interest of the CTOS membership in active participation at the Annual Meeting and the opportunities that it provides for the members.

Sincerely yours,

Irene Andrulis, PhD
2017 CTOS Program Co-Chair

Damon Reed, MD
2017 CTOS Program Co-Chair

Steve Lessnick, MD, PhD
2017 CTOS President

Welcome

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Maui 2017

2017 Board of Directors

2017 Annual Meeting

Program At-a-Glance

Wednesday, 8 November, 2017

11:00 am – 5:00 pm	Poster Set Up	*Haleakala 2 & 3*
12:00 pm – 5:00 pm	Registration	*Haleakala Foyer*
5:00 pm – 7:00 pm	Welcome Reception	*Chapel Garden*

Thursday, 9 November, 2017

6:30 am – 6:00 pm	Registration	*Haleakala Foyer*
7:00 am – 8:00 am	Continental Breakfast and Poster Viewing	*Haleakala Foyer*
8:00 am – 8:30 am	**Welcome / Opening Remarks**	*Haleakala 1*
8:30 am – 9:30 am	**SESSION 1 – Surgical Oncology**	*Haleakala 1*
9:30 am – 10:30 am	**SESSION 2 – Radiation Oncology**	*Haleakala 1*
10:30 am – 11:00 am	Coffee Break and Poster Viewing	*Haleakala Foyer*
11:00 am – 12:30 pm	**SYMPOSIUM 1 – Medical, Pediatric and Young Adult Oncology**	*Haleakala 1*
12:30 pm – 1:30 pm	Lunch	*Haleakala Foyer*
1:30 pm – 2:15 pm	**SPECIAL SESSION 1 – Sarcoma of the Year: Epithelioid Sarcoma**	*Haleakala 1*
2:15 pm – 3:00 pm	**SESSION 3 – Soft Tissue Sarcoma**	*Haleakala 1*
3:00 pm – 3:15 pm	Afternoon Break and Poster Viewing	*Haleakala Foyer*
3:15 pm – 3:45 pm	**SESSION 4 – Pathology**	*Haleakala 1*
3:45 pm – 5:15 pm	**SYMPOSIUM 2 – Basic Science**	*Haleakala 1*
5:15 pm – 5:45 pm	**Young Investigator Award Winners**	*Haleakala 1*
5:45 pm – 6:30 pm	Poster Session 1 and Reception	*Haleakala 2 & 3*

Friday, 10 November, 2017

6:30 am – 5:00 pm	Registration	*Haleakala Foyer*
7:00 am – 8:00 am	Continental Breakfast and Poster Viewing	*Haleakala 2 & 3*
8:00 am – 9:45 am	**SPECIAL SESSION 2 – Trials/Approaches in Rarer Sarcomas, Desmoid Tumor**	*Haleakala 1*
9:45 am – 10:30am	**SESSION 5 – GIST**	*Haleakala 1*
10:30 am – 11:00 am	Coffee Break and Poster Viewing	*Haleakala 2 & 3*
11:00 am – 12 noon	**Nina Axelrad Lecture: "Ewing Sarcoma: The Dumb Drugs Have Gotten Us a Long Way...." – Holcombe Grier**	*Haleakala 1*
12 noon – 1:00 pm	**Mentorship Lunch**	*Haleakala Foyer*
1:00 pm – 2:00 pm	**SESSION 6 – Osteosarcoma & Chondrosarcoma**	*Haleakala 1*
2:00 pm – 3:00 pm	**SESSION 7 – Ewing Sarcoma**	*Haleakala 1*
3:00 pm – 4:00 pm	Poster Session 2 and Afternoon Break	*Haleakala 2 & 3*
4:00 pm – 5:00 pm	**SYMPOSIUM 3 – New Research Technologies**	*Haleakala 1*
5:30 pm – 10:00 pm	Gala – Luau	*Molokini Garden*
10:00 pm	Gala After Party	*Haleakala 4 & 5*

Saturday, 11 November, 2017

6:30 am – 5:00 pm	Registration	*Haleakala Foyer*
7:00 am – 8:00 am	Executive Board Meeting	*Pikake Room*
7:00 am – 8:00 am	Continental Breakfast and Poster Viewing	*Haleakala 2 & 3*
8:00 am – 10:00 am	**SARC**	*Haleakala 1*
10:00 am – 10:30 am	Coffee Break and Poster Viewing	*Haleakala 2 & 3*
10:30 am – 12 noon	**PARALLEL BREAKOUT SESSION 1 – Surgical/Clinical**	*Haleakala 1*
10:30 am – 12 noon	**PARALLEL BREAKOUT SESSION 2 – Basic Science/Translational**	*Haleakala 4 & 5*
12 noon – 1:00 pm	**HERMAN SUIT LECTURE – Benjamin A. Alman**	*Haleakala 1*
1:00 pm – 2:00 pm	Lunch	*Haleakala Foyer*
1:00 pm – 2:00 pm	Board of Directors Meeting	*Pikake Room*
2:00 pm – 3:00 pm	**SESSION 8 – Population Sciences, Survivorships**	*Haleakala 1*
3:00 pm – 3:30 pm	Afternoon Break	*Haleakala Foyer*
3:30 pm – 5:00 pm	**PLENARY SESSION – Future Multidisciplinary Collaborative**	*Haleakala 1*
5:00 pm – 6:00 pm	CTOS Members' Business Meeting	*Haleakala 1*
6:00 pm	ADJOURN	

Hong Hu, Research Advisor,
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Wednesday, 8 November, 2017

5:00 pm – 7:00 pm	Welcome Reception	*Chapel Garden*

Thursday, 9 November, 2017

6:30 am – 6:00 pm	Registration	*Haleakala Foyer*
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8:00 am – 8:30 am	Welcome / Opening Remarks	*Haleakala 1*

8:30 am – 9:30 am — – SESSION 1 – — *Haleakala 1*

Surgical Oncology

Moderators: **Carolyn Nessim** & **William Tseng**

Paper 001 #2756819

INACCURACY IN SARCOMA CASE CODING: UNDERESTIMATION OF THE BURDEN OF SARCOMA WITHIN A SINGLE INSTITUTION

Heather Lyu, MD[1]*; Leah A. Stein*[1]*; Lily V. Saadat*[1]*; Sheila N. Phicil*[1]*; Jiping Wang*[1]*; Marco Ferrone*[2]*; John E. Ready*[2]*; Monica M. Bertagnolli*[1]*; Chandrajit P. Raut, MD*[1]
[1]*Surgery, Brigham and Women's Hospital, Boston, MA, USA;*
[2]*Orthopedic Surgery, Brigham and Women's Hospital, Boston, MA, USA*

Paper 002 #2782851

PREDICTING SURVIVAL IN PATIENTS (PTS) UNDERGOING RESECTION FOR LOCOREGIONALLY RECURRENT RETROPERITONEAL SARCOMA (LRRPS): A STUDY AND NOMOGRAM FROM THE TRANSATLANTIC RETROPERITONEAL SARCOMA WORKING GROUP (TARPSWG)

Chandrajit P. Raut, MD[1]*; Dario Callegaro*[2]*; Francesco Barretta*[2]*; Piotr Rutkowski, MD, PhD*[3]*; Jean-Yves Blay*[4]*; Guy Lahat*[5]*; Dirk C. Strauss*[6]*; Ricardo Gonzalez*[7]*; Nita Ahuja*[8]*; Giovanni Grignani*[9]*; Vittorio Quagliuolo*[10]*; Eberhard Stoeckle*[11]*; Antonino de Paoli*[12]*; Venu Pillarisetty*[13]*; Carolyn Nessim*[14]*; Carol J. Swallow*[15]*; Sanjay Bagaria*[16]*; Robert Canter*[17]*; John Mullen*[18]*; Hans J. Gelderblom*[19]*; Elisabetta Pennacchioli*[20]*; Frits van Coevorden*[21]*; Kenneth Cardona*[22]*; Rosalba Miceli*[2]*; Alessandro Gronchi*[2]
[1]*Brigham and Women's Hospital, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA;* [2]*Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy;* [3]*Maria Sklodowska-Curie Memorial Cancer Center, Institute of Oncology, Warsaw, Poland;* [4]*Centre Leon Berard, Lyon, France;* [5]*Tel Aviv Sourasky Medical Center, Tel Aviv, Israel;* [6]*Royal Marsden Hospital, London, UK;* [7]*Moffitt Cancer Center, Tampa, FL, USA;* [8]*Johns Hopkins University School of Medicine, Baltimore, MD, USA;* [9]*Istituto di Candiolo IRCCS, Torino, Italy;* [10]*Istituto Clinico Humanitas IRCCS, Milan, Italy;* [11]*Institut Bergonié, Regional Cancer Centre, Bordeaux Cedex, France;* [12]*Centro di Riferimento Oncologico,*

Aviano, Italy; [13]Seattle Cancer Care Alliance, University of Washington School of Medicine, Seattle, WA, USA; [14]The Ottawa Hospital, University of Ottawa, Ottawa, Canada; [15]Mount Sinai Hospital, Princess Margaret Hospital, University of Toronto, Toronto, Canada; [16]Mayo Clinic Jacksonville, Jacksonville, FL; [17]University of California-Davis School of Medicine, Davis, CA, USA; [18]Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; [19]Leiden University Medical Center, Leiden, Netherlands; [20]Istituto Europeo di Oncologia, Milano, Italy; [21]Netherlands Cancer Institute, Amsterdam, The Netherlands; [22]Emory University School of Medicine, Atlanta, GA, USA

Paper 003 #2797875

NEEDLE TRACT RECURRENCES FOLLOWING CORE BIOPSIES IN RETROPERITONEAL SARCOMA

***Winan J. van Houdt, MD, PhD**[1]; A. M. Schrijver[2]; Ruben Cohen-Hallalah[1]; Nikolaos Memos, Clinical Fellow[1]; Myles J. Smith[1]; Nikos Fotiades[3]; Andrew J. Hayes[1]; Frits van Coevorden[2]; Dirk C. Strauss[1]*

[1]Department of Surgical Oncology, the Royal Marsden Hospital, London, United Kingdom; [2]Department of Surgical Oncology, Netherlands Cancer Institute, Amsterdam, Netherlands; [3]Department of Radiology, the Royal Marsden Hospital, London, United Kingdom

Paper 004 #2792834

ISOLATED LIMB PERFUSION FOR LOCALLY ADVANCED ANGIOSARCOMA IN EXTREMITIES: A MULTI-CENTER STUDY

***Eva A. Huis in 't Veld, BSc**[1]; Dirk J. Grünhagen[2]; Kees Verhoef[2]; Henry G. Smith[1]; Alexander C. van Akkooi[3]; Robin L. Jones[4]; Frits van Coevorden[3]; Andrew J. Hayes[1]; Winan J. van Houdt[1]*

[1]Sarcoma and Melanoma Surgery, Royal Marsden Hospital, London, United Kingdom; [2]Department of Surgical Oncology, Erasmus MC - Daniel den Hoed Cancer Center, Rotterdam, Netherlands; [3]Department of Surgical Oncology, Netherlands Cancer Institute - Antoni van Leeuwenhoek, Amsterdam, Netherlands; [4]Sarcoma Unit, Royal Marsden Hospital and Institute of Cancer Research, London, United Kingdom

9:30 am – 10:30 am – SESSION 2 – *Haleakala 1*

Radiation Oncology

Moderators: **Beth Baldini** & **David Kirsch**

Paper 005 #2804480

5-DAY HYPOFRACTIONATED PREOPERATIVE RADIOTHERAPY IN SOFT TISSUE SARCOMA: PRELIMINARY TOXICITY AND PATHOLOGIC OUTCOMES FROM A PROSPECTIVE PHASE 1/2 CLINICAL TRIAL

***Anusha Kalbasi, MD**[1]; Mitchell Kamrava[2]; Scott Nelson[1]; Sarah M. Dry[1]; Jackie Hernandez[1]; Bartosz Chmielowski[1]; Noah Federman[1]; Arun Singh, MD[1]; Susan Bukata[1]; Nicholas Bernthal[1]; Michael Steinberg[1]; Fritz Eilber[1]*

[1]University of California, Los Angeles, Los Angeles, CA, USA; [2]Cedars-Sinai Medical Center, Los Angeles, CA, USA

Paper 006 #2774385

SUBSTANTIAL VOLUME CHANGES DURING PREOPERATIVE RADIOTHERAPY IN EXTREMITY SOFT TISSUE SARCOMA PATIENTS

***Rick Haas, MD, PhD**; Suzanne van Beek; Anja Betgen; Shaheen Ali; Christoph Schneider; Fenna Heres Diddens; Astrid Scholten; Peter Remeijer*

NKI-AVL, Amsterdam, Netherlands

Paper 007 #2804922

A COMPARISION OF DIFFERENT TREATMENT PARADIGMS FOR SACRAL CHORDOMA: DOES PREOPERATIVE RADIOTHERAPY IMPROVE OUTCOME?

Matthew T. Houdek, MD[1]*; Peter Rose*[1]*; Joseph Schwab*[2]*; Michael Yaszemski*[1]*; Jay S. Wunder*[3]*; John Healey*[4]*; Francis Hornicek*[5]*; Patrick Boland*[4]*; Franklin H. Sim*[1]*; Peter Ferguson*[3]
[1]Orthopedic Surgery, Mayo Clinic, Rochester, MN, USA; [2]Orthopedic Surgery, Harvard University, Boston, MA, USA; [3]Orthopedic Oncology, Mount Sinai Hospital, Toronto, ON, Canada; [4]Orthopedic Surgery, Memorial Sloan Kettering, New York, NY, USA; [5]Orthopedic Surgery, University of California, Los Angeles, Los Angles, CA, USA

Paper 008 #2772139

MRI SURVEILLANCE FOR LOCAL RECURRENCE IN EXTREMITY SOFT TISSUE SARCOMA

Jong Woong Park[2]*; Han-Soo Kim*[1]*; Yong Sung Kim*[1]*;* ***Ilkyu Han, MD, PhD***[1]
[1]Orthopedic Surgery, Seoul National University Hospital, Seoul, Korea (the Republic of); [2]National Cancer Center, Goyang-Si, Korea (the Republic of)

10:30 am – 11:00 am Coffee Break and Poster Viewing *Haleakala Foyer*

11:00 am – 12:30 pm – SYMPOSIUM 1 – *Haleakala 1*

Medical, Pediatric and Young Adult Oncology

Moderators: **Lara Davis** & **Andy Wagner**

Paper 009 #2762964

ANTITUMOR ACTIVITY OF AXITINIB PLUS PEMBROLIZUMAB IN A PHASE II TRIAL FOR PATIENTS WITH ADVANCED ALVEOLAR SOFT PART SARCOMA (ASPS) AND OTHER SOFT TISSUE SARCOMAS

Breelyn A. Wilky, MD[1]*; Eric Wieder*[1]*; Despina Kolonias*[1]*; Ty Subhawong*[2]*; Matteo Trucco*[3]*; Andrew Rosenberg*[4]*; Darcy Kerr*[4]*; Deukwoo Kwon*[5]*; Efrosyni Sfakianaki*[2]*; Krishna Komanduri*[1]*; Jonathan Trent*[1]
[1]Hematology/Oncology, Sylvester Comprehensive Cancer Center - University of Miami Miller School of Medicine, Miami, FL, USA; [2]Radiology, University of Miami Miller School of Medicine, Miami, FL, USA; [3]Pediatrics, University of Miami Miller School of Medicine, Miami, FL, USA; [4]Pathology, University of Miami Miller School of Medicine, Miami, FL, USA; [5]Biostatistics, Sylvester Comprehensive Cancer Center, Miami, FL, USA

Paper 010 #2804799

A PHASE II MULTI-ARM STUDY TO TEST THE EFFICACY OF DURVALUMAB AND TREMELIMUMAB IN MULTIPLE SARCOMA SUBTYPES

Neeta Somaiah, MD[1]*; Anthony Conley, MD*[1]*; Heather Lin*[3]*; Beatriz Sanchez-Espiridion*[2]*; Behrang Amini*[4]*; Vinod Ravi*[1]*; Dejka Araujo*[1]*; Shreyaskumar Patel*[1]*; Robert Benjamin*[1]*; M. Alejandra Zarzour*[1]*; Sharjeel Sabir*[4]*; Wei-Lien Wang, MD*[2]*; Alexander Lazar*[2]*; Ignacio Wistuba*[2]*; Patrick Hwu*[1]
[1]Sarcoma Medical Oncology, MD anderson Cancer Center, Houston, TX, USA; [2]Pathology, MDACC, Houston, TX, USA; [3]Biostatistics, MDACC, Houston, TX, USA; [4]Radiology, MDACC, Houston, TX, USA

Paper 011 #2785448

PHASE I STUDY OF TALAZOPARIB AND IRINOTECAN IN CHILDREN AND YOUNG ADULTS WITH RECURRENT OR REFRACTORY SOLID MALIGNANCIES

Sara M. Federico, MD[1]*; Elizabeth Stewart, MD*[1]*; Jamie L. Coleman*[2]*; Michael W. Bishop, MD, MS*[1]*; Victor Santana*[1]*; Catherine Lam*[1]*; Dana Hawkins*[1]*; Jianrong Wu*[3]*; Shenghua Mao*[3]*; Alberto S. Pappo*[1]*; Michael Dyer*[4]
[1]Oncology, St. Jude Children's Research Hospital, Memphis, TN, USA; [2]Radiology, St. Jude Children's Research Hospital, Memphis, TN, USA; [3]Statistics, St. Jude Children's Research Hospital, Memphis, TN, USA; [4]Developmental Neurobiology, St. Jude Children's Research Hospital, Memphis, TN, USA

Paper 012 #2804636

OPEN LABEL NON-RANDOMIZED MULTI-COHORT PILOT STUDY OF GENETICALLY ENGINEERED NY-ESO-1 SPEAR T-CELLS IN HLA-A2+ PATIENTS WITH SYNOVIAL SARCOMA (NCT01343043)

Sandra P. D'Angelo[2]; William D. Tap[2]; John Glod[3]; Mihaela Druta[11]; Warren A. Chow[4]; Dejka Araujo[5]; Stephan Grupp[6]; Brian A. Van Tine[7]; Albiruni Razak[8]; George Demetri[9]; Breelyn A. Wilky, MD[10]; ***Karen Chagin****[1]; Erin Van Winkle[1]; Trupti Trivedi[1]; Crystal L. Mackall[12]*

[1]Adaptimmune, Philadelphia, PA, USA; [2]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [3]National Cancer Institute, Bethesda, MD, USA; [4]City of Hope, Duarte, CA, USA; [5]MD Anderson Cancer Center, Houston, TX, USA; [6]Children's Hospital of Philadelphia, Philadelphia, PA, USA; [7]Washington University in St. Louis School of Medicine, St. Louis, MO, USA; [8]Princess Margaret Cancer Centre, Toronto, ON, Canada; [9]Dana-Farber Cancer Institute, Boston, MA, USA; [10]University of Miami Sylvester Cancer Center, Miami, FL, USA; [11]Moffit Cancer Center, Tampa, FL, USA; [12]Stanford University, Palo Alto, CA, USA

Paper 013 #2789203

A PHASE 2 TRIAL OF CABOZANTINIB (XL184) IN METASTATIC REFRACTORY SOFT TISSUE SARCOMA

Alice Chen, MD*[1]; Geraldine O'Sullivan Coyne[1]; Robert Meehan[1]; Shivaani Kummar[2]; Lamin Juwara[3]; Jennifer Zlott[1]; Larry Rubinstein[4]; Richard Piekarz[4]; Mary Quinn[1]; Naoko Takebe[1]; John Wright[4]; James Doroshow[4]*

[1]Developmental Therapeutics Clinic, National Cancer Instititute, Bethesda, MD, USA; [2]Stanford, Stanford, CA, USA; [3]Leidos Biomedical, Bethesda, MD, USA; [4]Division of Cancer Treatment and Diagnosis, Bethesda, MD, USA

Paper 014 #2797611

PREOPERATIVE PAZOPANIB IN HIGH-RISK SOFT TISSUE SARCOMA (STS): PHASE II WINDOW-OF-OPPORTUNITY STUDY OF THE GERMAN INTERDISCIPLINARY SARCOMA GROUP (NOPASS/GISG-04)

Ulrich Ronellenfitsch, MD*[1]; Antonia Dimitrakopoulou-Strauss[2]; Jens Jakob[3]; Bernd Kasper, MD, PhD[4]; Kai Nowak[3]; Lothar Pilz[5]; Ulrike Attenberger[6]; Timo Gaiser[7]; Derigs Hans-Günter[8]; Matthias Schwarzbach[9]; Peter Hohenberger[10]*

[1]Department of Vascular Surgery and Endovascular Surgery, University Hospital Heidelberg, Heidelberg, Germany; [2]Clinical Cooperation Unit Nuclear Medicine, German Cancer Research Center, Heidelberg, Germany; [3]Department of Surgery, University Medical Center Mannheim, Mannheim, Germany; [4]ITM - Interdisciplinary Tumor Center Mannheim, Sarcoma Unit, University Medical Center Mannheim, Mannheim, Germany; [5]Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany; [6]Institute of Clinical Radiology and Nuclear Medicine, University Medical Center Mannheim, Mannheim, Germany; [7]Institute of Pathology, University Medical Center Mannheim, Mannheim, Germany; [8]Department of Hematology and Oncology, Klinikum Frankfurt-Höchst, Frankfurt am Main, Germany; [9]Department of Surgery, Klinikum Frankfurt-Höchst, Frankfurt am Main, Germany; [10]Surgical Oncology and Thoracic Surgery, University Medical Center Mannheim, Mannheim, Germany

12:30 pm – 1:30 pm **Lunch** *Haleakala Foyer*

1:30 pm – 2:15 pm | – SPECIAL SESSION 1 – | *Haleakala 1*

Sarcoma of the Year: Epithelioid Sarcoma

Moderators: **Mark Agulnik**, **Richard Riedel** & **Ilkyu Han**

Paper 015 #2767796

PHASE I STUDY OF EVEROLIMUS (MTOR INHIBITOR) IN COMBINATION WITH VANDETANIB (MULTIKINASE INHIBITOR OF EGFR, VEGFR, AND RET) IN CHILDREN, ADOLESCENTS AND YOUNG ADULTS WITH SARCOMA AND OTHER ADVANCED SOLID TUMORS

Sheetal Phadnis[2]; Winston Huh[2]; Cynthia E. Herzog[2]; Najat C. Daw, MD[2]; Douglas J. Harrison[2]; Erica N. Ward[2]; Sarina Piha-Paul[1]; Tarak Bhatt[1]; Estella P. Mote[2]; Richard Gorlick[2]; Funda Meric-Bernstam[1]; Cindy L. Schwartz[3]; ***Vivek Subbiah, MD[1]***

[1]Investigational Cancer Therapeutics, UT MD Anderson Cancer Center, Houston, TX, USA; [2]Pediatrics, UT MD Anderson Cancer Center, Houston, TX, USA; [3]Pediatrics, Children's Hospital of WI/ Medical College of WI. Milwaukee, Milwaukee, WI, USA

Paper 016 #2799040

EZH2 INHIBITOR TAZEMETOSTAT IN ADULT AND PEDIATRIC PATIENTS WITH EPITHELIOID SARCOMA: RESULTS FROM 3 PROSPECTIVE CLINICAL TRIALS

Mrinal Gounder[12]*; Silvia Stacchiotti[2]; Patrick Schöffski[3]; Lindsey Hoffman[4]; Rashmi Chugh[5]; Victor M. Villalobos[6]; Franck Bourdeaut[7]; Steven Attia[8]; Jill Rodstrom[9]; Stephen Blakemore[9]; Alicia Clawson[9]; Maria Roche[9]; Susan Chi[10]; Gregory M. Cote, MD PhD[11];* ***Antoine Italiano[12]***

[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]Fondazione IRCCS Istituto Nazioale Tumori, Milan, Italy; [3]University Hospitals Leuven, Leuven Cancer Institute, Leuven, Belgium; [4]Children's Hospital Colorado, Aurora, CO, USA; [5]Michigan Medicine Comprehensive Cancer Center, Ann Arbor, MI, USA; [6]University of Colorado, Denver, CO, USA; [7]Curie Institute, Paris, France; [8]Mayo Clinic in Florida, Jacksonville, FL, USA; [9]Epizyme, Cambridge, MA, USA; [10]Dana Farber Cancer Institute, Boston, MA, USA; [11]Massachusetts General Hospital, Boston, MA, USA; [12]Intitut Bergonie, Bordeaux, France

Paper 017 #2804779

ANTHRACYCLINE, GEMCITABINE AND PAZOPANIB IN EPITHELIOD SARCOMA: UPDATED RESULTS OF A RETROSPECTIVE MULTI-INSTITUTIONAL CASE SERIES

Anna Maria Frezza[1]*; Naofumi Asano, MD, PhD[2]; Robin L. Jones[3]; Ravin Ratan, MD[4]; Eytan Ben-Ami, MD[5]; Pawel Teterycz[6]; Hans J. Gelderblom[7]; Kjetil Boye, MD, PhD[8]; Mehdi Brahmi[9]; Emanuela Palmerini[10]; Nadia Hindi, MD, MSc[11]; Alexander Fedenko[12]; Bruno Vincenzi[13]; Paolo G. Casali[1]; Silvia Stacchiotti, MD[1]*

[1]Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [2]National Cancer Center Research Institute, Tokyo, Japan, Tokyo, Japan; [3]Royal Marsden Hospital, London, United Kingdom; [4]MD Anderson Cancer Center, Huston, TX, USA; [5]Dana Farber Cancer Institution, Boston, MA, USA; [6]Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland; [7]Leiden University Medical Center, Leiden, Netherlands; [8]Oslo University Hospital, Oslo, Norway; [9]Centre Léon Bérard, Lyon, France; [10]Istituto Ortopedico Rizzoli, Bologna, Italy; [11]Virgen Del Rocio University Hospital, Sevilla, Spain; [12]N.N. Blokhin Russian Cancer Research Center, Moscow, Russian Federation; [13]Univeristà Campus Bio-Medico, Roma, Italy

2:15 pm – 3:00 pm — – SESSION 3 – — *Haleakala 1*

Soft Tissue Sarcoma

Moderators: **Richard Riedel** & **Ilkyu Han**

Paper 018 #2758507

BENEFIT OF ADJUVANT CHEMOTHERAPY COMBINED WITH ACCELERATED RADIOTHERAPY IN HIGH-RISK SOFT TISSUE SARCOMA DEFINED BY SIZE, VASCULAR INVASION, NECROSIS AND GROWTH PATTERN - A SCANDINAVIAN SARCOMA GROUP STUDY (SSG XX)

Kirsten S. Hall, PhD[1]*; Øyvind S. Bruland*[2]*; Bodil Bjerkehagen*[3]*; Jacob Engellau*[4]*; Oskar Hagberg*[5]*; Clement Trovik*[6]*; Mikael Eriksson*[4]

[1]*Department of Oncology, Norwegian Radium Hospital, Oslo University Hospital, Oslo, Norway;* [2]*Department of Oncology,Norwegian Radium Hospital,Oslo University Hospital, Institute of Clinical Medicine,University of Oslo, Oslo, Norway;* [3]*Department of Pathology, Oslo University Hospital, Oslo, Norway;* [4]*Department of Oncology, Skane University Hospital, Lund, Sweden;* [5]*Regional Cancer Centre South, Lund, Sweden;* [6]*Musculo-Skeletal Tumor Center, Haukeland University Hospital, Bergen, Norway*

Paper 019 #2803418

IMPROVED OVERALL SURVIVAL (OS) BY NEOADJUVANT THERAPY IN PATIENTS (PTS) WITH HIGH-RISK SOFT TISSUE SARCOMA (HR-STS) OF EXTREMITY (E) AND NON-EXTREMITY (NE)

Lars H. Lindner[1]*; Rolf D. Issels, MD, PhD*[1]*; Jaap Verweij*[2]*; Peter Reichardt*[3]*; Rüdiger Wessalowski*[4]*; Christoph Salat*[1]*; Alessandro Gronchi*[5]

[1]*Medical Clinic III, University Hospital Medical Center Grosshadern, Munich, Germany;* [2]*Erasmus Medical Center, Rotterdam, Netherlands;* [3]*HELIOS Klinikum Berlin-Buch GmbH, Berlin, Germany;* [4]*Universität Düsseldorf, Düsseldorf, Germany;* [5]*Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

Paper 020 #2794748

CANCER IMMUNOTHERAPY USING TRABECTEDIN AND NIVOLUMAB IN ADVANCED SOFT TISSUE SARCOMA: A RETROSPECTIVE ANALYSIS

Sant Chawla[1]*; Kamalesh Sankhala*[1]*; Stumpf Nathan*[1]*; Seth Kim*[1]*; Susan Arasheben*[1]*; Leong Bryan*[1]*; Grace Kang*[1]*; William W. Tseng, MD*[2]*;* ***Erlinda M. Gordon, MD***[1]

[1]*Sarcoma Oncology Center, Santa Monica, CA, USA;* [2]*Surgery, USC Keck School of Medicine, Los Angeles, CA, USA*

3:00 pm – 3:15 pm — Afternoon Break and Poster Viewing — *Haleakala Foyer*

3:15 pm – 3:45 pm — – SESSION 4 – — *Haleakala 1*

Pathology

Moderators: **Elizabeth Demicco** & **Kevin Jones**

Paper 021 #2804859

INFILTRATION OF IMMUNE CO-INHIBITORY CHECKPOINT BIOMARKERS LAG3 AND TIM3 IN SARCOMAS

Amanda R. Dancsok, MD, PhD Student[1]*; Jean-Yves Blay*[5]*; David Thomas, FRACP, PhD*[4]*; Robert Maki*[3]*; Torsten O. Nielsen*[1]*; Elizabeth G. Demicco*[2]

[1]*Pathology and Laboratory Medicine, University of British Columbia, Vancouver, BC, Canada;* [2]*Mount Sinai Hospital, Toronto, ON, Canada;* [3]*Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, USA;* [4]*Garvan Institute, Sydney, NSW, Australia;* [5]*Centre Leon Berard, Lyon, France*

Paper 022 #2783068

A 22-YEAR EVALUATION OF MUSCULOSKELETAL ONCOLOGY IN-OFFICE CORE NEEDLE BIOPSY ERROR RATES FOLLOWING CONSULTATION WITH MUSCULOSKELETAL TRAINED PATHOLOGISTS VERSUS COMMUNITY PATHOLOGISTS

Ashley Startzman, DO[1]*; Ryan Durfee*[2]*; H. T. Temple*[1]
[1]*Orthopedics, Nova Southeastern University, Fort Lauderdale, FL, USA;*
[2]*Orthopaedics, The Center for Orthopaedic Innovations, Miami, FL, USA*

3:45 pm – 5:15 pm – SYMPOSIUM 2 – *Haleakala 1*

Basic Science

Moderators: **Rebecca Gladdy**, **Jack Shern** & **David van Mater**

Paper 023 #2804666

IMMUNE CORRELATES OF RESPONSE TO CHECKPOINT BLOCKADE IN SOFT TISSUE AND BONE SARCOMAS PATIENTS TREATED WITH PEMBROLIZUMAB (SARC028)

Melissa Burgess[1]*; Vanessa Bolejack*[3]*; Ruth Salazar*[2]*; Alexander Lazar*[2]*; Edwin Roger Parra Cuentas*[2]*; Jamie Rodriguez-Canales*[2]*; Ignacio Wistuba*[2]*; Lisa Butterfield*[1]*; Jason Roszik*[2]*; Brian Van Tine*[7]*; Scott Schuetze*[6]*; James Hu*[5]*; Sandra P. D'Angelo*[4]*; Hussein Tawbi*[2]*; SARC028 Investigators*[8]
[1]*University of Pittsburgh, Pittsburgh, PA, USA;* [2]*The University of Texas - MD Anderson, Houston, TX, USA;* [3]*Cancer Research and Biostatistics (CRAB), Seattle, WA, USA;* [4]*Memorial Sloan Kettering Cancer Center, New York, NY, USA;* [5]*USC/Norris Cancer Hospital, Los Angeles, CA, USA;* [6]*University of Michigan, Ann Arbor, MI, USA;* [7]*Washington University School of Medicine, St. Louis, MO, USA;* [8]*SARC, Ann Arbor, MI, USA*

Paper 024 #2786772

DETECTING STRUCTURAL VARIANTS IN THE CIRCULATING TUMOR DNA OF PATIENTS WITH PEDIATRIC SARCOMAS

Kelly Klega; Alma Imamovic-Tuco; Gavin Ha; Andrea Clapp; Abigail Ward; Catherine Clinton; Anwesha Nag; Eliezer Van Allen; Katherine Janeway; Matthew Meyerson; Aaron Thorner;
Brian Crompton, MD
Pediatric Oncology, Dana-Farber Cancer Institute, Boston, MA, USA

Paper 025 #2804624

FORMATION MECHANISMS OF CANONICAL GENE FUSIONS IN BONE AND SOFT TISSUE TUMORS

Nathaniel Anderson, BSc[1]*; Richard de Borja*[1]*; Matthew Young*[2]*; Andrej Rosic*[1]*; Nicola Roberts*[2]*; Fabio Fuligini*[1]*; Adrienne Flanagan*[3]*; Peter Campbell*[2]*; Mary Shago*[1]*; Jay S. Wunder*[4]*; Irene Andrulis*[5]*; David Malkin*[1]*; Sam Behjati*[2]*;* ***Adam Shlien***[1]
[1]*SickKids, Toronto, ON, Canada;* [2]*Wellcome Trust Genome Campus, Wellcome Trust Sanger Institute, Hinxton, United Kingdom;* [3]*Royal National Orthopaedic Hospital NHS Trust, Stanmore, United Kingdom;* [4]*University Musculoskeletal Oncology Unit, Mount Sinai Hospital, Toronto, ON, Canada;* [5]*Lunenfeld-Tanenbaum Research Institute, Sinai Health System, Toronto, ON, Canada*

Paper 026 #2773162

INTEGRATIVE GENOMIC AND TRANSCRIPTOMIC ANALYSIS OF LEIOMYOSARCOMA

Priya Chudasama, PhD[1]*; Sadaf S. Mughal*[2]*; Mathijs A. Sanders*[3]*; Daniel Hübschmann*[4]*; Inn Chung*[5]*; Aurélie Ernst*[6]*; Bernd Kasper, MD, PhD*[7]*; Hans-Georg Kopp*[8]*; Sebastian Bauer*[9]*; Karsten Rippe*[5]*; Benedikt Brors*[2]*; Marcus Renner*[10]*; Peter Hohenberger*[7]*; Claudia Scholl*[1]*; Stefan Fröhling*[1]
[1]*Translational Oncology, German Cancer Research Center (DKFZ) and National Center for Tumor Diseases (NCT), BW, Germany;* [2]*Division of Applied Bioinformatics, DKFZ and NCT, Heidelberg, Germany;* [3]*Department of Hematology, Erasmus Medical Center, Rotterdam, Netherlands;* [4]*Division of Theoretical Bioinformatics, DKFZ, Heidelberg, Germany;* [5]*Research Group Genome Organization and Function, DKFZ and BioQuant Center, Heidelberg, Germany;* [6]*Division of Molecular Genetics, DKFZ, Heidelberg, Germany;* [7]*Sarcoma Unit, Interdisciplinary Tumor Center Mannheim, Mannheim University Medical Center, Mannheim, Germany;* [8]*Department of Hematology and Oncology, Eberhard Karls University, Tübingen, Germany;* [9]*Sarcoma Center, Western German Cancer Center, Essen, Germany;* [10]*Institute of Pathology, Heidelberg, Germany*

Paper 027 #2801967

UTILIZING SLEEPING BEAUTY TRANSPOSON MOUSE SCREENS TO IDENTIFY NATURALLY OCCURRING DRIVER EVENTS IN HUMAN AND CANINE OSTEOSARCOMA

Aaron L. Sarver, PhD*; Nuri Temiz; Branden Moriarity; Jinhua Wang; Subbaya Subramanian; Jaime Modiano; David A. Largaespada, PhD*
Masonic Cancer Center, University of Minnesota, Minneapolis, MN, USA

Paper 028 #2804871

AUTOPHAGY IN ALVEOLAR SOFT PART SARCOMA CONFERS MECHANISMS OF RESISTANCE TO CHEMOTHERAPY

Jared J. Barrott, PhD; ***Kevin B. Jones***
Orthopaedics, University of Utah, Salt Lake City, UT, USA

5:15 pm – 5:45 pm **Young Investigator Award Winners** *Haleakala 1*

Paper 029 #2739815

SEVERITY CLASSIFICATION ON MRI IN TENOSYNOVIAL GIANT CELL TUMOURS

Monique Mastboom, Drs.[1]*; Floortje Verspoor*[2]*; David Hanff*[3]*; Maaike Gademan*[4]*; P.D.Sander Dijkstra*[1]*; Bart Schreuder*[2]*; Hans Bloem*[1]*; Robert van der Wal*[1]*; Michiel V. Sande*[1]
[1]*Orthopaedics Oncology, Leiden University Medical Center, Amsterdam, Netherlands;* [2]*Orthopaedics Oncology, Radboud University Medical Center, Nijmegen, Netherlands;* [3]*Radiology, Leiden University Medical Center, Leiden, Netherlands;* [4]*Epidemiology, Leiden University Medical Center, Leiden, Netherlands*

Paper 030 #2803705

HOW LONG AND HOW OFTEN SHOULD WE FOLLOW-UP PATIENTS WITH LOCALIZED SOFT TISSUE SARCOMA AFTER CURATIVE RESECTION? EVIDENCE FOR A TIME- AND RISK-ADAPTED APPROACH TO AFTERCARE FROM A MULTICENTER ANALYSIS OF 835 CASES

Florian Posch, MD, MSc[1]*; Maria Smolle*[2]*; Madeleine Willegger*[3]*; Per-Ulf Tunn*[5]*; Elisabeth Goldenitsch*[4]*; Jakob M. Riedl*[1]*; Bernadette Liegl-Atzwanger*[6]*; Armin Gerger*[1]*; Martin Pichler*[1]*; Joannis Panotopoulos*[3]*; Carmen Döller*[7]*; Herbert Stöger*[1]*; Reinhard Windhager*[3]*; Andreas Leithner*[2]*; Joanna Szkandera*[1]
[1]*Division of Oncology, Department of Internal Medicine, Medical University of Graz, Graz, Austria;* [2]*Department of Orthopaedics and Trauma Surgery, Medical University of Graz, Graz, Austria;* [3]*Department of Orthopaedic Surgery, Medical University of Vienna, Vienna, Austria;* [4]*Department of Orthopaedics, Orthopaedic Hospital Gersthof, Vienna, Austria;* [5]*Division of Tumor Orthopaedics, Department of Orthopaedics and Trauma Surgery, HELIOS Hospital Berlin-Buch, Berlin, Germany;* [6]*Institute of Pathology, Medical University of Graz, Graz, Austria;* [7]*Department of Therapeutic Radiology and Oncology, Medical University of Graz, Graz, Austria*

5:45 pm – 6:30 pm Poster Session 1 and Reception *Haleakala 2 & 3*

Friday, 10 November, 2017

6:30 am – 5:00 pm	Registration	*Haleakala Foyer*
7:00 am – 8:00 am	Continental Breakfast and Poster Viewing	*Haleakala 2 & 3*

8:00 am – 9:45 am — – SPECIAL SESSION 2 – — *Haleakala 1*

Trials/Approaches in Rarer Sarcomas, Desmoid Tumor

Moderators: **Abha Gupta** & **Beth Stewart**

Paper 031 #2774046

CASPS (CEDIRANIB IN ALVEOLAR SOFT PART SARCOMA), AN INTERNATIONAL RANDOMISED PHASE II TRIAL

Ian Judson, MD[1]*; James Morden*[3]*; Michael Leahy*[2]*; Vivek Bhadri*[4]*; Quentin Campbell-Hewson*[5]*; Ricardo Cubedo*[6]*; Adam Dangoor*[7]*; Ivo Hennig*[8]*; Warren Joubert*[9]*; Antonio López Pousa*[10]*; Beatrice Seddon*[12]*; Claire Snowdon*[3]*; Martin Tattersall*[4]*; Javier Martinez Trufero*[11]*; Judith Bliss*[3]

[1]Royal Marsden Hospital, London, United Kingdom; [2]The Christie NHS Foundation Trust, Manchester, United Kingdom; [3]Institute of Cancer Research Clinical Trials & Statistics Unit (ICR-CTSU), London, United Kingdom; [4]Chris O'Brien Lifehouse, Sydney, NSW, Australia; [5]Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom; [6]Hospital Puerta de Hierro, Madrid, Spain; [7]University Hospitals Bristol NHS Foundation Trust, Bristol, United Kingdom; [8]Nottingham University Hospitals NHS Trust, Nottingham, United Kingdom; [9]Princess Alexandra Hospital, Brisbane, QLD, Australia; [10]Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; [11]Hospital Miguel Servet, Zaragoza, Spain; [12]University College London Hospitals NHS Foundation Trust, London, United Kingdom

Paper 032 #2762187

THE USE OF LAROTRECTENIB IN THE MANAGEMENT OF LOCALLY ADVANCED PEDIATRIC *NTRK*-FUSION SARCOMA

Steven G. DuBois[1]*; Theodore W. Laetsch, MD*[2]*; Noah Federman*[3]*; Catherine M. Albert*[4]*; Brian Turpin*[5]*; Ramamoorthy Nagasubramanian*[6]*; Mark Reynolds*[7]*; Scott Cruickshank*[7]*; Michael C. Cox*[7]*; Douglas S. Hawkins*[4]*; Leo Mascarenhas*[8]*; Alberto S. Pappo*[9]

[1]Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, MA, USA; [2]University of Texas Southwestern Medical Center/Children's Health, Dallas, TX, USA; [3]University of California, Los Angeles, Los Angeles, CA, USA; [4]Seattle Children's Hospital, University of Washington, Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [5]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA; [6]Nemours Children's Hospital, Orlando, FL, USA; [7]Loxo Oncology, South San Francisco, CA, USA; [8]Children's Hospital Los Angeles, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA; [9]St Jude Children's Research Hospital, Memphis, TN, USA

Paper 033 #2803531

AXITINIB IN PROGRESSIVE ADVANCED SOLITARY FIBROUS TUMOR: RESULTS FROM AN EXPLORATORY ITALIAN PHASE 2 CLINICAL STUDY

Silvia Stacchiotti, MD[1]*; Carlo Morosi*[2]*; Anna Maria Frezza*[1]*; Alessandra Casale*[2]*; Elena Palassini*[1]*; Alessandro Gronchi*[3]*; Silvana Pilotti*[4]*; Paola Collini*[4]*; Salvatore Renne*[4]*; GianPaolo Dagrada*[5]*; Paolo G. Casali*[1]

[1]Cancer Medicine, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [2]Radiology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [3]Surgery, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [4]Pathology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [5]Molecular Biology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Paper 034 #2804367

PRELIMINARY DATA ON SYSTEMIC THERAPY IN A MULTICENTER CASES SERIES OF PERIVASCULAR EPITHELIOID CELL TUMOURS (PECOMA)

Roberta Sanfilippo[1]*; Salvatore Provenzano*[1]*; Robin L. Jones*[2]*; Georgios Antoniou*[2]*; Vittoria Colia*[1]*; Elena Fumagalli*[1]*; Rossella Bertulli*[1]*; Jean-Yves Blay*[3]*; Axel Lecesne*[4]*; Mehdi Brahmi*[3]*; Armelle Dufresne*[3]*; Nadia Hindi MD, MSc*[5]*; Alessandro Gronchi*[1]*; Angelo Paolo Dei Tos*[6]*; Paolo G. Casali*[1]

[1]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [2]Royal Marsden Hospital, London, United Kingdom; [3]Centre Léon Bérard, Lyon, France; [4]Institut Gustave Roussy, Villejuif, France; [5]Virgen del Rocìo University Hospital, Seville, Spain; [6]Treviso Hospital, Treviso, Italy

Paper 035 #2797930

PROGNOSIS OF DESMOID TUMOURS INITIALLY MANAGED WITH SURVEILLANCE ONLY AT ALL ANATOMICAL LOCATIONS

Winan J. van Houdt, MD, PhD, MSc[1]*; Alisha Patel*[1]*; Robin L. Jones*[2]*; Myles J. Smith*[1]*; Aisha Miah*[3]*; Charlotte Benson*[2]*; Shane Zaidi*[3]*; Christina Messiou*[4]*; Eleanor Moskovic*[4]*; Dirk C. Strauss*[1]*; Andrew J. Hayes*[1]*; Olga Husson*[2]*; Winette van der Graaf*[2]

[1]Department of Surgical Oncology, The Royal Marsden Hospital, London, United Kingdom; [2]Department of Medical Oncology, the Royal Marsden Hospital, London, United Kingdom; [3]Department of Clinical Oncology, the Royal Marsden Hospital, London, United Kingdom; [4]Department of Radiology, the Royal Marsden Hospital, London, United Kingdom

Paper 036 #2762720

AN UPDATE ON THE MANAGEMENT OF SPORADIC DESMOID-TYPE FIBROMATOSIS: A EUROPEAN CONSENSUS INITIATIVE BETWEEN SARCOMA PATIENTS EURONET (SPAEN) AND EUROPEAN ORGANISATION FOR RESEARCH AND TREATMENT OF CANCER (EORTC) / SOFT TISSUE AND BONE SARCOMA GROUP (STBSG)

Bernd Kasper, MD, PhD[1]*; Christina Baumgarten*[2]*; Jesica Garcia*[2]*; Sylvie Bonvalot*[3]*; Rick Haas, MD, PhD*[4]*; Florian Haller*[5]*; Peter Hohenberger*[1]*; Nicolas Penel*[6]*; Christina Messiou*[7]*; Winette van der Graaf*[8]*; Alessandro Gronchi*[9]

[1]Interdisciplinary Tumor Center, Mannheim University Medical Center, Mannheim, Germany; [2]Sarcoma Patients EuroNet (SPAEN), Wölfersheim, Germany; [3]Department of Surgical Oncology, Institut Curie, PSL University, Paris, France; [4]Department of Radiotherapy, The Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands; [5]Institute of Pathology, Friedrich Alexander University Erlangen, Erlangen, Germany; [6]Department of Medical Oncology, Centre Oscar Lambret, Lille, France; [7]Radiology, The Royal Marsden Hospital, London, United Kingdom; [8]Division of Clinical Studies, The Institute of Cancer Research, London, United Kingdom; [9]Department of Surgery, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Paper 037 #2794088

AUTOPHAGY INHIBITION OVERCOMES SORAFENIB RESISTANCE IN *CTNNB1* MUTANT S45F DESMOID TUMORS

Danielle Braggio, PhD[1]*; David Koller*[2]*; Feng Jin*[3]*; Nanda Siva*[4]*; Abeba Zewdu*[1]*; Gonzalo Lopez*[1]*; Kara Batte*[1]*; Lucia Casadei, PhD*[1]*; Meng Welliver*[3]*; Anne Strohecker*[1]*; Raphael Pollock*[2]*; Dina Lev*[5]

[1]Comprehensive Cancer Center, The Ohio State University, Columbus, OH, USA; [2]Department of Surgery, The Ohio State University, Columbus, OH, USA; [3]Radiation Oncology Department, The Ohio State University, Columbus, OH, USA; [4]Department of Chemical and Biomedical Engineering, West Virginia University Statler College of Engineering and Mineral Resources, Morgantown, WV, USA; [5]Surgery B, Sheba Medical Center, Tel Aviv, Israel

9:45 am – 10:30am | – SESSION 5 – | *Haleakala 1*

GIST

Moderators: **Victor Villalobos** & **Jason Sicklick**

Paper 038 #2803523

CLINICAL ACTIVITY OF BLU-285 A HIGHLY POTENT AND SELECTIVE KIT/PDGFRα INHIBITOR DESIGNED TO TREAT GASTROINTESTINAL STROMAL TUMOR (GIST)

Michael Heinrich[1]*; Robin L. Jones*[2]*; Margaret von Mehren*[3]*; Patrick Schoffski*[4]*; Sebastian Bauer*[5]*; Olivier Mir*[6]*; Philippe A. Cassier*[7]*; Ferry Eskens*[9]*; Hongliang Shi*[8]*; Terri Alvarez-Diez*[8]*; Oleg Schmidt-Kittler*[8]*; Mary Ellen Healy*[8]*; Beni B. Wolf*[8]*; Suzanne George*[10]

[1]Knight Cancer Institute, OHSU, Portland, OR, USA; [2]Royal Marsden Hospital/Institute of Cancer Research, London, United Kingdom; [3]Fox Chase Cancer Center, Temple University Health System, Philadelphia, PA, USA; [4]Leuven Cancer Institute University Hospitals Leuven, Leuven, Belgium; [5]West German Cancer Center, University Hospital, Essen, Germany; [6]Gustave Roussy, Villejuif, France; [7]Centre Leon Berard, Lyon, France; [8]Blueprint Medicines, Cambridge, MA, USA; [9]Erasmus MC Cancer Institute, Rotterdam, Netherlands; [10]Dana-Farber Cancer Center/Brigham and Women's Hospital, Boston, MA, USA

Paper 039 #2804377

DCC-2618, A NOVEL PAN-KIT AND PDGFRA KINASE SWITCH CONTROL INHIBITOR DEMONSTRATES ENCOURAGING ACTIVITY IN PATIENTS (PTS) WITH GASTROINTESTINAL STROMAL TUMORS (GIST)

Neeta Somaiah, MD[1]*; Albiruni Razak*[2]*; Michael Gordon*[3]*; Filip Janku*[4]*; Sharon Friedlander*[5]*; Daniel Flynn*[5]*; Michael Kaufman*[5]*; Jama PItman*[5]*; Rodrigo Ruiz-Soto*[5]*; Bryan Smith*[5]*; Deborah Westwood*[5]*; Julia Jennings*[6]*; Jerilynn Jacobson*[5]*; Oliver Rosen*[5]*; Suzanne George*[6]

[1]Sarcoma Medical Oncology, MD Anderson Cancer Center, Houston, TX, USA; [2]Princess Margaret Cancer Centre, Toronto, ON, Canada; [3]Pinnacle Oncology Hematology, Scottsdale, AZ, USA; [4]Phase I, University of Texas MD Anderson, Houston, TX, USA; [5]Clinical Research, Deciphera Pharmaceuticals, Waltham, MA, USA; [6]Center for Sarcoma and Bone Oncology, Dana-Farber Cancer Institute, Boston, MA, USA

Paper 040 #2760542

KIT MUTATION ZYGOSITY IMPACTS TKI SENSITIVITY IN GIST

Armelle Dufresne[1]*; Nacef Bahri*[2]*; Alexandra Lauria*[2]*; Inga Marie Schaefer*[2]*; Adrian Marino Enriquez*[2]*; Jonathan Fletcher*[2]

[1]Centre Leon Berard, Lyon, France; [2]Brigham and Women's Hospital, Boston, MA, USA

10:30 am – 11:00 am | Coffee Break and Poster Viewing | *Haleakala 2 & 3*

11:00 am – 12 noon | – Nina Axelrad Lecture – | *Haleakala 1*

"Ewing Sarcoma: The Dumb Drugs Have Gotten Us a Long Way...."

Holcombe Grier

12 noon – 1:00 pm | **Mentorship Lunch** | *Haleakala Foyer*

1:00 pm – 2:00 pm | – SESSION 6 – | *Haleakala 1*

Osteosarcoma & Chondrosarcoma

Moderators: **Anthony Conley** & **Kurt Weiss**

Paper 041 #2784460

PERIOPERATIVE RH-ENDOSTATIN WITH CHEMOTHERAPY IMPROVES THE SURVIVAL OF OSTEOSARCOMA PATIENTS

Xiaohui Niu; *Hairong Xu, MD; Zhen Huang*
Department of Orthopaedic Oncology, Beijing Ji Shui Tan Hospital, Peking Universtiy, Beijing, China

Paper 042 #2753015

PHASE 2 TRIAL OF THE GPNMB-TARGETED ANTIBODY-DRUG CONJUGATE, CDX-011 (GLEMBATUMUMAB VEDOTIN) IN RECURRENT/REFRACTORY OSTEOSARCOMA (OS): A REPORT FROM THE CHILDREN'S ONCOLOGY GROUP (COG)

Lisa M. Kopp[1]; *Suman Malemati*[4]; *Mark Karilo*[5]; *Brenda Weigel*[3]; *Yun Gao, MS*[5]; *Lisa A. Teot*[2]; *Justin Cates*[8]; *Amy R. Newman*[10]; *Victor M. Villalobos*[7]; *Robert L. Randall*[9]; *Joel M. Reid*[11]; *Grace Lin*[12]; *Alisa Eicher*[4]; *Justin Davis*[5]; *Richard Gorlick*[6]; *Katherine Janeway*[2]
[1]*University of Arizona, Tucson, AZ, USA;* [2]*Dana Farber Cancer Institute, Boston, MA, USA;* [3]*University of Minnesota/Masonic Cancer Center, Minneapolis, MN, USA;* [4]*Oregon Health and Science University, Portland, OR, USA;* [5]*Children's Oncology Group, Monrovia, CA, USA;* [6]*MD Anderson Cancer Center, Houston, TX, USA;* [7]*University of Colorado Denver, Aurora, CO, USA;* [8]*Vanderbilt University/Ingram Cancer Center, Nashville, TN, USA;* [9]*Primary Children's Hosptial, Salt Lake City, UT, USA;* [10]*Midwest Children's Cancer Center, Milwaukee, WI, USA;* [11]*Mayo Clinic, Rochester, MN, USA;* [12]*Lucile Packard Children's Hospital Stanford University, Palo Alto, CA, USA*

Paper 043 #2758475

TAS-115, A NOVEL ORAL MET/VEGFR/CSF1R INHIBITOR, REVEALED THE PRELIMINARY ANTI-TUMOR ACTIVITY AGAINST OSTEOSARCOMA AND RARE SUBTYPES OF SOFT TISSUE SARCOMA IN THE PHASE I STUDY

Yoichi Naito[1]; *Kenji Nakano*[2]; *Shigehisa Kitano*[3]; *Takahiro Kogawa*[1]; *Akihiko Shimomura*[3]; *Kan Yonemori*[3]; *Mai Onomura*[2]; *Toshihiko Doi*[1]; *Noboru Yamamoto*[3]; *Shunji Takahashi*[2]; *Uemura Hiroji*[4]; *Nobuhito Araki*[5]; *Akira Kawai*[3]
[1]*National Cancer Center Hospital East, Kashiwa, Japan;* [2]*Cancer Institute Hospital of JFCR, Tokyo, Japan;* [3]*National Cancer Center Hospital, Tokyo, Japan;* [4]*Yokohama City University Medical Center, Yokohama, Japan;* [5]*Osaka International Cancer Institute, Osaka, Japan*

Paper 044 #2795749

GRM4 AND IL23 ARE NOVEL THERAPEUTIC TARGETS IMPLICATED IN OSTEOSARCOMA SUSCEPTIBILITY AND PROGRESSION

David Thomas, FRACP, PhD; *Maya Kansara*
Cancer, Garvan Institute of Medical Research, Sydney, NSW, Australia

2:00 pm – 3:00 pm — – SESSION 7 – — *Haleakala 1*

Ewing Sarcoma

Moderators: **Joshua Schiffman** & **Pooja Hingorani**

Paper 045 #2783571

THE INFLUENCE OF LOCAL TREATMENT ON OUTCOME OF LOCALIZED PELVIC EWING SARCOMA - A RETROSPECTIVE ANALYSIS OF THE EURO-EWING99 TRIAL

Dimosthenis Andreou, MD[1]; *Andreas Ranft*[2]; *Daniel Baumhoer*[3]; *Henk van den Berg*[4]; *P.D. Sander Dijkstra*[5]; *Georg Gosheger*[1]; *Jendrik Hardes*[1]; *Ruth Ladenstein*[6]; *Andreas Leithner*[7]; *Sergiu Scobioala*[2]; *Arne Streitbuerger*[1]; *Per-Ulf Tunn*[8]; *Eva Wardelmann*[2]; *Heribert Juergens*[2]; *Uta Dirksen*[9]
[1]*Department of General Orthopedics and Tumororthopedics, Münster University Hospital, Münster, Germany;* [2]*Münster University Hospital, Münster, Germany;* [3]*University Hospital Basel, Basel, Switzerland;* [4]*University of Amsterdam, Amsterdam, Netherlands;* [5]*Leiden University Medical Center, Leiden, Netherlands;* [6]*St. Anna Kinderspital, Vienna, Austria;* [7]*Medical University Graz, Graz, Austria;* [8]*HELIOS Klinikum Berlin-Buch, Berlin, Germany;* [9]*University Hospital Essen, Essen, Germany*

Paper 046 #2801616

GERMLINE ALTERATIONS AND FAMILY HISTORY CONTRIBUTE TO EWING SARCOMA SUSCEPTIBILITY, AN UPDATE FROM PROJECT GENESIS (GENETICS OF EWING SARCOMA INTERNATIONAL STUDY, CHILDREN'S ONCOLOGY GROUP AEPI10N5)

Erin Young, PhD[1]; *Schuyler O'Brien*[1]; *Trent Fowler*[1]; *Barry Moore*[5]; *Rosann Robinson*[1]; *Jamie Gardiner*[1]; *Nathan Pankratz*[2]; *Spencer Kelley*[2]; *Mark Yandell*[5]; *Gabor Marth*[4]; *Aaron Quinlan*[6]; *Wendy Kohlmann*[1]; *Stephen Lessnick*[3]; *Logan G. Spector, Ph.D.*[2]; *Joshua D. Schiffman*[7]
[1]*Huntsman Cancer Institute, University of Utah, SLC, UT, USA;* [2]*Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN, USA;* [3]*Center for Childhood Cancer and Blood Diseases, Nationwide Children's Hospital, Columbus, OH, USA;* [4]*Department of Pathology, University of Utah, Salt Lake City, UT, USA;* [5]*Department of Human Genetics, University of Utah, Salt Lake City, UT, USA;* [6]*Base2 Genomics, LLC, Salt Lake City, UT, USA;* [7]*Department of Pediatrics, University of Utah, Salt Lake City, UT, USA*

Paper 047 #2776419

A NOVEL ROLE FOR THE EWS PORTION OF EWS/FLI IN BINDING GGAA-MICROSATELLITES REQUIRED FOR ONCOGENIC TRANSFORMATION IN EWING SARCOMA

Kirsten Johnson, BS; *Stephen Lessnick*
Center for Childhood Cancer & Blood Disorders, The Research Institute at Nationwide Children's Hospital, Columbus, OH, USA

Paper 048 #2768194

EFFICACY AND SAFETY OF LURBINECTEDIN (PM1183) IN EWING SARCOMA: RESULTS FROM A PHASE 2 STUDY

Vivek Subbiah, MD[1]; *Kumar Sankhala*[2]; *Enrique Sanz-Garcia*[3]; *Valentina Boni*[4]; *Ahmad Awada*[5]; *Victor M. Villalobos*[6]; *Pilar Lardelli*[7]; *Mariano Siguero*[7]; *Carmen Kahatt*[7]; *Arturo Soto-Matos*[7]; *Stefano Ferrari*[8]
[1]*The University of Texas MD Anderson Cancer Center, Houston, TX, USA;* [2]*Sarcoma Oncology Center, Santa Monica, CA, USA;* [3]*Hospital Vall D'Hebron, Barcelona, Spain;* [4]*Hospital Universitario Madrid Sanchinarro, Madrid, Spain;* [5]*Institut Jules Bordet, Université Libre de Bruxelles, Bruxelles, Belgium;* [6]*University of Colorado Cancer Center, Denver, CO, USA;* [7]*PharmaMar, Madrid, Spain;* [8]*Istituti Ortopedici Rizzoli, Bologna, Italy*

3:00 pm – 4:00 pm — Poster Session 2 and Afternoon Break — *Haleakala 2 & 3*

4:00 pm – 5:00 pm | – SYMPOSIUM 3 – | *Haleakala 1*

New Research Technologies

Moderators: **Katia Scotlandi** & **Brian Crompton**

Paper 049 #2784070

DETECTION OF *EWSR1* FUSIONS IN CIRCULATING CELL FREE DNA IS ASSOCIATED WITH DISEASE FEATURES AND POOR OUTCOMES IN EWING SARCOMA (EWS): A REPORT FROM THE CHILDREN'S ONCOLOGY GROUP (COG)

David .S. Shulman[1]*; Kelly Klega*[1]*; Alma Imamovic-Tuco*[1]*; Andrea Clapp*[6]*; Anwesha Nag*[6]*; Aaron Thorner*[6]*; Stephen Lessnick*[2]*; Richard Gorlick*[3]*; Katherine Janeway*[1]*; Kieuhoa T. Vo*[4]*; David Hall*[5]*; Mark Krailo*[5]*; Don Barkauskas*[5]*; Steven G. DuBois*[1]*; Brian Crompton*[1]

[1]Pediatric Oncology, Dana-Farber / Boston Children's Cancer and Blood Disorders Center, Boston, Massachusetts, USA; [2]Center for Childhood Cancer and Blood Disorders, Nationwide Children's Hospital, Columbus, Ohio, USA; [3]Division of Pediatrics, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA; [4]Department of Pediatrics, UCSF Benioff Children's Hospital, San Francisco, California, USA; [5]Children's Oncology Group, Los Angeles, California, USA; [6]Cancer Genome Discovery, Dana-Farber Cancer Institute, Boston, Massachusetts, USA

Paper 050 #2772873

A NOVEL CHIMERIC ANTIGEN RECEPTOR (CAR) TARGETING B7-H3 MEDIATES REGRESSION OF ESTABLISHED TUMORS AND CURE OF LOCALIZED AND METASTATIC OSTEOSARCOMA XENOGRAFTS

Robbie G. Majzner[1]*; Sabine Heitzeneder*[1]*; Johanna Theruvath*[1]*; Anandani Nellan*[2]*; Karen Cui*[2]*; Crystal L. Mackall*[1]

[1]Pediatrics, Stanford University School of Medicine, Palo Alto, California, USA; [2]Pediatric Oncology Branch, National Cancer Institute, Bethesda, Maryland, USA

Paper 051 #2766846

NEXT GENERATION SEQUENCING IDENTIFIES IMMUNOTHERAPY TARGETS IN SOFT TISSUE SARCOMA

Jason Roszik*, Vivek Subbiah; J.A. Livingston; Neeta Somaiah; Vinod Ravi; Wei-Lien Wang; Cassian Yee; P. Andrew Futreal; Alexander Lazar; Anthony P. Conley*

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

Paper 052 #2804366

HARVESTING PATIENT-GENERATED INFORMATION FROM INTERNET DISCUSSION FORUMS

G. van Oortmerssen[1]*; H.J. Gelderblom*[2]

[1]Tilburg Center for Cognition and Communication, Tilburg University, Naarden, Netherlands; [2]Medical Oncology, Leiden University Medical Center, Leiden, Netherlands

5:30 pm- 10:00 pm | Gala – Luau | *Molokini Garden*

10:00 pm | Gala After Party | *Haleakala 4 & 5*

Saturday, 11 November, 2017

6:30 am – 5:00 pm	Registration	*Haleakala Foyer*
7:00 am – 8:00 am	Executive Board Meeting	
7:00 am – 8:00 am	Continental Breakfast and Poster Viewing	*Haleakala 2 & 3*
8:00 am – 10:00 am	– SARC – (The SARC meeting is open to all attendees of CTOS)	*Haleakala 1*
10:00 am – 10:30 am	Coffee Break and Poster Viewing	*Haleakala 2 & 3*

CTOS provides a home for all aspects of sarcoma clinical practice and research. As members, we are the very heart of the organization and its future. Let's have a an engaging and constructive conversation about where we want to go together and how we can make our great organization even greater and more inclusive.

For these reasons, there will be two sessions running in parallel to address questions on how we might collaborate as investigators in laboratory science and clinical research. Please join the session that you have the most to contribute to.

10:30 am – 12 noon	**PARALLEL BREAKOUT SESSION 1** **Surgical / Clinical** Moderators: **Peter Ferguson** & **Margaret von Mehren**	*Haleakala 1*
10:30 am – 12 noon	**PARALLEL BREAKOUT SESSION 2** **Basic Science / Translational** Moderators: **Alex Lazar** & **David Kirsch**	*Haleakala 4 & 5*
12 noon – 1:00 pm	**– Herman Suit Lecture –** **Benjamin A. Alman**	*Haleakala 1*
1:00 pm – 2:00 pm	Lunch	*Haleakala Foyer*
1:00 pm – 2:00 pm	Board of Directors Meeting	
2:00 pm – 3:00 pm	– SESSION 8 – **Population Sciences, Survivorships** Moderators: **Tom Chen** & **Lisa Kopp**	*Haleakala 1*

Paper 053 #2783913

EXERCISE STRATEGIES IN A TUMOR MODEL TO DECREASE ACUTE AND LATE DOXORUBICIN-INDUCED CARDIOTOXICITY

Eugenie S. Kleinerman, MD; *Fei Wang; Joya Chandra; Keri Schadler*

Pediatrics, M.D. Anderson Cancer Center, Houston, TX, USA

Paper 054 #2791329

NEOADJUVANT RADIOTHERAPY IS ASSOCIATED WITH R0 RESECTION AND IMPROVED SURVIVAL IN EXTREMITY SOFT TISSUE SARCOMA PATIENTS UNDERGOING SURGERY: AN NCDB ANALYSIS

Alicia Gingrich[1]; Sarah Bateni[1]; Amanda Kirane[1]; Steven W. Thorpe[3]; Arta Monjazeb[2]; ***Robert J. Canter***[1]
[1]Surgery, UC Davis, Sacramento, CA, USA; [2]Radiation Oncology, UC Davis, Sacramento, CA, USA; [3]Orthopedics, UC Davis, Sacramento, CA, USA

Paper 055 #2804809

QUALITY OF LIFE AND DISTRESS IN SARCOMA PATIENTS PRESENTING TO A TERTIARY REFERRAL CENTER

Elizabeth T. Loggers, MD, PhD[1]*; Seth M. Pollack[1]; Gabrielle Kane[3]; Edward Y. Kim[3]; Darin Davidson[4]; Chris Johnson[4]; Matthew Thompson[4]; Lee D. Cranmer[2]*
[1]Clinical Research, Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [2]Medical Oncology, University of Washington, Seattle, WA, USA; [3]Radiation Oncology, University of Washington, Seattle, WA, USA; [4]Orthopedic Surgery, University of Washington, Seattle, WA, USA

Paper 056 #2796148

IMPACT OF VITAMIN D SUPPLEMENTATION DURING AND AFTER CHEMOTHERAPY ON BONE MINERAL DENSITY IN YOUNG EWING'S AND OSTEOSARCOMA PATIENTS

Ulrike M. Pirker-Frühauf, Resident[2]*; Susanne Scheipl, MD, PhD[2]; Daniela Sperl[3]; Franz Quehenberger[1]; Barbara Obermayer-Pietsch[4]; Andreas Leithner[2]*
[1]Institute for Medical Informatics, Statistics and Medical Documentation, Medical University of Graz, Graz, Austria; [2]Orthopaedics and Traumatology, Medical University of Graz, Graz, Austria; [3]Paediatric Oncology and Haematooncology, Medical University of Graz, Graz, Austria; [4]Internal Medicine, Subdivision Endocrinology and Metabolism, Medical University Graz, Graz, Austria

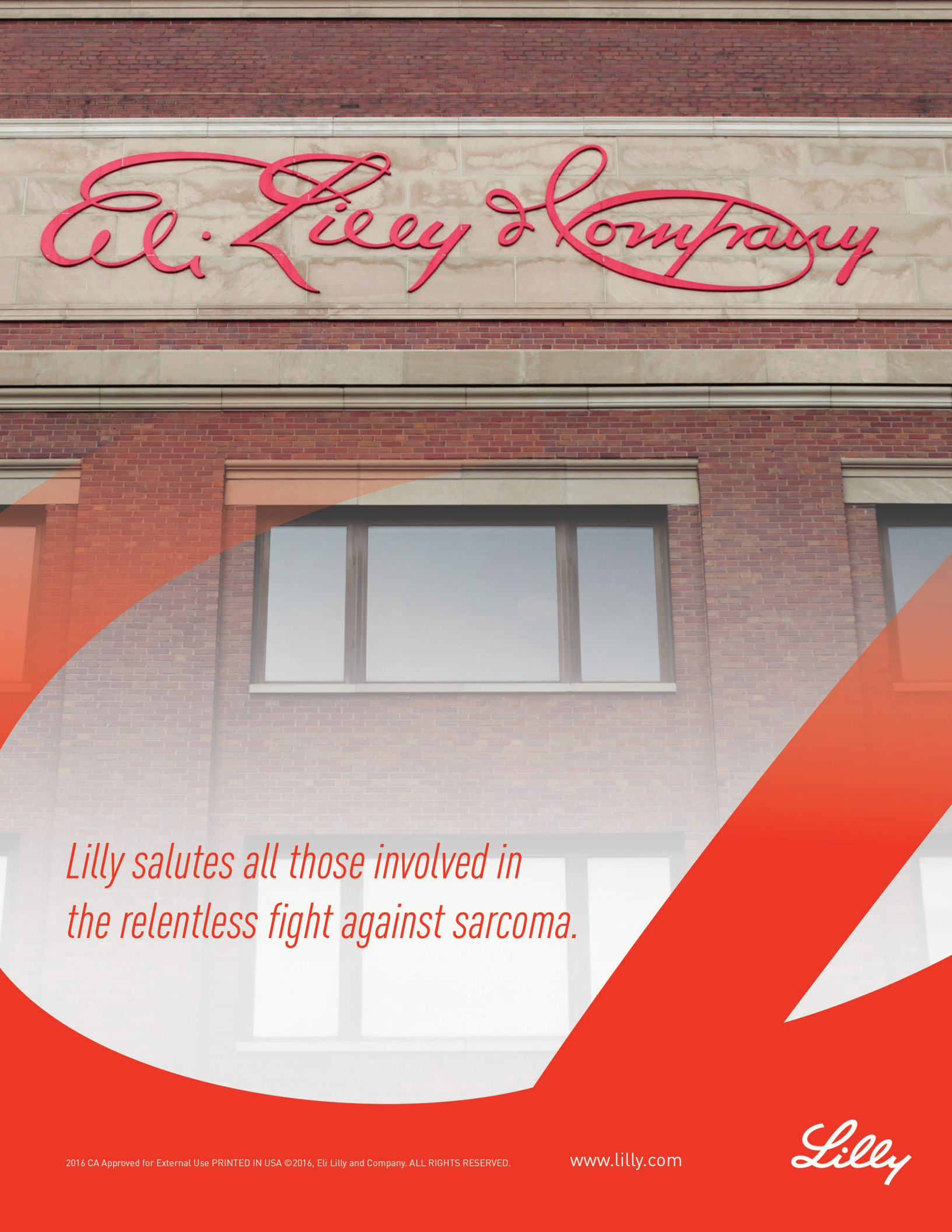
3:00 pm – 3:30 pm Afternoon Break *Haleakala Foyer*

3:30 pm – 5:00 pm **– Plenary Session –** *Haleakala 1*

Future Multidisciplinary Collaborative Work Wrap Up

5:00 pm – 6:00 pm CTOS Members' Business Meeting *Haleakala 1*

6:00 pm ADJOURN



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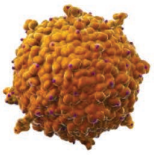
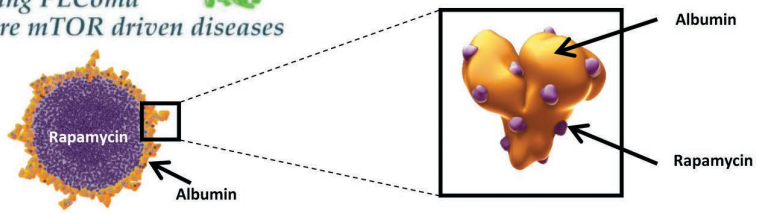
ABI-009 Clinical Trials in Sarcoma

AADi

Targeting PEComa and rare mTOR driven diseases

ABI-009, nanoparticle albumin-bound rapamycin (*nab*-rapamycin) and dissociated complex





Artists' Impression

See if your patient qualifies

A phase 2 multi-center investigation of efficacy of ABI-009 in patients with advanced malignant perivascular epithelioid cell tumor (PEComa)

ClinicalTrials.gov – NCT02494570

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For patients, naïve to mTOR inhibitors, with malignant PEComa, that is either metastatic or locally advanced and for which surgery is not a recommended option

Dana Farber
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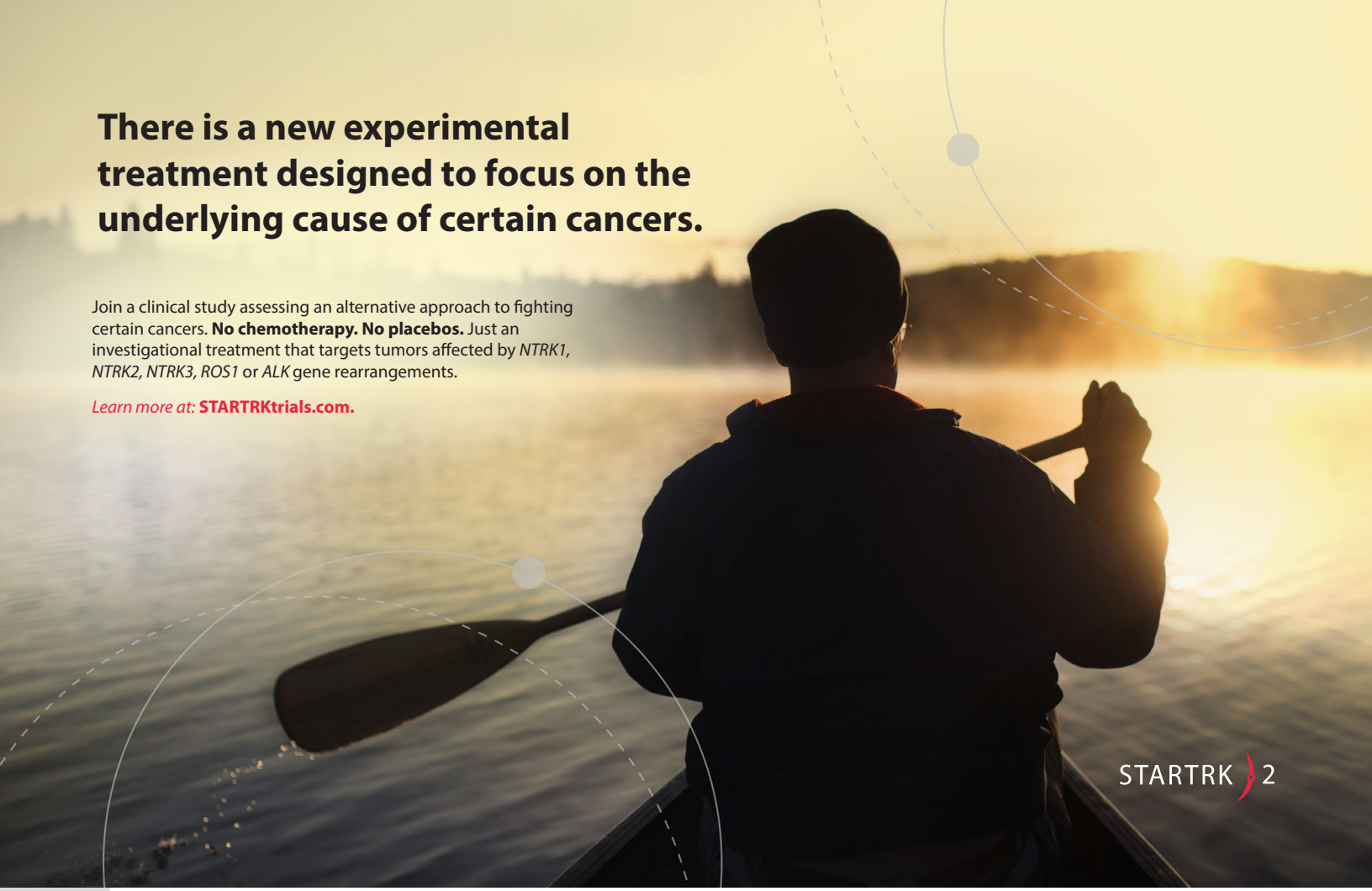
Aadi Bioscience, Inc., Pacific Palisades, CA, USA ~ www.aadibio.com ~ Contact: Berta Grigorian at bgrigorian@aadibio.com



Immune Design
Global Phase 3 Pivotal Trial Opening in 2018

Immune Design is planning to open a Phase 3 trial to evaluate the survival impact of CMB305 in patients with synovial sarcoma
CMB305 is an active immunotherapy regimen designed to generate and expand anti-NY-ESO-1 T cells.

- **Study Design**
  - Randomized, Double blind, Placebo controlled phase 3 study
- **Treatment:**
  - Arm A CMB305 versus Arm B Placebo in the maintenance setting after first line chemotherapy
- **Patient Population:**
  - NY-ESO-1 positive synovial sarcoma patients
  - No evidence of progression following first-line anthracycline or ifosfamide containing regimen for locally advanced unresectable or metastatic disease
- **Endpoints:**
  - PFS & OS
- **Study participation:**
  - Global

For further information contact MedicalMonitor1702@immunedesign.com

IMMUNE DESIGN

8:30 am – 9:30 am
– SESSION 1 –
Surgical Oncology

Paper 001 #2756819

INACCURACY IN SARCOMA CASE CODING: UNDERESTIMATION OF THE BURDEN OF SARCOMA WITHIN A SINGLE INSTITUTION

Heather Lyu, MD[1]*; Leah A. Stein*[1]*; Lily V. Saadat*[1]*; Sheila N. Phicil*[1]*; Jiping Wang*[1]*; Marco Ferrone*[2]*; John E. Ready*[2]*; Monica M. Bertagnolli*[1]*; Chandrajit P. Raut, MD*[1]
[1]Surgery, Brigham and Women's Hospital, Boston, MA, USA; [2]Orthopedic Surgery, Brigham and Women's Hospital, Boston, MA, USA

Objective: Coding of sarcoma cases by surgical coders and tumor registrars can be challenging. Depending on institutional policies, cancer cases may be coded based on organ site rather than type of malignancy. We sought to characterize inaccuracies in coding practices to identify errors which could have implications on the validity and accuracy of national databases, such as the National Inpatient Sample (NIS) and National Cancer Database (NCDB).

Methods: Sarcoma cases at a single high-volume sarcoma center were identified by departmental administrators as logged by the surgeon. Diagnosis of sarcoma was confirmed from operative pathology reports. All non-sarcoma cases and operations on sarcoma patients unrelated to their sarcoma diagnosis (e.g., bowel resection for adhesive bowel obstruction) were excluded. Operative diagnosis codes (ICD-9 or ICD-10) and tumor registrar diagnosis codes (ICD-O-3) for these cases were compared for each patient to determine the variation in coding.

Results: From January 1, 2012 to December 31, 2016, 2,715 individual soft tissue and bone oncologic cases were performed by 5 surgical and orthopedic oncologists. Of these, 1,237 had a histologic diagnosis of sarcoma confirmed by pathology. Based on ICD-9/ICD-10 codes, 764 (63%) cases were accurately coded as sarcoma resections, 180 (16%) were coded with a "non-oncologic" diagnosis, and 260 (22%) were coded by organ system including gastrointestinal, breast, hematologic, gynecological, thoracic, cutaneous, or as "other cancer." For instance, 41 of 156 (26%) gastric GIST and 24 of 46 (52%) breast angiosarcoma were coded as gastric and breast cancer, respectively. By specialty, 276 of 382 (72%) orthopedic oncology and 487 of 855 (57%) surgical oncology sarcoma cases were coded accurately. Based on ICD-O-3 codes during an overlapping 4-year period, 631 of 1054 (60%) patients were accurately coded, 26 (2%) were coded with a "other cancer" diagnosis, and 397 (38%) were not listed in the tumor registry. Furthermore, 46% gastric GISTs and 72% breast angiosarcomas were coded incorrectly.

Conclusion: ICD9/10 coding of sarcoma cases is inaccurate. Inaccuracies if confirmed by other institutions could undermine the validity of the NCDB, which pulls its data from institutional tumor registries, and the NIS, which uses ICD diagnosis codes, among other national datasets for evaluation of sarcoma case volumes and outcomes. Regional and national forecasts can be impacted as well.

Paper 002 #2782851

PREDICTING SURVIVAL IN PATIENTS (PTS) UNDERGOING RESECTION FOR LOCOREGIONALLY RECURRENT RETROPERITONEAL SARCOMA (LRRPS): A STUDY AND NOMOGRAM FROM THE TRANSATLANTIC RETROPERITONEAL SARCOMA WORKING GROUP (TARPSWG)

Chandrajit P. Raut, MD[1]*; Dario Callegaro*[2]*; Francesco Barretta*[2]*; Piotr Rutkowski, MD, PhD*[3]*; Jean-Yves Blay*[4]*; Guy Lahat*[5]*; Dirk C. Strauss*[6]*; Ricardo Gonzalez*[7]*; Nita Ahuja*[8]*; Giovanni Grignani*[9]*; Vittorio Quagliuolo*[10]*; Eberhard Stoeckle*[11]*; Antonino de Paoli*[12]*; Venu Pillarisetty*[13]*; Carolyn Nessim*[14]*; Carol J. Swallow*[15]*; Sanjay Bagaria*[16]*; Robert Canter*[17]*; John Mullen*[18]*; Hans J. Gelderblom*[19]*; Elisabetta Pennacchioli*[20]*; Frits van Coevorden*[21]*; Kenneth Cardona*[22]*; Rosalba Miceli*[2]*; Alessandro Gronchi*[2]
[1]Brigham and Women's Hospital, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [2]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [3]Maria Sklodowska-Curie Memorial Cancer Center, Institute of Oncology, Warsaw, Poland; [4]Centre Leon Berard, Lyon, France; [5]Tel Aviv Sourasky Medical Center, Tel Aviv, Israel; [6]Royal Marsden Hospital, London, UK; [7]Moffitt Cancer Center, Tampa, FL, USA; [8]Johns Hopkins University School of Medicine, Baltimore, MD, USA; [9]Istituto di Candiolo IRCCS, Torino, Italy; [10]Istituto Clinico Humanitas IRCCS, Milan, Italy; [11]Institut Bergonié, Regional Cancer Centre, Bordeaux Cedex, France; [12]Centro di Riferimento Oncologico, Aviano, Italy; [13]Seattle Cancer Care Alliance, University of Washington School of Medicine, Seattle, WA, USA; [14]The Ottawa Hospital, University of Ottawa, Ottawa, Canada; [15]Mount Sinai Hospital, Princess Margaret Hospital, University of Toronto, Toronto, Canada; [16]Mayo Clinic Jacksonville, Jacksonville, FL; [17]University of California-Davis School of Medicine, Davis, CA, USA; [18]Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; [19]Leiden University Medical Center, Leiden, Netherlands; [20]Istituto Europeo di Oncologia, Milano, Italy; [21]Netherlands Cancer Institute, Amsterdam, The Netherlands; [22]Emory University School of Medicine, Atlanta, GA, USA

Objective: The role of surgery for lrRPS (first relapse) is uncertain, as further recurrence is common. There are

limited data and only one single-institution nomogram on the management of pts with lrRPS. We report the outcomes of the largest series of pts with lrRPS and propose a new nomogram.

Methods: Consecutive pts with lrRPS without distant metastases undergoing definitive resection for their recurrence (2nd surgery) at 22 centers from 2002-2011 were included. Primary endpoints were disease-free and overall survival (DFS, OS) and crude-cumulative-incidence (CCI) of local relapse and distant metastasis from 2nd surgery. Variable selection was performed through a random forest model for survival data using permutation tests. Nomogram for OS was developed using a multivariable Cox model; internal validation was assessed by examining calibration plots and discrimination (bootstrap-corrected Harrell C index).

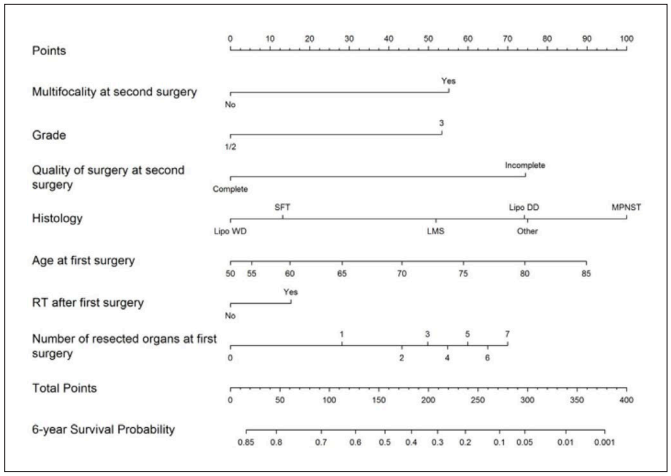
Results: Full data were available for 603 of 684 pts identified (Table). Surgery for the primary RPS was performed at TARPSWG institutions in 188 pts (31%) and elsewhere in 415 (69%). At a median time from initial surgery of 119 months (IQR, 80-169) and from 2nd surgery of 75 months (IQR, 50-105), the 3- and 5-year DFS were 34% (95% CI, 30-38%) and 23% (95% CI, 19-27%) and OS were 70% (95% CI, 66-74%) and 58% (95% CI, 54-63). CCI of second locoregional recurrence and distant metastasis as 1st event from 2nd surgery at 5 years was 58% and 12%, respectively. Metastasis 2 years after 2nd surgery was rare, while risk of 2nd locoregional recurrence continued progressively. On multivariable analysis, institution of first surgery was not significant in predicting outcome after second surgery. Multifocality at 2nd surgery, higher grade, incomplete 2nd surgery, histology other than well-differentiated liposarcoma, older age at 1st surgery, radiation at 1st surgery, and higher number of organs resected at 1st surgery independently predicted overall survival and were incorporated into the nomogram (Figure; C=0.703). Calibration plots for patients undergoing initial surgery at TARPSWG institutions or elsewhere did not differ from the one derived from the entire cohort.

Conclusion: We developed a nomogram predictive of 6-year OS for pts undergoing curative-intent resection for lrRPS. The internally validated nomogram provides an individualized and disease-relevant estimation of OS in pts with lrRPS to assist clinical decision-making. External validation is warranted.

Locoregionally Recurrent RPS

Characteristic		N	% or (1st-3rd quartile)
Gender	Female Male	312 291	51.7 48.3
Age at first surgery (years)	Median	56	(47-64)
Tumor size at first surgery (cm)	Median	18.0	(11.8-26.0)
FNCLCC grade	I II III	195 170 238	32.3 28.2 39.5
Histological subtype	DD LPS WD LPS LMS SFT MPNST Other	266 169 74 14 7 73	44.1 28.0 12.3 2.3 1.2 12.1
Completeness of first surgery	R0/R1 R2 Not available	399 118 74	66.2 19.6 12.3
Resected organs at first surgery	Median None One More than one	1 265 146 192	(0-2) 43.9 24.2 31.8
Tumor rupture at first surgery	No Yes Not available	363 77 163	60.2 12.8 27.0
Multifocality at first surgery	No Yes Not available	400 57 146	66.3 9.5 24.2
Chemotherapy at first surgery	Given (pre/post/pre and post) Not given	88 (18/65/5) 515	14.6 (3.0/10.8/0.8) 85.4
Radiotherapy at first surgery	Given (pre/intra/post/pre and post) Not given	75 (18/3/52/2) 528	12.4 (3.0/0.5/8.6/0.3) 87.6
Tumor size at second surgery (cm)	Median	11.0	(6.4-18.0)
Completeness of second surgery	R0/R1 R2	517 86	85.7 14.3
Resected organs at second surgery	Median None One More than one	2 127 152 324	(1-3) 21.1 25.2 53.7
Tumor rupture at second surgery	No Yes Not available	521 68 14	86.4 11.3 2.3
Multifocality at second surgery	No Yes	378 225	62.7 37.3
Chemotherapy at second surgery	Given (pre/post/pre + post/unknown) Not given	167 (109/42/14/2) 436	27.7 (18.1/7.0/2.3/0.3) 72.3 30.7
Radiotherapy at second surgery	Given (pre/intra/post/pre and post) Not given	185 (85/27/66/4) 418	30.7 (14.1/4.5/11.0/0.7) 69.3
Disease free interval after first surgery (months)	Median	19	(6-41)

Abbreviations: FNCLCC, Federation Nationale des Centres de Lutte Contre le Cancer; LMS, leiomyosarcoma; DD, dedifferentiated; WD, well differentiated; LPS, liposarcoma; MPNST, malignant peripheral nerve sheath tumor; SFT, solitary fibrous tumor; R0, macroscopically complete resection with negative microscopic margins; R1, macroscopically complete resection with positive microscopic margins; R2; macroscopically incomplete resection.



Paper 003 #2797875

NEEDLE TRACT RECURRENCES FOLLOWING CORE BIOPSIES IN RETROPERITONEAL SARCOMA

Winan J. van Houdt, MD, PhD[1]*; A. M. Schrijver*[2]*; Ruben Cohen-Hallalah*[1]*; Nikolaos Memos, Clinical Fellow*[1]*; Myles J. Smith*[1]*; Nikos Fotiades*[3]*; Andrew J. Hayes*[1]*; Frits van Coevorden*[2]*; Dirk C. Strauss*[1]

[1]Department of Surgical Oncology, the Royal Marsden Hospital, London, United Kingdom; [2]Department of Surgical Oncology, Netherlands Cancer Institute, Amsterdam, Netherlands; [3]Department of Radiology, the Royal Marsden Hospital, London, United Kingdom

Objective: Retroperitoneal tumours often require a preoperative core needle biopsy to establish a histological diagnosis. Literature is scarce regarding the risk of biopsies in retroperitoneal sarcomas, so the aim of this study is to identify the potential risks of core needle biopsies causing needle tract recurrences or local recurrences.

Methods: Patients who underwent resection of a primary retroperitoneal sarcoma between 1990 and 2014 were identified from a prospectively maintained database from two tertiary referral centers. Patient demographics, tumor characteristics, biopsy details and follow up data were obtained from either the database or patient files. The primary endpoints were needle tract recurrences and intra-abdominal recurrence.

Results: 498 patients were included in the analysis. The most common histological subtypes were liposarcoma (66%) and leiomyosarcoma (18%). Of the 498 patients that underwent resection, 255 patients were diagnosed with a preoperative biopsy. Details regarding the biopsies are shown in table 1. Five patients (2%) developed a biopsy site recurrence, (3 leiomyosarcomas and 2 dedifferentiated liposarcomas) with a latency period of 0,5-7 years (table 2). All needle tract recurrences occurred after transabdominal biopsies and were not performed with a co-axial technique. Although the number of events was low, a non co-axial technique was signficantly correlated with a higher needle tract recurrence rate (p=0.02), while a trans-abdominal route was not significanlty correlated with a higher needle tract recurrence rate (p=0.11). There was no significant difference in intra-abdominal recurrence rate between the patients with or without a biopsy (=0.30) or between trans-abdominal or trans-retroperitoneal biopsy routes (p=0.72).

Table 1: Biospy details of all patients

Biopsy details n=255	Number of patients (%)
Biopsy route:	-
Trans-abdominal	101 (40%)
Trans-retroperitoneal	55 (22%)
Open	3 (1%)
Trans-rectal	3 (1%)
Transvaginal	1 (0%)
Unknown	92 (36%)
Biopsy technique:	-
Co-axial	109 (43%)
Non-co-axial	102 (40%)
unknown	44 (17%)
Image-guided:	-
Yes	188 (74%)
No	65 (25%)
Unknown	2 (2%)

Table 2: Characteristics of patients that developed needle tract metastases

Age, Gender	Diagnosis	Operation	Latency (years)	Other metastatic disease	Route	Technique
46, M	Grade 2 leiomyosarcoma	R0 Resection and left hemicolectomy	5,5	Yes	Trans-abdominal	non co-axial
73, M	Grade 2 leiomyosarcoma	R0 Resection	7	No	Trans-abdominal	non co-axial
68, M	Grade 2 leiomyosarcoma	R0 Resection, right nephrectomy, right hemicolectomy	6	No	Trans-abdominal	non co-axial
54, F	De-differentiated liposarcoma	R0 Resection, right nephrectomy, right hemicolectomy	2	No	Trans-abdominal	non co-axial
56, M	De-differentiated liposarcoma	R0 Resection	0,5	Yes	Trans-abdominal	non co-axial

Conclusion: The risk of a needle tract recurrence after core needle biopsy for retroperitoneal sarcoma is very low but not zero. The safest method seems a trans-retroperitoneal approach with a co-axial technique. Local recurrence rate is not altered after doing a core needle biopsy.

Paper 004 #2792834

ISOLATED LIMB PERFUSION FOR LOCALLY ADVANCED ANGIOSARCOMA IN EXTREMITIES: A MULTI-CENTER STUDY

Eva A. Huis in 't Veld, BSc[1]*; Dirk J. Grünhagen*[2]*; Kees Verhoef*[2]*; Henry G. Smith*[1]*; Alexander C. van Akkooi*[3]*; Robin L. Jones*[4]*; Frits van Coevorden*[3]*; Andrew J. Hayes*[1]*; Winan J. van Houdt*[1]
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Objective: Angiosarcomas are rare and aggressive sarcomas that account for 2% of all soft tissue sarcomas. The only potential curative treatment is complete surgical excision, but a large subset of patients present with locally advanced disease, which would require morbid surgery or amputation. The aim of this study was to evaluate the effectiveness of Isolated Limb Perfusion (ILP) with high dose melphalan and TNF-α as an alternative treatment option for locally advanced angiosarcoma in the extremities.

Methods: All patients who underwent an ILP for angiosarcomas between 1991 and 2016 in three tertiary referral centres were identified from 3 prospectively maintained databases. Demographics, tumour characteristics, treatment modalities, treatment response, and the disease course were all obtained from either the database or patient files. Statistical analysis was performed using SPSS statistics.

Results: A total of 39 patients were included. The median age was 66 (range, 24-95) years. Of these patients, 23 (58,9%) patients had a complete response after ILP, 10 (25.6%) patients had a partial response, 4 (10.3%) had stable disease and 2 (5.1%) patients had local progression immediately after ILP. Of all patients, a total of 22 patients developed local progression (56,4%) while 10 (25.6%) developed distant metastases. Median time to progression was 7,4 months (95% CI: 3-14,9) and median time to distant metastasis was 6,4 months (95% CI: 1,5-44,9). The 23 (58,9%) patients with a complete response had a significantly prolonged median local progression free survival (15,4 vs. 7,3 months) when compared to all other patients (with partial response, stable- and progressive disease), and a non-significant trend towards better median overall survival (81,2 vs 14,5 months) (p=0,015), and (p=0,054) respectively. A total of 5 patients underwent multiple ILP's, whereby the complete response rate of the first, second and third ILP were 60% (n=4/6), 80% (n=4/5) and 67% (n=2/3) respectively. Only 13 (33,3%) patients needed further surgical intervention, consisting of resection in 8 patients (20,5%) and amputation in 5 patients (12,8%).

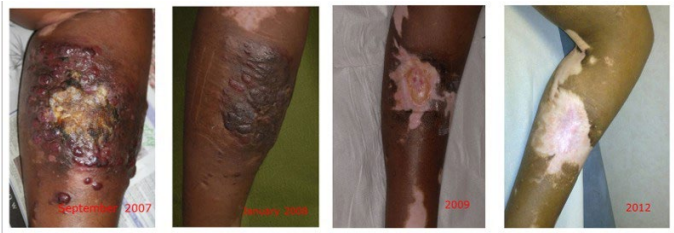

Figure 1. Course of a complete response After ILP for angiosarcoma of the leg. The first picture shows the extensive angiosarcoma before ILP. The other three pictures show the ongoing response after ILP.

Conclusion: ILP is an effective treatment modality for patients with locally advanced extremity angiosarcomas, resulting in a high number of complete responses, a high limb salvage rate, and prolonged local progression-free survival. ILP should be considered as a treatment option in the multidisciplinary management of patients with locally advance angiosarcoma in the extremities.

9:30 am – 10:30 am
– SESSION 2 –
Radiation Oncology

Paper 005 #2804480

5-DAY HYPOFRACTIONATED PREOPERATIVE RADIOTHERAPY IN SOFT TISSUE SARCOMA: PRELIMINARY TOXICITY AND PATHOLOGIC OUTCOMES FROM A PROSPECTIVE PHASE 1/2 CLINICAL TRIAL

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Objective: Conventional preoperative radiation therapy (RT) is an integral component of local control in soft tissue sarcoma (STS), but the 5-week treatment course is logistically challenging and burdensome for patients. Shorter hypofractionated regimens may improve utilization rates, and have been used with preoperative chemotherapy at our sarcoma program for over 20 years. Furthermore, hypofractionated RT may have biological advantages in STS. This prompted us to initiate a phase II study of hypofractionated preoperative RT (HyPORT) for STS. Here,

we report preliminary major wound complication and pathologic response rates from this ongoing study.

Methods: This is an IRB approved prospective phase II study of preoperative RT (6 Gy x 5 fractions delivered daily) for histologically confirmed STS of the extremity or trunk planning to undergo preoperative RT and resection of the primary lesion without neoadjuvant chemotherapy. In this preliminary analysis we evaluated the major wound complication rate using published criteria and also examined pathologic necrosis score (secondary endpoints).

Results: Since May 2016, 24 of 51 patients have completed preoperative RT and undergone surgical resection. Among these patients, median follow-up was 6.5 months (range 0 – 12.5). Median patient age was 60 years (range 30-90). Thirteen of 24 patients had disease involving the proximal lower extremity. The most common histology was undifferentiated pleomorphic sarcoma (25%). Median tumor size was 6.7 cm (range 1.9-28). Intensity-modulated RT was used for 67% of patients. Median time from completion of RT to surgery was 24 days (range 14-50). There was no grade 2 or higher acute radiation dermatitis. Major wound complications occurred in 4 patients (17%); the time from RT to surgery was 14 - 29 days in these patients. These included: (1) dehiscence, which healed after vacuum assisted closure; (2) infection and dehiscence, which healed after surgical revision; (3) dehiscence requiring seroma aspiration, which subsequently healed; and (4) dehiscence requiring vacuum assisted closure and flap reconstruction. The mean pathologic necrosis score after HyPORT was 52% (range 0-100%).

Conclusion: Preliminary data suggest that major wound complication and pathologic necrosis rates after 5-day HyPORT for STS are similar to data from historical controls treated with 5-weeks of conventionally fractionated preoperative RT. Additional patients and longer follow-up are needed to further evaluate this regimen.

Paper 006 #2774385

SUBSTANTIAL VOLUME CHANGES DURING PREOPERATIVE RADIOTHERAPY IN EXTREMITY SOFT TISSUE SARCOMA PATIENTS

Rick Haas, MD, PhD*; Suzanne van Beek; Anja Betgen; Shaheen Ali; Christoph Schneider; Fenna Heres Diddens; Astrid Scholten; Peter Remeijer*
NKI-AVL, Amsterdam, Netherlands

Objective: Except for myxoid liposarcomas (MLS), it is assumed that (extremity) soft tissue sarcomas (ESTS) do not change significantly during preoperative radiotherapy (RT). This study investigates the justification to continue the entire course with just one RT plan. Hereto we used an in-house developed traffic light protocol (TLP) to anticipate on anatomical changes during RT as appreciated by conebeam CT (CBCT).

Methods: In the years 2015-2016, 93 patients with ESTS were treated with either curative (n=73) or palliative intent (n=20) with a regimen of at least 10 fractions, all with the tumors in situ; 30 undifferentiated pleomorphic sarcomas, 19 liposarcomas (of which 12 MLS), 9 myxofibrosarcomas, 6 leiomyosarcomas and 29 other histologies. For all, the CTV- PTV margin was 1cm. Within the TLP, Action Levels (AL) are assigned by radiation technicians. AL Green (an acceptable plan) is defined as an extremity contour change (ECC) <1cm and/or tumor size change (TSC) <0.5cm. AL Orange is defined as any change of larger magnitude. In daily practice, this always results in a physician's action prior to the next fraction.

Results: 924 CBCT logfiles were studied (average 10 CBCT's per patient). In 52 patients the initial treatment plan was fully satisfactory throughout the entire RT course. However in 41 cases (44%) an AL Orange was observed. In 26 patients an increase of 11-34mm was noted (12x TSC only, 3x ECC, 11x both). In 19 patients a decrease of 11-38 mm was observed (16x TSC only, 1x ECC only and 2x both). In the overlapping 4 cases, contours initially increased and subsequently decreased on treatment. In 34 of these 41 cases, the dose distribution was estimated to adequately cover the GTV because of the 1cm PTV margin. For the remaining 7 (8%), the plan was adapted; in 4 on the original CT and in 3 a new CT was acquired. These contour changes were apparent already in the first week of treatment. Of note, in 12 MLS cases, we observed 11x tumor shrinkage of 6-24 mm in week 2-3 of the course. Nevertheless, among the other 81 patients, still in 38% these changes could also be observed.

Conclusion: ESTS change substantially during RT in 44% of all patients, leading to plan adaptations in 8% with PTV margins set at 1cm. RT departments applying smaller margins should be aware that in their setting this rate will be even higher. Daily critical observation of these patients is mandatory to avoid geographical misses (by increase in size) as well as overdosing of normal tissues (when masses shrink).

Paper 007 #2804922

A COMPARISION OF DIFFERENT TREATMENT PARADIGMS FOR SACRAL CHORDOMA: DOES PREOPERATIVE RADIOTHERAPY IMPROVE OUTCOME?

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Objective: The mainstay of treatment for sacrococcygeal chordomas is en-bloc excision with negative margins;

however this often leads to significant morbidity for patients. Even following complete surgical resection there remains a high rate of local recurrence. As such, some institutions combine preoperative radiotherapy with surgical excision in an attempt to reduce the risk of local recurrence in the setting of close resection margins which are inherent to these procedures

The purpose of this study was to compare cohorts from four large tertiary sarcoma centers in North America (USA and Canada) to determine if the addition of preoperative radiotherapy to the treatment protocol for patients with chordoma can improve outcomes, with a specific focus on (1) overall survival; (2) recurrence free survival; and (3) postoperative complications

Methods: We identified 239 patients who underwent surgical excision of a primary sacrococcygeal chordoma at our institutions from 1990-2015 from prospectively collected sarcoma databases. There were 84 females and 155 males, with a mean age of 59 years at the time of surgery and a mean follow-up for surviving patients of 6 years (range 1 to 25 years). The mean time to death was 4 years (range 0 days-14 years). All patients underwent resection with curative intent. Negative margins were obtained in 204 (85%) patients. The most frequent cephalad resection level was S2 (n=76). Neoadjuvant radiotherapy was administered to 105 patients (44%), with a mean dose of 41 Gy. There was no difference in the mean age (P=0.21), proportion of males (P=0.68), mean tumor volume (P=0.25), proportion of high sacral resections (P=0.24) and proportion of positive margins (P=0.10) between patients who did or did not receive radiation. Survival was analyzed using the Kaplan-Meir method with log-rank tests while Cox Proportion Hazard Regression Analysis was used to analyze risk of local recurrence in univariate and multivariate analysis.

Results: The 10-year recurrence-free and overall survival was 59% and 60%. Patients with tumor size greater than 9 cm in maximal dimension were at increased risk of mortality (HR 2.21, 95% CI 1.36-3.65, P=0.001) and disease recurrence (HR 1.94, 95% CI 1.17-3.22, P=0.01). Local recurrence occurred in 40 (17%) patients, with 10-year local recurrence-free survival of 74%. A positive surgical margin (R1 or R2) was strongly associated with local tumor recurrence (HR 2.24, 95% CI 1.07-4.36, P=0.03), and local recurrence was associated with an increased risk of metastatic disease (HR 2.76, 95% CI 1.41-5.22, P<0.001). Postoperative complications occurred in 54% of patients; most commonly wound break down (n=76) and sacral insufficiency fracture (n=27). Preoperative radiotherapy did not reduce the risk of mortality (HR 1.23, 95% CI 0.73-2.04, P=0.42), local recurrence (HR 0.69, 95% CI 0.33-1.35, P=0.29) or development of metastatic disease (HR 1.13, 95% CI 0.57-2.16, P=0.70). However, preoperative radiotherapy did increase the risk of postoperative wound complications (HR 2.85, 95% CI 1.78-4.66, P<0.001) and sacral fractures (HR 6.21, 2.57-17.42, P<0.001).

Table 1: Factors Affecting Overall- and Disease Free Survival Following Surgical Excision of a Sacral Chordoma

Patient Factors	Overall Survival Hazard Ratio (95% CI)	*P Value*	Disease Free Survival Hazard Ratio (95% CI)	*P Value*
Local Tumor Recurrence	1.63 (0.97-2.66)	0.06	-	-
Metastatic Disease	1.58 (0.91-2.67)	0.10	-	-
Positive Surgical Margin	0.90 (0.41-1.73)	0.77	1.55 (0.82-2.72)	0.16
Males	1.53(0.91-2.68)	0.10	1.12 (0.67-1.91)	0.65
Age ≤ 55 Years	0.81 (0.48-1.33)	0.42	1.23 (0.74-2.01)	0.40
Tumor Dimension ≥9 cm	**2.21 (1.36-3.65)**	**0.001**	**1.94 (1.17-3.22)**	**0.01**
Tumor Volume ≥460 cm^3	**1.82 (1.07-3.04)**	**0.02**	1.37 (0.73-2.29)	0.34
Preoperative Radiotherapy	1.23 (0.73-2.04)	0.42	0.82 (0.47-1.37)	0.46
High Sacral Resection	1.56 (0.93-2.69)	0.09	**1.73 (1.05-2.94)**	**0.03**
Patient Factors	**Local Disease Free Survival Hazard Ratio (95% CI)**	***P Value***	**Distant Disease Free Survival Hazard Ratio (95% CI)**	***P Value***
Local Tumor Recurrence	-	-	**3.36 (1.76-6.32)**	**<0.001**
Positive/Marginal Surgical Margin	**2.38 (1.17-4.54)**	**0.01**	1.23 (0.49-2.63)	0.62
Males	0.92 (0.49-1.75)	0.79	1.27 (0.66-2.61)	0.47
Age ≤ 55 Years	1.06 (0.56-1.97)	0.83	1.73 (0.91-3.26)	0.09
Tumor Dimension ≥9 cm	1.37 (0.72-2.56)	0.32	1.91 (0.98-3.70)	0.054
Tumor Volume ≥460 cm^3	1.02 (0.48-2.06)	0.93	0.90 (0.39-1.89)	0.80
Preoperative Radiotherapy	0.67 (0.32-1.29)	0.24	1.13 (0.57-2.16)	0.70
Postoperative Radiotherapy	0.81 (0.39-1.55)	0.54	1.11 (0.55-2.13)	0.74
High Sacral Resection	1.41 (0.76-2.71)	0.27	2.49 (1.26-5.25)	0.007

Conclusion: The ability to achieve a negative margin and tumor size were the most important predictive factors for mortality and local recurrence in the surgical treatment of patients with sacral chordoma. In this retrospective multi-center study, preoperative radiotherapy did not reduce the risk of mortality, local tumor recurrence or metastasis. However preoperative radiotherapy was associated with a significantly increased risk of wound complications and sacral fracture.

Paper 008 #2772139

MRI SURVEILLANCE FOR LOCAL RECURRENCE IN EXTREMITY SOFT TISSUE SARCOMA

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Objective: Local recurrence (LR) is associated with development of distant metastasis and subsequent death in extremity soft tissue sarcoma (STS). Early detection and surgical resection of LR is recommended to achieve best possible oncologic outcome. Thus, effective surveillance strategy for LR after surgery is needed in extremity STS. MRI is the most effective modality for evaluation of STS because of its high soft tissue contrast and its capability in imaging superficial and deep soft tissues. MRI is routinely used for staging and preoperative planning of extremity STS. However, the role of MRI in surveillance for early detection of LR remains uncertain in extremity STS. The aims of this study were 1) to examine the usefulness of MRI in detecting LR, 2) to identify the characteristics of LR detected by MRI, and 3) to examine whether MRI surveillance is associated with oncologic outcome.

Methods: Of the 477 patients who underwent regular surveillance for LR after surgery for extremity STS, surveillance was performed by MRI in 325 patients (MRI surveillance cohort) or other imaging modalities in 152 patients (non-MRI surveillance cohort). All LRs were confirmed by histologic assessment.

Results: The mean number of MRIs per patient was 7.4 (range 1-19) and the mean interval of MRIs was 6 months (range 2- 12). Ninety-six LRs were detected by MRI, clinical examination or ultrasound in 34 (36%), 33 (35%), and 27 (29%) of cases, respectively. The rate of MRI-detected LR, defined as clinically undetectable LR identified on MRI, was 11% in the MRI surveillance cohort (34/325). When characteristics of MRI-detected LRs (n=34) and non-MRI-detected LRs (n=62) were compared, MRI-detected LR were more commonly located in the pelvis or thigh (p=0.006), were smaller (p=0.002) and had LRs without mass formation (p=0.007). In the propensity-matched analysis with 107 pairs, the MRI surveillance cohort had significantly better disease-specific survival than the non-MRI surveillance cohort (p=0.009).

Conclusion: Routine MRI surveillance can detect significant number of asymptomatic LRs in extremity STS. MRI is effective in detecting LRs in the thigh or pelvis, small LRs or LRs without mass formation. Routine MRI surveillance for LR may translate into better oncologic outcome in extremity STS.

11:00 am – 12:30 pm
– SYMPOSIUM 1 –
Medical, Pediatric and Young Adult Oncology

Paper 009 #2762964

ANTITUMOR ACTIVITY OF AXITINIB PLUS PEMBROLIZUMAB IN A PHASE II TRIAL FOR PATIENTS WITH ADVANCED ALVEOLAR SOFT PART SARCOMA (ASPS) AND OTHER SOFT TISSUE SARCOMAS

Breelyn A. Wilky, MD[1]*; Eric Wieder*[1]*; Despina Kolonias*[1]*; Ty Subhawong*[2]*; Matteo Trucco*[3]*; Andrew Rosenberg*[4]*; Darcy Kerr*[4]*; Deukwoo Kwon*[5]*; Efrosyni Sfakianaki*[2]*; Krishna Komanduri*[1]*; Jonathan Trent*[1]
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Objective: Inhibition of programmed-death 1 (PD1) by pembrolizumab (P) monotherapy produced overall response rates (ORR) of 19% in SARC028, a Phase II study in advanced soft tissue sarcomas (STS). Vascular endothelial growth factor (VEGF) promotes accumulation of suppressive immune cell phenotypes and cytokines. Combinations of anti-VEGF receptor tyrosine kinase inhibitors (VEGFR-TKI) with checkpoint inhibitors increased immune cell infiltration and showed promising anti-tumor activity in other solid cancers. Axitinib (Ax) is a pan-VEGFR TKI with favorable progression-free survival (PFS) reported in Axi-STS, with acceptable toxicity in combination with P in renal cell carcinoma. We report initial toxicity and efficacy results of combination Ax plus P for patients (pts) with advanced STS.

Methods: We designed an open-label single institution Phase II trial of Ax plus P in 30 pts with advanced or metastatic STS, requiring radiographically progressing disease, adequate end-organ function and performance status. Pts received Ax at 5 mg PO twice daily with intrapatient dose escalation according to predefined toxicity thresholds, and concurrent P 200mg IV q21 days. Primary endpoint was progression-free rate at 3 months (PFR), with secondary endpoints of toxicity, ORR, PFS, and overall survival. All patients underwent mandatory tumor biopsies and peripheral blood sampling for correlative immunoprofiling at baseline, 12 weeks and at progression.

Results: 28 of 30 pts have accrued to date. Enrolled subtypes: ASPS (29%), UPS (18%), LMS (21%), and other (29%). 3-month PFR by RECIST 1.1 for 18 evaluable pts was 56%, and 4 pts (22%) achieved partial response (PR). Responders include 3/3 (100%) currently evaluable ASPS pts (median tumor size decrease of 70%), and 1 pt with non-uterine LMS (tumor size decrease 55%). Clinical benefit was observed in 3 pts with RECIST progression at 3 months, suggesting a need for alternative response criteria such as Choi criteria. Ax plus P was overall well-tolerated, with P-related grade 3/4 toxicities in 3 pts (autoimmune hepatitis, arthritis and hyperglycemia), and Ax-related grade 3/4 toxicities in 2 pts (hypertriglyceridemia, spontaneous pneumothorax). Updated response and toxicity data will be presented. Correlative immunoprofiling is ongoing.

Conclusion: Combination Ax plus P is feasible and well-tolerated, and shows early evidence of activity, particularly in ASPS pts. Clinical trial information: NCT02301039.

Paper 010 #2804799

A PHASE II MULTI-ARM STUDY TO TEST THE EFFICACY OF DURVALUMAB AND TREMELIMUMAB IN MULTIPLE SARCOMA SUBTYPES

Neeta Somaiah, MD[1]*; Anthony Conley, MD*[1]*; Heather Lin*[3]*; Beatriz Sanchez-Espiridion*[2]*; Behrang Amini*[4]*; Vinod Ravi*[1]*; Dejka Araujo*[1]*; Shreyaskumar Patel*[1]*; Robert Benjamin*[1]*; M. Alejandra Zarzour*[1]*; Sharjeel Sabir*[4]*; Wei-Lien Wang, MD*[2]*; Alexander Lazar*[2]*; Ignacio Wistuba*[2]*; Patrick Hwu*[1]
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Objective: Single agent anti-PD1 therapy has shown responses in certain sarcoma subtypes. Durvalumab (D) is a human IgG1 kappa mAb directed against PD-L1

and tremelimumab (T) is a human IgG2 mAb specific for CTLA-4, with no cross-reactivity to related human proteins. Given that combination checkpoint blockade leads to improved efficacy, we designed this study to evaluate the clinical benefit of D and T in multiple sarcomas and identify immune markers of response or resistance.

Methods: This single-center phase II study enrolled patients (pts) (age ≥12 years) with previously treated metastatic sarcoma into the following arms: liposarcoma (LPS), leiomyosarcoma (LMS), angiosarcoma, undifferentiated pleomorphic sarcoma (UPS), synovial sarcoma, osteosarcoma, alveolar soft part sarcoma (ASPS) and others. Pts received D 1500 mg and T 75 mg q4wks for 4 cycles followed by D 1500 mg q4wks. Primary endpoint was PFS rate at 12 wks. Statistical design based on Bayesian modeling monitored pts in cohorts of 5 per arm. If the PFS at 12 wks was unlikely to be > 40% or unacceptable toxicity rate was likely to be > 30%, then that arm would close. Secondary objectives included defining safety / tolerability, response (irRC and RECIST) and survival. Biopsies were collected at baseline and at 6 wks for flow, immunohistochemistry (IHC), PD-L1, multiplex IHC staining and sequencing.

Results: Of the 49 pts enrolled so far, 46 started therapy and were included in the preliminary efficacy analyses. Pt characteristics in Table 1. PR by irRC were seen in UPS (1/4, 25%), angiosarcoma (1/5, 20%) and ASPS (1/5, 20%). With a median follow-up (fu) of 3.7 mo (range 0.9-14.8), the median OS (95% CI) is 14.5 mo (4.7, not reached) and the median PFS (95% CI) is 4.1 mo (2.8, 5.5). The 6 ASPS pts remain on study with 3 showing decrease in tumor volume (median fu 4.8 mo, range 1.8 – 8.2 mo). A total of 17 grade ≥3 related adverse events were recorded in 10 (21.7%) pts and included colitis, nausea, cardiac dysfunction, thyroiditis, pneumonitis, hepatitis, myositis, anemia and fatigue. All patients had baseline tumor (45 fresh, 4 FFPE) and 37 had on-treatment biopsies. Quality check revealed that 92% of baseline and 100% of wk 6 biopsies had >10% tumor cells. An increase in immune infiltrate (CD3+) on treatment was noted in WD/DD LPS (2/4 analyzed), UPS (1/1 analyzed), osteosarcoma (3/3 analyzed) and ASPS (2/3 analyzed).

Conclusion: D and T showed acceptable tolerance with an encouraging PFS and OS in heavily pretreated sarcoma pts. Increase in immune infiltrate might be an indicator of response or disease stabilization. Promising activity noted in the ASPS arm that remains open for enrollment.

Patient Characteristics

Arms	Frequency	Age Mean (SD)	Gender (M/F)	ECOG (0,1,2)	Prior lines of chemotherapy
LPS (WD/DD, pleomorphic)	6 (5,1)	64.2 (8.4)	5/1	4,2,0	2 (1-5)
Vascular Sarcomas (angiosarcoma, LMS, Solitary fibrous tumor)	11 (5,5,1)	53.9 (12.5)	3/8	9,1,1	4 (1-6)
Undifferentiated pleomorphic sarcoma	4	56.4 (18.6)	3/1	2,2,0	5 (3-7)
Synovial Sarcomas	4	32.8 (6.5)	2/2	4,0,0	1.5 (1-7)
Osteosarcoma	5	45.8 (17.4)	3/2	1,4,0	3 (2-5)
ASPS	6	37.8 (10.4)	2/4	5,1,0	1.5 (1-6)
Other	10	43.2 (16.4)	6/4	5,5,0	3 (1-6)
Total	46	48.3 (15.8)	24/22	30,15,1	3 (1-7)

Paper 011 #2785448

PHASE I STUDY OF TALAZOPARIB AND IRINOTECAN IN CHILDREN AND YOUNG ADULTS WITH RECURRENT OR REFRACTORY SOLID MALIGNANCIES

Sara M. Federico, MD[1]*; Elizabeth Stewart, MD*[1]*; Jamie L. Coleman*[2]*; Michael W. Bishop, MD, MS*[1]*; Victor Santana*[1]*; Catherine Lam*[1]*; Dana Hawkins*[1]*; Jianrong Wu*[3]*; Shenghua Mao*[3]*; Alberto S. Pappo*[1]*; Michael Dyer*[4]

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Objective: Poly (ADP-ribose) Polymerase inhibitors (PARPi) target tumors with deficiencies in DNA repair mechanisms. Talazoparib, a potent PARP inhibitor, demonstrated significant efficacy in the treatment of a murine Ewing sarcoma model when combined with DNA-damaging irinotecan. We performed a phase I trial to determine the maximum tolerated doses (MTDs) of talazoparib and irinotecan in pediatric patients with solid malignancies.

Methods: Cohorts of 3-6 eligible patients with recurrent/refractory solid tumors received escalating doses of oral (PO) talazoparib and intravenous (IV) irinotecan in a 3+3 design (Table 1). Talazoparib was administered on days 1-6 and irinotecan was given on days 2-6. Each course lasted 21 days. Serum for talazoparib and irinotecan pharmacokinetics (PK) were obtained during course 1. Toxicities were assessed using CTCAE v.4 and responses were evaluated by RECIST v.1.1.

Results: Twenty-four patients (9 male; median age, 11 years; 18 recurrent) received a median of 2 courses (range, 1-19). Patients had recurrent or refractory Ewing sarcoma (n=12), rhabdomyosarcoma (n=3), osteosarcoma (n=3), synovial sarcoma (n=2) and 1 each with neuroblastoma, wilm's tumor, adrenocortical carcinoma and desmoplastic small round cell tumor. Fifteen patients had prior exposure to irinotec-

Table 1. Dose escalation schema and dose limiting toxicities per dose level.

Dose Level	Talazoparib mcg/m^2/dose PO	Talazoparib Schedule Days (D)	Maximum Talazoparib (mcg/dose)	Irinotecan mg/m^2/ dose, IV daily	# of pts	DLT course 1 (# of pts)
1	400	D 1-6: daily	800mcg	20	6	Thrombocytopenia (1), GGT (1)
2	600	D 1: twice a day D 2-6: daily	D 1: max 500mcg/dose D 2-6: max 1000mcg/dose	20	3	0
3	600	D 1: twice a day D 2-6: daily	D 1: max 500mcg/dose D 2-6: max 1000mcg/dose	30	6	Neutropenia (1)
4	600	D 1: twice a day D 2-6: daily	D 1: max 500mcg/dose D 2-6: max 1000mcg/dose	40	6	Neutropenia (1)
5	600	D 1: twice a day D 2-6: daily	D 1: max 500mcg/dose D 2-6: max 1000mcg/dose	50	3	Thrombocytopenia (2), neutropenia (2), GGT (1), colitis (1)

an. Table 1 summarizes the dose-limiting toxicities (DLTs) experienced in course 1. The most common grade 3 or higher non-hematologic and hematologic toxicities in 95 evaluable courses were febrile neutropenia (4), elevated gamma-glutamyltransferase (GGT, 2), neutropenia (12) and lymphopenia (17). Three of 24 evaluable patients had a response (CR Ewing sarcoma, 19 courses; PR synovial sarcoma, 10 courses; PR Ewing sarcoma, 7+ courses) and 9 had disease stabilization, median 4 courses (range, 4-10). Results of PK tests will be presented.

Conclusion: Administration of talazoparib with irinotecan is feasible and well-tolerated in a pediatric population. The recommended phase II doses are oral talazoparib 600mcg/m2 (max 1000mcg/dose), days 1-6 and intravenous irinotecan 40mg/m2/day, days 2-6. This regimen demonstrated anti-tumor activity in a subset of solid malignancies, specifically Ewing sarcoma. Additional studies are warranted.

Paper 012 #2804636

OPEN LABEL NON-RANDOMIZED MULTI-COHORT PILOT STUDY OF GENETICALLY ENGINEERED NY-ESO-1 SPEAR T-CELLS IN HLA-A2+ PATIENTS WITH SYNOVIAL SARCOMA (NCT01343043)

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NY-ESO-1 is expressed in approximately 70% of synovial sarcomas (SS). Specific peptide enhanced affinity receptor (SPEAR) T-cells (NY-ESO-1c259T-cells) recognizing an NY-ESO-1 derived peptide complexed with HLA-A*02 are being studied in SS.

Methods: Eligible patients are HLA-A*02:01, 02:05 or 02:06, with unresectable, metastatic or recurrent SS expressing NY-ESO-1. Primary endpoint of ORR (CR+PR) is evaluated in high (≥ 50% tumor cells express 2+/3+) and low (≥ 1+ in ≥ 1% cells, not exceeding 2+/3+ in ≥ 50% cells) NY-ESO-1 expressers with different lymphodepleting regimens (Table). Secondary endpoints are safety, DOR, PFS, OS, and gene-marked cell persistence. Lymphocytes are obtained by leukapheresis, isolated, activated, transduced to express NY-ESO-1c259T, and expanded. Target dose is 1–6 × 109 cells. Disease is assessed at weeks 4, 8 and 12 post-T-cell infusion, and then every 3 months.

Results: 39 patients have been enrolled with 28 treated. 51% are male; median age is 32 yr (range 15 – 73). 12/15 patients in cohort 1 were treated. ORR was 50% (1 CR; 5 PR). Time to response was 6 wk (range 4-9) and median DOR 31 wk (range 13-72), and median OS of ~120 wk (95% CI 37, NE). Cohort 3 was closed due to only 1 PR out of 5 pt. Evaluation is ongoing in cohorts 2 (6 enrolled; 5 treated, 2 PRs) and 4 (10 enrolled; 6 treated, 3 PR, 3 SD, with limited post infusion follow up). The most common AEs are leukopenia (93%), pyrexia (89%), nausea (86%), neutropenia and thrombocytopenia (79%), anemia (75%), and lymphopenia (71%). 12 events of CRS were reported (3 G3; 1 G4); all resolved with supportive therapy. There have been no events of seizure, cerebral edema or fatal neurotoxicity to date. One fatal SAE (bone marrow failure) occurred in cohort 2; investigations have not identified a mechanism by which NY-ESO-1c259T may have caused this event.

Conclusion: NY-ESO-1 SPEAR T-cell therapy has promising efficacy and acceptable safety. CRS is not associated with severe neurotoxicity and appears manageable with appropriate supportive care. Cohort 3 data indicate

that fludarabine may be important for efficacy. Efficacy and safety data from Cohorts 2 and 4 will be further evaluated and presented.

Cohort	NY-ESO-1 expression	Lymphodepletion
1*	high	Fludarabine (Flu) 30 mg/m2/day × 4 cyclophosphamide (Cy) 1800 mg/m2/day × 2
2	low	Flu 30 mg/m2/day × 4 Cy 1800 mg/m2/day × 2
3*	high	Cy 1800 mg/m2/day × 2
4	high	Flu 30 mg/m2/day × 3, Cy 600 mg/m2/day × 3

*Closed

Paper 013 #2789203

A PHASE 2 TRIAL OF CABOZANTINIB (XL184) IN METASTATIC REFRACTORY SOFT TISSUE SARCOMA

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Objective: Soft tissue sarcomas (STS) are a rare group of tumors (~1 % of adult cancers) arising mainly from embryonic mesoderm. Increased expression of VEGF and MET has been reported both in sarcoma cell lines and patients (pts) with STS. Cabozantinib, a multi-kinase inhibitor of MET, VEGFR2, AXL, RET, ROS1 is approved for treatment of renal cell carcinoma and medullary thyroid cancer. Dual targeting of VEGF and MET pathways with cabozantinib is hypothesized to result in clinical benefit for pts with STS. We are conducting a 2-stage, open-label, phase II trial of cabozantinib monotherapy (NCT 01755195) evaluating a dual-endpoint of response rate (CR+PR) of 30% vs. 10%, and a 6-month PFS rate of 65% vs 45% in pts with STS. Secondary objectives include measuring circulating levels of HGF, VEGF-A, soluble VEGFR2 (sVEGFR2), and soluble MET (sMET) pre- and post-treatment, which will be collected in the second stage pts.

Methods: Cabozantinib is administered orally at 60 mg po qd for 28d cycles. Eligibility criteria includes pts ≥18 years; ECOG PS ≤ 1, adequate organ functions. No cavitating mass or vessel-encasing lesions are permitted. Antitumor responses are determined using RECIST 1.1 criteria.

Results: The study has accrued 27 pts at NCI (Alveolar soft part sarcoma (ASPS) (6), leiomyosarcoma (5), clear cell sarcoma (3), liposarcoma (2), synovial sarcoma (2) and one each of embryonal sarcoma, MPNST, myxoid chondrosarcoma (MC), myoepithelioma, myxoid cell sarcoma, GIST). At time of analysis, 5 pts remain on study. Time on study 7-47 months. Four pts have confirmed PRs (2 ASPS, 1 liposarcoma, 1 MC); time to PR was 4 – 22 months and response duration averaged 39 months. Twelve pts have SD for six months. Median PFS was 9.6 months. Drug related grade 3/4 adverse events include 5 HTN (21%), 3 neutropenia (13%), 2 abdominal pain (8%), 2 lipase elevation (8%), 2 thromboembolic events (8%), and one each (4%) of left ventricular dysfunction, alkaline phosphatase elevation, enterocolitis, fatigue, mucositis, nausea, hand-foot syndrome, transaminitis. 8 pts required dose reductions, including 2 reductions in 3 pts.

Conclusion: This is the first phase II study of cabozantinib in STS. Having met our first stage response objective, we are accruing at multi-sites with plans to assess a total of 50 patients.

Paper 014 #2797611

PREOPERATIVE PAZOPANIB IN HIGH-RISK SOFT TISSUE SARCOMA (STS): PHASE II WINDOW-OF-OPPORTUNITY STUDY OF THE GERMAN INTERDISCIPLINARY SARCOMA GROUP (NOPASS/GISG-04)

Ulrich Ronellenfitsch, MD[1]*; Antonia Dimitrakopoulou-Strauss*[2]*; Jens Jakob*[3]*; Bernd Kasper, MD, PhD*[4]*; Kai Nowak*[3]*; Lothar Pilz*[5]*; Ulrike Attenberger*[6]*; Timo Gaiser*[7]*; Derigs Hans-Günter*[8]*; Matthias Schwarzbach*[9]*; Peter Hohenberger*[10]

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Objective: Preoperative devascularisation might improve the local control and by this way the outcome of patients (pts) with primary high-risk STS. The multikinase inhibitor pazopanib is approved for treatment of metastatic STS and has pronounced antiangiogenic effects. We conducted a trial of preoperative pazopanib therapy in high-risk STS.

Methods: The trial was single arm phase II with exact sin-

gle-stage design. Eligible pts had resectable, non-metastatic, untreated high-risk (G2/3, ≥5 cm) STS of any location and ECOG PS < 2 with adequate organ function and no relevant comorbidity. Pts received pazopanib 800 mg daily during wait time for surgery (21 days 'window-of-opportunity') followed by surgery 7-14 days later. Primary end-point was the metabolic response rate (MRR; proportion of pts with a 50% reduction of the mean standardized uptake value [SUVmean] in post- vs. pretreatment FDG-PET-CT). Treatment was considered ineffective at an MRR≤0.2 (H0) and effective at an MRR≥0.4 (H1). Planned sample size was 35 pts (type I error 5%, type II error 20%). H0 was to be rejected if ≥12 pts had metabolic response. ClinicalTrials.gov: NCT01543802

Results: A futility analysis was performed after 21 pts (m/f 10/11, mean[range] age 67[46-81] yrs; extremity n = 9, trunk/retroperitoneum (RPS) n = 12 , liposarcoma 15/21). 17/21 pts were evaluable for the primary endpoint (2 withdrew, 1 PD, 1 no hypermetabolism in PET). The MRR was 1/17 (5.9%, 95%CI < 0.01-0.29) with the patient experiencing a 65% decrease in SUV. Mean change in SUVmean of post- vs. pretreatment PET was minus 6% (i.e. 6% decrease), the range was minus 65% to plus 34%, thus indicating tumor progression. 7/21(33.3%) pts had 12 grade 3/4 toxicities. 20/21(95.2%) pts were resected (all R0), of these, one pt (4.8%) with a RPS suffered a grade 4 postoperative complication (anastomotic leakage).

Conclusion: Preoperative pazopanib for STS failed to reduce tumor metabolism and cannot be recommended in this indication. Its preoperative use does not increase surgical morbidity. Future studies could address the combination of the drug with radiation.

1:30 pm – 2:15 pm

– SPECIAL SESSION 1 –
Sarcoma of the Year: Epithelioid Sarcoma

Paper 015 #2767796

PHASE I STUDY OF EVEROLIMUS (MTOR INHIBITOR) IN COMBINATION WITH VANDETANIB (MULTIKINASE INHIBITOR OF EGFR, VEGFR, AND RET) IN CHILDREN, ADOLESCENTS AND YOUNG ADULTS WITH SARCOMA AND OTHER ADVANCED SOLID TUMORS

Sheetal Phadnis[2]; Winston Huh[2]; Cynthia E. Herzog[2]; Najat C. Daw, MD[2]; Douglas J. Harrison[2]; Erica N. Ward[2]; Sarina Piha-Paul[1]; Tarak Bhatt[1]; Estella P. Mote[2]; Richard Gorlick[2]; Funda Meric-Bernstam[1]; Cindy L. Schwartz[3]; ***Vivek Subbiah, MD[1]***

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Objective: Early phase clinical trials are often limited to adults, reducing the opportunity to explore safety and efficacy of new agents in children. Pre-clinical models have shown that combining an mTOR inhibitor (everolimus) with a multikinase VEGFR2 inhibitor (vandetanib) overcomes intrinsic and /or acquired resistance to either agent alone. Since this combination may have activity against pediatric cancer, pediatric patients including sarcoma were eligible for enrollment (NCT01582191).

Methods: We designed a conventional 3+3 Phase I study to determine the safety, maximum tolerated dose (MTD), recommended Phase II dose (RP2D), and dose-limiting toxicities (DLTs) of this combination using oral vandetanib and oral everolimus in pediatric patients with advanced cancers. Younger patients were enrolled at the accruing dose level, with BSA-based dose adjustments for smaller children. Tumor responses were assessed using RECIST v1.1.

Results: Among the 21 pts enrolled to date median age was 18 years (range 8-24 years) & 8 pts (38%) were male. The most common diagnosis was sarcoma (n=14; 11 soft tissue and 3 bone). Five pts (24%) had 2 or more sites of metastases. One pt was treated at dose level 0 (vandetanib 100 mg daily + everolimus 2.5 mg daily), another at dose level 1 (vandetanib 200 mg daily + everolimus 2.5 mg daily), and 19 patients at RP2D/MTD dose level 4 (vandetanib 300 mg daily + everolimus 10 mg daily). The most common adverse events observed in pts across different dose levels included G1 rash (n=7); G1-G2 fatigue (n=4); G1 diarrhea (n=3); G1-G2 hypertension (n=1); G1-G2 QTc prolongation (n=2); G1 hypertriglyceridemia/hypercholesterolemia (n=3); G1-G4 transaminitis (n=9); G1-G4 thrombocytopenia (n=5). Fourteen patients (66%) were taken off study due to disease progression and three patients (14%) due to drug toxicity. One patient with epithelioid fibrosarcoma with CDKN2A/B loss, who had rapid hyperprogressive disease on PDL1 inhibitor, continues on trial with disease stabilization after 8 months of therapy. Another patient with epithelioid sarcoma had a PR (74% tumor size reduction). Two patients with alveolar soft part sarcoma had stable disease for up to 14 months. Clinical benefit rate (PR+ SD >4mo) was 33%.

Conclusion: Evidence of response was noted in heavily pre-treated pediatric patients with sarcomas including 2 epithelioid sarcoma patients. Including younger patients in institutional phase I trials provides a mechanism to study new combinations in the pediatric population.

Paper 016 #2799040

EZH2 INHIBITOR TAZEMETOSTAT IN ADULT AND PEDIATRIC PATIENTS WITH EPITHELIOID SARCOMA: RESULTS FROM 3 PROSPECTIVE CLINICAL TRIALS

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Objective: Epithelioid sarcoma (ES) accounts for <1% of all soft tissue sarcomas (STS). Local disease may be indolent, but ES can rapidly spread, and patients (pts) with distant metastases are often resistant to systemic therapy with 1-year survival of <50%. The defining molecular feature of ES is absence of tumor expression of INI1 (SMARCB1), a SWI/SNF subunit member involved in chromatin remodeling. Tazemetostat, a potent and selective EZH2 inhibitor, demonstrated tumor regressions in INI1-negative preclinical malignant rhabdoid tumors models. The proposed mechanism of tazemetostat sensitivity is that INI1 loss compromises SWI/SNF activity and tumor dependence on PRC2 activity (of which EZH2 is the catalytic subunit).

Methods: Three open-label multicenter trials (Ph1 pediatric, Ph1 and Ph2 adult) including pts with advanced ES evaluated preliminary safety and efficacy of oral tazemetostat. Primary and/or secondary endpoints in all studies included overall response rate (ORR), disease control rate (DCR; objective confirmed response of any duration or stable disease [SD] lasting ≥32 wks), duration of response, progression-free survival (PFS), overall survival, safety/tolerability, pharmacokinetics and response biomarkers (e.g. H3K27me3), and recommended Ph2 dose (RP2D) (Ph1 only).

Results: As of May 1, 2017, of 3 ES pts in the Ph1 adult study, 1 had progressive disease (400 mg twice daily [BID]); 2 had SD (800 mg BID) through 80 and 88 weeks, respectively, and both continue on study drug at 121 weeks. Of 2 ES pts in the pediatric study, 1 pt had SD (300 mg/m2) but discontinued, and 1 had confirmed CR and remains on study at 24 weeks (700 mg/m2).

In the ongoing Ph2 study (n=31; treated at RP2D of tazemetostat 800 mg BID), interim results show 4 pts had confirmed partial response and 6 pts had SD ≥32 weeks (ORR = 13% and DCR = 32%; median PFS = 5.7 months); with 8 pts remaining on treatment. Tazemetostat was well tolerated; no pts discontinued due to an adverse event (AE). Grade 1/2 fatigue (42%), nausea (26%), and decreased appetite (26%) were the most frequently reported AEs regardless of attribution. Study expanded to include an additional 30 adult ES pts.

Conclusion: The clinical experience of tazemetostat monotherapy to date across adult and pediatric ES pts includes both encouraging antitumor activity consisting of objective responses and prolonged stable disease, along with a favorable safety/tolerability profile.

Paper 017 #2804779

ANTHRACYCLINE, GEMCITABINE AND PAZOPANIB IN EPITHELIOD SARCOMA: UPDATED RESULTS OF A RETROSPECTIVE MULTI-INSTITUTIONAL CASE SERIES

Anna Maria Frezza[1]*; Naofumi Asano, MD, PhD*[2]*; Robin L. Jones*[3]*; Ravin Ratan, MD*[4]*; Eytan Ben-Ami, MD*[5]*; Pawel Teterycz*[6]*; Hans J. Gelderblom*[7]*; Kjetil Boye, MD, PhD*[8]*; Mehdi Brahmi*[9]*; Emanuela Palmerini*[10]*; Nadia Hindi, MD, MSc*[11]*; Alexander Fedenko*[12]*; Bruno Vincenzi*[13]*; Paolo G. Casali*[1]*; Silvia Stacchiotti, MD*[1]

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Objective: To update the results previously reported on a multi-institution retrospective study on the activity of anthracycline-based (Ab) and gemcitabine-based (Gb) regimens as well as pazopanib (P) in patients with advanced epithelioid sarcoma (ES) treated within 16 sarcoma reference centres in Europe, US and Japan.

Methods: Patients with a histologically confirmed diagnosis of locally advanced/metastatic ES were selected. Classic and distal subtypes were defined based on morphology (WHO 2014). INI1 was evaluated. Response was assessed by RECIST. Progression-free survival (PFS) and overall survival (OS) were computed by Kaplan-Meier method.

Results: One-hundred-five ES patients were identified (Table 1). They were treated with Ab (81), Gb (40) and

P (20); 32 patients received more than one treatment. The median follow-up for Ab, Gb and P groups was 32, 23 and 22 months, respectively. The response rate (RR) for Ab was 25%, with a median PFS and OS of 6 and 17 months. One complete response was reported. The RR for Gb was 27% (95% CI 10% - 42%), with 2 complete responses and a median PFS and OS of 5 and 22 months. In the P group, no objective responses were reported, and median PFS and OS were 2 and 14 months. A non-statistically significant trend towards a greater RR in proximal than classic subtype was seen in Ab (30% vs 18%) but not in the Gb group.

Table 1. Population characteristics

	Ab (N=81)	Gb (N=40)	P (N=20)
Median age (IQR)	32 (25-47)	35 (27-46)	29 (20-43)
Gender (%) Male Female	- 54 (67) 27 (33)	- 24 (60) 16 (40)	- 13 (65) 7 (25)
Primary site (%) Distal Proximal	- 36 (50) 36 (50)	- 19 (48) 21 (52)	- 11 (55) 9 (45)
Histological subtype (%) Classic Proximal	- 35 (43) 46 (57)	- 20 (50) 20 (50)	- 9 (45) 11 (55)
Stage (%) Locally advanced Metastatic	- 27 (33) 54 (67)	- 5 (13) 35 (87)	- 4 (20) 16 (80)
Previous lines of treatments (%) 0 1 2 > 2	- 71 (88) 8 (10) 0 2 (2)	- 13 (33) 19 (48) 6 (15) 2 (5)	- 2 (10) 9 (45) 5 (25) 4 (20)

Conclusion: This retrospective series, the largest currently available, confirms the activity of Ab and Gb in ES, with a similar RR and PFS in both groups. In this population, the value of P seems limited, although it was administered as a later line of therapy. These data may serve as a benchmark for trials of novel agents in ES.

2:15 pm – 3:00 pm
– SESSION 3 –
Soft Tissue Sarcoma

Paper 018 #2758507

BENEFIT OF ADJUVANT CHEMOTHERAPY COMBINED WITH ACCELERATED RADIOTHERAPY IN HIGH-RISK SOFT TISSUE SARCOMA DEFINED BY SIZE, VASCULAR INVASION, NECROSIS AND GROWTH PATTERN - A SCANDINAVIAN SARCOMA GR

Kirsten S. Hall, PhD[1]*; Øyvind S. Bruland*[2]*; Bodil Bjerkehagen*[3]*; Jacob Engellau*[4]*; Oskar Hagberg*[5]*; Clement Trovik*[6]*; Mikael Eriksson*[4]

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Objective: Adjuvant chemotherapy to improve survival rates in high-grade soft tissue sarcomas(STS) remains controversial. This prospective, non-randomized study (SSG XX) was designed to examine the feasibility and benefits of adjuvant chemotherapy(CT) with interposed radiotherapy(RT) in a defined subgroup with specific morphological characteristics previously shown to have a high risk of metastases. The 5-years cumulative incidence of metastases in patients with the same risk-profile has previously been reported to be about 50% (Engellau J et al. Eur J Cancer 2007; 43:1927-34).

Methods: High-risk STS was defined as having high-grade morphology (FNCLCC II and III) and either vascular invasion or at least 2 of the following criteria: tumor size >8 cm, necrosis, and infiltrative growth, determined morphologically. Six cycles of doxorubicin (60mg/m2) and ifosfamide (6mg/m2) were prescribed. For subcutanous tumors excised with a wide margin or radical amputation CT only was given (A1). Hyperfractionated/accelerated RT to 36 Gy (1.8 Gy twice daily) was interposed between the third and fourth cycle after wide margins for deeply located tumors and marginal margins for all tumors (A2). A boost of 9 Gy was added in case of intralesional margins (A3).

Results: Median follow-up was 4.4 years (range 0.2-8.7). The SSG Pathology Reference Group reviewed the morphology, grading, vascular invasion and growth pattern. For the 150 eligible patients out of 160 included the 5-year metastasis-free survival (MFS) was 70.4% (95% CI 63.1-78.4) and overall survival (OS) 76.1% (95% CI 68.8-84.2) . For A1(19 patients) MFS was 72.2 % (95% CI 54.2-96.2) and OS 83.3% (95% CI 67.8-100) and for A2

(119 patients) 67.2% (95% CI 58.9-76.5) and 72.9% (95% CI 64.4-82.5), respectively. For A3 (12 patients) both MFS and OS were 100% (95% CI 74.5-100). Tumor size(>10 cm), deep location, and reduced CT dose
(< 70%) had a negative impact on survival. Radiotherapy including local recurrences and toxicity will be presented elsewhere.

Conclusion: A benefit of adjuvant chemotherapy was demonstrated in STS patients with defined poor prognostic factors. Vascular invasion, tumor size, growth pattern and necrosis should be considered to depict patients for adjuvant chemotherapy.

Paper 019 #2803418

IMPROVED OVERALL SURVIVAL (OS) BY NEOADJUVANT THERAPY IN PATIENTS (PTS) WITH HIGH-RISK SOFT TISSUE SARCOMA (HR-STS) OF EXTREMITY (E) AND NON-EXTREMITY (NE)

Lars H. Lindner[1]*; Rolf D. Issels, MD, PhD*[1]*;*
Jaap Verweij[2]*; Peter Reichardt*[3]*; Rüdiger Wessalowski*[4]*;*
Christoph Salat[1]*; Alessandro Gronchi*[5]
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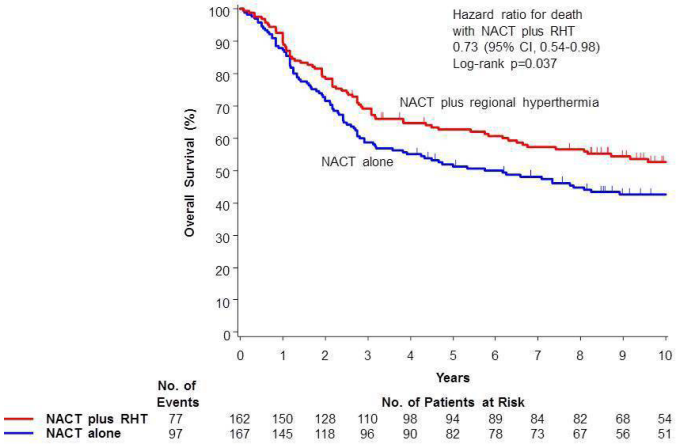
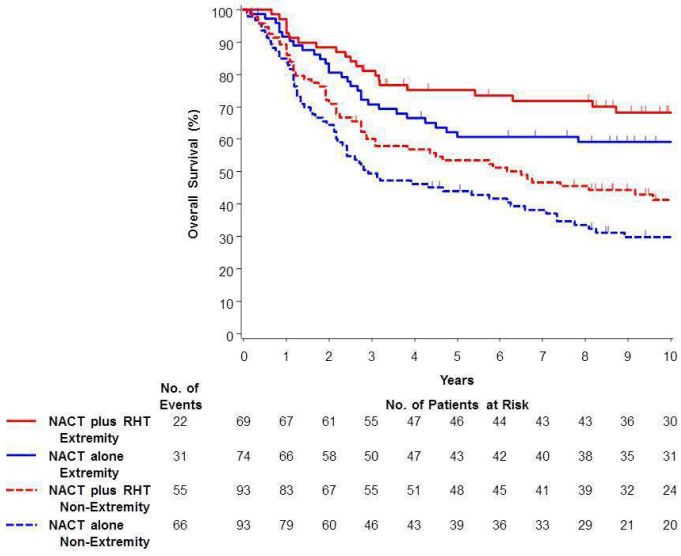
Objective: Neoadjuvant chemotherapy (NACT) is increasingly used and demonstrated an improved OS for HR-STS (Gronchi 2016). By adding regional hyperthermia to NACT within a randomized phase 3 trial we could demonstrate an improved LPFS as the primary endpoint after 34 months follow-up (Issels 2010).The long-term results for OS of patients with HR-STS of E or NE -mainly retroperitoneal and visceral tumors- are presented.

Methods: Pts were recruited between1997 and 2006. Pts with localized, HR-STS (≥5cm, FNCLCC grade 2 or 3, deep),were randomly assigned to either NACT or combined with regional hyperthermia (NACT plus RHT). Unresectable tumors were not excluded. Pts were stratified according to site (E vs NE), presentation of tumor (primary vs recurrent vs prior surgery), and center. OS was defined as the time to death due to disease or treatment.

Results: 329 randomized pts were eligible. Compared to NACT alone, the addition of RHT improved OS (74.4 months vs 184.8 months; HR 0.73; log-rank P=0.037). The OS showed an absolute 11.4% improvement at 5-years (62.7% vs 51.3%) and 11.7% improvement at 9-years (54.4% vs 42.7%). We noted a delayed separation of OS curves between the treatment groups at 14 months. The landmark analysis for OS excluding pts prior this time point remained significant in favour of NACT + RHT (log-rank P=0.043). For E tumors, the 5-year-OS was 75% vs 60%, and 10-year OS was 68% vs 58%. For NE tumors, the 5-year OS was 53% vs 43%, and 10-year OS was 39% vs 29%. The higher OS due to NACT+RHT was consistent across all subgroup factors (age, site, disease status, type of surgical resection, radiotherapy, size, grade and histologic subtype).We further analyzed the reasons of improved OS in pts with E and NE tumors. In E tumors, regional hyperthermia increased curative R0 resections from 39.6% to 62.5%, reduced distant metastases from 43.2% to 33.3%, and finally, reduced mortality due to distant disease from 39.2% to 29.4%. In NE tumors, curative R0 resections (42.6% vs 40.4%) and distant metastases (49.5% vs 51.6%) were similar. The OS benefit was related to improved local control. Local failure rate was reduced from 32.3% to 20.4% and mortality due to local failure was reduced from 23.7% to 10.8%.



Overall Survival by Treatment Group (N=329)



Overall Survival Stratified by Extremity (N=143) vs Non-Extremity (N=186)

Conclusion: With a median long-term follow-up of 11.3 years, the results provide robust evidence that regional hyperthermia added to anthracycline and ifosfamide based NACT should be considered a new treatment modality for improving OS of pts with HR-STS of E and NE.

Paper 020 #2794748

CANCER IMMUNOTHERAPY USING TRABECTEDIN AND NIVOLUMAB IN ADVANCED SOFT TISSUE SARCOMA: A RETROSPECTIVE ANALYSIS

Sant Chawla[1]; Kamalesh Sankhala[1]; Stumpf Nathan[1]; Seth Kim[1]; Susan Arasheben[1]; Leong Bryan[1]; Grace Kang[1]; William W. Tseng, MD[2];
Erlinda M. Gordon, MD[1]
[1]Sarcoma Oncology Center, Santa Monica, CA, USA; [2]Surgery, USC Keck School of Medicine, Los Angeles, CA, USA

Objective: Trabectedin, an alkylating agent, is cytocidal to tumor cells and depletes M2 growth promoting macrophages in the tumor microenvironment. Nivolumab inhibits the immune checkpoint molecule, PD-1, which restores anti-tumor activity in tumor-infiltrating T cells. The objectives are to retrospectively assess the safety/toxicity and efficacy of sequential administration of trabectedin and nivolumab in patients with advanced soft tissue sarcoma (STS).

Methods: Twenty patients with locally-advanced and/or metastatic STS were evaluated. Each patient received one dose of single-agent trabectedin (1.5 mg/m2 continuous intravenous infusion, CIV, for 24 hours), followed by sequential administration of trabectedin CIV every 3 weeks, and nivolumab (3 mg/kg IV over 30 minutes) every 2 weeks, starting 2 weeks after the second trabectedin dose. Safety/toxicity was analyzed using the NIH/NCI CTCAE v.4.03 in all patients. Efficacy was assessed by RECIST v1.1 and immune-related response criteria (ir-RECIST).

Results: Histologic subtypes in 20 patients include malignant fibrous histiocytoma / undifferentiated pleomorphic sarcoma (n = 8), leiomyosarcoma (n = 4), synovial sarcoma (n = 3), myxoid liposarcoma (n = 4) and chondrosarcoma (n = 1). All patients had metastatic disease and a median of 4 lines of prior chemotherapy. Safety analysis: Grade 3 treatment emergent adverse events include anemia (n=2), fatigue (n = 1), decreased platelet count (n=1), decreased granulocyte count (n=1) and increased creatine kinase (n=1). Efficacy analysis: Thirteen patients were followed for at least 6 months. There were 3 partial responses (PR), 7 stable disease (SD) and 3 progressive disease (PD), with best overall response rate (BORR) of 23.1%, DCR of 76.9%, median PFS of >7.8 months (range: 3.5->10.4 months), median OS of >8.4 months (3.6->10.4 months), 6 month PFS rate of 69.2%, and 6 month OS rate of 92%. In a Phase 3 study, the median PFS was 4.2 months using trabectedin alone (Demetri et al., 2015).

Conclusion: Taken together, the data suggest that paired administration of trabectedin and nivolumab is safe, and that this chemo-/immuno-therapy approach has synergistic activity.

3:15 pm – 3:45 pm
– SESSION 4 –
Pathology

Paper 021 #2804859

INFILTRATION OF IMMUNE CO-INHIBITORY CHECKPOINT BIOMARKERS LAG3 AND TIM3 IN SARCOMAS

Amanda R. Dancsok, MD, PhD Student[1]; *Jean-Yves Blay[5]; David Thomas, FRACP, PhD[4]; Robert Maki[3]; Torsten O. Nielsen[1]; Elizabeth G. Demicco[2]*
[1]Pathology and Laboratory Medicine, University of British Columbia, Vancouver, BC, Canada; [2]Mount Sinai Hospital, Toronto, ON, Canada; [3]Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, USA; [4]Garvan Institute, Sydney, NSW, Australia; [5]Centre Leon Berard, Lyon, France

Objective: First generation checkpoint inhibitors are under investigation in sarcomas, mainly targeting PD1/PDL1. Multiple co-inhibitory receptors can be expressed concurrently on activated immune cells, providing functional redundancy, such that inhibition of a single immune checkpoint may not be sufficient. LAG3 (Lymphocyte Activation Gene 3) and TIM3 (T-cell immunoglobulin- and mucin-domain-containing molecule), are co-inhibitory immune checkpoints expressed in multiple cancer types, often in association with PD1 expression. In both preclinical models and human correlative studies, these markers are enriched following treatment with another checkpoint inhibitor. We assessed LAG3 and TIM3 expression in sarcoma as a preliminary assessment of which tumors might benefit most from emerging immunotherapy trials targeting these receptors in combination with PDL1 or CTLA4 blockade.

Methods: This work provides a broad survey of LAG3 and TIM3 expression by immunohistochemistry in >1500 tissue microarray specimens spanning 23 sarcoma subtypes. Markers are scored by absolute count (per 0.6mm core) of tumor-infiltrating lymphocytes (TILs) exhibiting positive cytomembranous staining. Statistical evaluation was by Kruskall-Wallis independent samples test and Spearman's nonparametric correlation.

Results: LAG3+ and TIM3+ TILs were scarce across most sarcoma subtypes, seen in 34% and 31% of cases, respectively. Most cases positive for either marker had relatively few positive infiltrates (median LAG3+ was 1.5TILs/core; median TIM3+ was 1.0 TILs/core). Positive cases (≥1 LAG3/TIM3+ TIL/core) were most common among dedifferentiated liposarcoma (73% LAG3+ and 87% TIM3+; n=77), myxofibrosarcoma (68% LAG3+ and 82% TIM3+; median n=53), and undifferentiated pleomorphic sarcoma (61% LAG3+ and 71% TIM3+; n=76). LAG3+ and TIM3+ infiltrates were moderately correlated (rho=0.553, p<0.001). Of cases with PD1+ infiltrates, 75% also had LAG3+ TILs and 77% had TIM3+ TILs. Among cases in which tumor cells are negative for PDL1, LAG3+ and TIM3+ TILs are seen in only 30% and 26% of cases,

respectively[egd1] ; however, in samples with at least 1% tumor cells staining PDL1+, the proportion of cases infiltrated by LAG3+ and TIM3+ TILs increases to 69% and 64%, respectively.

Conclusion: While lymphocytes expressing LAG3 or TIM3 are not found infiltrating most sarcomas, they are more predominant in a select subset of pleomorphic sarcomas. These markers show enrichment in the presence of PD(L)1 signaling suggesting cooperation among inhibitory immune checkpoints.

Paper 022 #2783068

A 22-YEAR EVALUATION OF MUSCULOSKELETAL ONCOLOGY IN-OFFICE CORE NEEDLE BIOPSY ERROR RATES FOLLOWING CONSULTATION WITH MUSCULOSKELETAL TRAINED PATHOLOGISTS VERSUS COMMUNITY PATHOLOGISTS

Ashley Startzman, DO[1]*; Ryan Durfee*[2]*; H. T. Temple*[1]
[1]Orthopedics, Nova Southeastern University, Fort Lauderdale, FL, USA; [2]Orthopaedics, The Center for Orthopaedic Innovations, Miami, FL, USA

Objective: In-office core needle biopsies are a time and cost-effective method for diagnosing a musculoskeletal tumor. The diagnostic accuracy of a biopsy is multifactorial. This study investigates if there is a difference in the diagnostic accuracy of a core needle biopsy based on a pathologist's sub-specialization. We hypothesize that biopsies read by a non-musculoskeletal trained pathologist will generate more errors than those specimens that are read by a fellowship trained musculoskeletal pathologist.

Methods: IRB approval was obtained for a prospective study evaluating musculoskeletal tumor in-office biopsies performed by a fellowship trained orthopedic oncologist. Between November 1995-April 2015 (Group 1) biopsies were performed at an academic institution with musculoskeletal pathologists as consultants. From May 2015-April 2017 (Group 2) biopsies were performed at a community hospital with non-musculoskeletal pathologists as the consultants. In Group 2 a musculoskeletal pathologist was consulted as a second reader of the pathology in some cases, as deemed necessary by the primary surgeon or primary pathologist. The collected data was then retrospectively reviewed.

Results: 1203 in-office core needle biopsies were performed. 161 patients were excluded. 907 patients were in Group 1 and 134 in Group 2. There were a total of 66 errors (6%) made in the initial diagnosis, 46 (5%) in Group 1 and 26 (19%) in Group 2. Biopsies were deemed nondiagnostic in 2.8% of patients.

Conclusion: In-office core needle biopsies provide diagnostic results with a low rate of error. This is the first study, to our knowledge, to look at the diagnostic accuracy of a core needle biopsy specimen based on the sub-specialization of the reading pathologist. Adequate tissue sampling was achieved in 97% of biopsies over 22-years with an error rate of only 6%. Despite this, a clear difference in error rates is evident based on the consultation of a musculoskeletal trained versus community trained pathologist, nearly quadrupling from 5% to 19% when a specimen was initially read by a community trained pathologist alone. The results indicate that there is less error when specimens are reviewed at a specialized institution by musculoskeletal trained pathologists.

Number of Errors and Classification

Error Made	Group 1	Group 2
Malignant to Benign	0	1
Benign to Benign	19	11
Benign to Malignant	19	7
Malignant to Malignant	2	7

3:45 pm – 5:15 pm
– SYMPOSIUM 2 –
Basic Science

Paper 023 #2804666

IMMUNE CORRELATES OF RESPONSE TO CHECKPOINT BLOCKADE IN SOFT TISSUE AND BONE SARCOMAS PATIENTS TREATED WITH PEMBROLIZUMAB (SARC028)

Melissa Burgess[1]*; Vanessa Bolejack*[3]*; Ruth Salazar*[2]*; Alexander Lazar*[2]*; Edwin Roger Parra Cuentas*[2]*; Jamie Rodriguez-Canales*[2]*; Ignacio Wistuba*[2]*; Lisa Butterfield*[1]*; Jason Roszik*[2]*; Brian Van Tine*[7]*; Scott Schuetze*[6]*; James Hu*[5]*; Sandra P. D'Angelo*[4]*; Hussein Tawbi*[2]*; SARC028 Investigators*[8]
[1]University of Pittsburgh, Pittsburgh, PA, USA; [2]The University of Texas - MD Anderson, Houston, TX, USA; [3]Cancer Research and Biostatistics (CRAB), Seattle, WA, USA; [4]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [5]USC/Norris Cancer Hospital, Los Angeles, CA, USA; [6]University of Michigan, Ann Arbor, MI, USA; [7]Washington University School of Medicine, St. Louis, MO, USA; [8]SARC, Ann Arbor, MI, USA

Background: Sarcoma is a heterogeneous disease with distinct immunologic profiles. SARC 028 is a multicenter open label Phase II study of pembrolizumab (P) monotherapy in patients with advanced bone (BS) and soft tissue sarcoma (STS). We sought to determine predictors of response to P from tumor biopsies (bx) obtained at baseline and while on therapy in pts enrolled on SARC028.

Methods: Pre-treatment (Rx) tumor bx and on-Rx bx were obtained within 28 days prior to enrollments and at 8 week of therapy, respectively, from all pts enrolled on SARC028. To determine pre-Rx PD-L1 expression, FFPE

blocks from baseline core bx were analyzed using the 22C3 clone. All samples were examined for tumor content and quality, and all stained samples underwent independent review by 3 pathologists. We defined PD-L1 positivity as >1% membranous staining on tumor cells. To investigate the tumor immune infiltrates, multiplex immunofluorescence (IF) immunohistochemistry was performed using the Vectra system and whole slide images analyzed with Phenochart software. Panel 1 (CD3, CD8, CD68, PD1, PDL1, DAPI) and Panel 2 (CD3, CD8, CD45RO, FoxP3, Granzyme B, DAPI) were performed on all evaluable bx. Each multiplex IF image was analyzed using inForm image analysis software to develop spectral signatures. A trained pathologist used this information to identify distinct cell phenotypes. Pre- and post-Rx changes in the immune infiltrate were analyzed.

Results: In 86 patients enrolled, pre-Rx biopsies were obtained from >90% and post-Rx from 72% of pts. 70 pre-treatment cases were analyzable for PD-L1 testing and 3 (4.3%) were PD-L1 positive. PD-L1+ cases were restricted to the UPS cohort. 2 were evaluable for response (1 CR, 1PR). Two additional osteosarcoma samples were noted to be PD-L1+ on multiplex testing and 1 correlated with a PR. No post-treatment cases were PD-L1+. In paired tumor samples, responders had an increased number of CD3 and CD8 cytotoxic T cells at baseline. Histologic subtypes that had little or no response- Ewing, leiomyosarcoma, and synovial sarcoma- exhibited a similar pattern of very low immune infiltrates and more tumors had a CD68+ infiltrate. Similarly osteosarcoma tumors had very low T cell infiltrates and remarkably high CD68+ infiltrates at baseline highlighting the role of the monocyte/macrophage lineage and suggesting a role for mifarmutide in this disease. Histologic subtypes with clinical activity- UPS and LPS- demonstrated a pattern of increasing immune infiltrates including a higher percentage of effector/memory T cells and regulatory T cells at baseline and post-Rx correlating with response. Additional analyses including geographic distribution and spatial relationships within tumor tissues will be presented at the meeting.

Conclusion: P has promising clinical activity in specific histologic subtypes of STS and increased pre-treatment immune infiltrates appear to correlate with response across and within specific histologic subtypes. An immune-suppressed tumor microenvironment seems to be prevalent in sarcomas that are refractory to checkpoint blockade indicating a role for targeting the monocyte/macrophage lineage in future studies. Immunotherapy drug development in sarcoma will require histology-tailored therapies and a deeper understanding of the tumor microenvironment and immune response in sarcoma.

Paper 024 #2786772

DETECTING STRUCTURAL VARIANTS IN THE CIRCULATING TUMOR DNA OF PATIENTS WITH PEDIATRIC SARCOMAS

Kelly Klega; Alma Imamovic-Tuco; Gavin Ha; Andrea Clapp; Abigail Ward; Catherine Clinton; Anwesha Nag; Eliezer Van Allen; Katherine Janeway; Matthew Meyerson; Aaron Thorner;
Brian Crompton, MD
Pediatric Oncology, Dana-Farber Cancer Institute, Boston, MA, USA

Objective: Circulating tumor DNA (ctDNA) levels in the blood of patients with cancer have been shown to correlate with disease burden. Most liquid biopsy approaches developed for adult malignancies focus on detecting a specific somatic single-nucleotide variant (SNV) or panel of SNVs. However, comprehensive sequencing efforts reveal that pediatric sarcomas have few highly recurrent SNVs. Instead, studies show that recurrent somatic events in pediatric sarcomas are primarily structural variants (SV). Therefore, we developed a next-generation sequencing approach to detect and quantify ctDNA in the blood of patients with pediatric sarcomas that is tailored to the somatic events most commonly observed in these malignancies.

Methods: Next-generation sequencing techniques were adapted to detect common translocations and genome-wide copy-number events in the blood of patients with pediatric sarcomas. A custom hybrid-capture assay was developed, termed TranSS-Seq (Translocation-Specific Sarcoma Sequencing) to identify translocations specific to Ewing sarcoma, Ewing-like sarcoma, and alveolar rhabdomyosarcoma. In addition, a recently validated algorithm was applied to detect chromosomal copy-number alterations from plasma DNA sequenced with ultra-low passage whole-genome sequencing (ULP-WGS). These assays were applied to plasma samples collected from newly diagnosed and relapsed patients with pediatric sarcomas. For a subset of patients, multiple samples were also profiled during treatment. Whenever available, we also applied these assays to tumor DNA obtained from the same patient.

Results: TranSS-Seq detected ctDNA in 15 of 21 samples (71%) collected from patients with translocation-positive sarcomas. Copy-number changes were identified by ULP-WGS in 11 plasma samples collected from 16 patients (69%) with translocation-negative sarcomas. In all cases for which DNA from tumor samples were available, the same translocations and copy-number changes were identified in the tumor and plasma pairs. Furthermore, changes in ctDNA levels over time corresponded to treatment responses and relapses.

Conclusion: This study demonstrates that liquid biopsy approaches that detect somatic SV in ctDNA are well suited for pediatric sarcomas. This approach can be applied to plasma samples even when matched tumor is

unavailable suggesting that these assays may be ideal for multi-institutional prospective trials where access to tumor tissue is often limited.

Paper 025 #2804624

FORMATION MECHANISMS OF CANONICAL GENE FUSIONS IN BONE AND SOFT TISSUE TUMORS

*Nathaniel Anderson, BSc[1]; Richard de Borja[1]; Matthew Young[2]; Andrej Rosic[1]; Nicola Roberts[2]; Fabio Fuligini[1]; Adrienne Flanagan[3]; Peter Campbell[2]; Mary Shago[1]; Jay S. Wunder[4]; Irene Andrulis[5]; David Malkin[1]; Sam Behjati[2]; **Adam Shlien**[1]*

[1]SickKids, Toronto, ON, Canada; [2]Wellcome Trust Genome Campus, Wellcome Trust Sanger Institute, Hinxton, United Kingdom; [3]Royal National Orthopaedic Hospital NHS Trust, Stanmore, United Kingdom; [4]University Musculoskeletal Oncology Unit, Mount Sinai Hospital, Toronto, ON, Canada; [5]Lunenfeld-Tanenbaum Research Institute, Sinai Health System, Toronto, ON, Canada

Objective: Sarcomas are cancers of the bone and soft tissue often defined by their gene fusions. However, the timing, context, and processes by which these pathogenic fusions arise are unknown. We explored this in Ewing sarcoma, a cancer driven by EWSR1-ETS gene fusions, with very few cooperating mutations.

Methods: We used whole genome sequencing, combined with enhanced informatics, to study the mechanisms underlying the formation of EWSR1-ETS fusions. Targeted deep sequencing and karyotyping were used for validation.

Results: We found that the EWSR1-ETS fusion arose from striking rearrangement clusters in 40% of cases (50/125). Notably, these were organized in loops that universally contained the fusion at their center, while also weaving up to 18 genes together with it. We found the same pattern of rearrangements in three additional tumor types.

Conclusion: From these data, we define a new signature for sarcoma fusions that precedes other somatic changes, in the earliest replicating DNA of the genome. This dramatic process impinges on many genes – simultaneously generating multiple driver events, with the disease-defining gene fusion at its core.

Paper 026 #2773162

INTEGRATIVE GENOMIC AND TRANSCRIPTOMIC ANALYSIS OF LEIOMYOSARCOMA

***Priya Chudasama, PhD**[1]; Sadaf S. Mughal[2]; Mathijs A. Sanders[3]; Daniel Hübschmann[4]; Inn Chung[5]; Aurélie Ernst[6]; Bernd Kasper, MD, PhD[7]; Hans-Georg Kopp[8]; Sebastian Bauer[9]; Karsten Rippe[5]; Benedikt Brors[2]; Marcus Renner[10]; Peter Hohenberger[7]; Claudia Scholl[1]; Stefan Fröhling[1]*

[1]Translational Oncology, German Cancer Research Center (DKFZ) and National Center for Tumor Diseases (NCT), BW, Germany; [2]Division of Applied Bioinformatics, DKFZ and NCT, Heidelberg, Germany; [3]Department of Hematology, Erasmus Medical Center, Rotterdam, Netherlands; [4]Division of Theoretical Bioinformatics, DKFZ, Heidelberg, Germany; [5]Research Group Genome Organization and Function, DKFZ and BioQuant Center, Heidelberg, Germany; [6]Division of Molecular Genetics, DKFZ, Heidelberg, Germany; [7]Sarcoma Unit, Interdisciplinary Tumor Center Mannheim, Mannheim University Medical Center, Mannheim, Germany; [8]Department of Hematology and Oncology, Eberhard Karls University, Tübingen, Germany; [9]Sarcoma Center, Western German Cancer Center, Essen, Germany; [10]Institute of Pathology, Heidelberg, Germany

Objective: Leiomyosarcoma (LMS) is an aggressive mesenchymal malignancy of smooth-muscle origin with a recurrence/metastasis rate of 40%. Patients with disseminated LMS are usually incurable, as reflected by a median survival of 12 months. This study is aimed towards (i) better understanding of the mechanisms underlying LMS development and (ii) identifying clinically actionable genetic vulnerabilities that could serve as novel therapeutic targets.

Methods: We performed whole-exome sequencing (WES) and RNA sequencing (RNA-seq) in a large LMS patient cohort (n=49 and n=37, respectively) to detect single-nucleotide variants, small insertions and deletions, DNA copy number alterations, structural rearrangements, gene expression profiles, and fusion transcripts. C-circle assays were used to detect alternative lengthening of telomeres (ALT). Clonogenic assays were employed to determine the sensitivity of LMS cell lines towards the poly(ADP-ribose) polymerase (PARP) inhibitor olaparib and cisplatin.

Results: Integrative analysis of WES and RNA-seq data revealed that LMS tumors are characterized by substantial mutational heterogeneity, near-universal inactivation of TP53 and RB1, widespread DNA copy number alterations, chromothripsis, and frequent whole-genome duplication. Furthermore, we detected ALT in 78% of cases, the highest frequency reported to date for any tumor entity, and identified recurrent alterations in telomere maintenance genes such as ATRX, RBL2, and SP100, providing novel insight into the genetic basis of this mechanism. Finally, most tumors displayed hallmarks of “BRCAness”,

including alterations in homologous recombination DNA repair genes, multiple structural rearrangements, and enrichment of specific mutational signatures, and cultured LMS cells harboring aberrations of multiple genes that are synthetic lethal to PARP inhibition are sensitive towards olaparib and cisplatin.

Conclusion: This first comprehensive "omics" analysis of LMS has uncovered several key biological features, including therapeutically tractable genetic lesions, and our data provide a rich resource for guiding future investigations into the mechanisms underlying the development of LMS, as well as other cancers with complex genetics, and the design of novel therapeutic strategies for this intractable disease.

Paper 027 #2801967

UTILIZING SLEEPING BEAUTY TRANSPOSON MOUSE SCREENS TO IDENTIFY NATURALLY OCCURRING DRIVER EVENTS IN HUMAN AND CANINE OSTEOSARCOMA

Aaron L. Sarver, PhD*; Nuri Temiz; Branden Moriarity; Jinhua Wang; Subbaya Subramanian; Jaime Modiano; David A. Largaespada, PhD*
Masonic Cancer Center, University of Minnesota, Minneapolis, MN, USA

Objective: Cancers are extremely complex and heterogenous, however a common feature appears to be the presence of critical driver events (e.g. genetic mutations in tumor suppressors) that drive tumor formation and progression. Key driver events, such as mutations in TP53, have been identified in many well-studied tumors. However, many human solid tumors do not have clearly identified driver events, even after common oncogenes and tumor suppressors have been systematically examined. We have termed this the "missing driver" problem.

Methods: Our approach to solve the "missing driver" problem is to use forward genetic screens for tumor formation in mice to identify genomic locations to systematically and exhaustively investigate within naturally occurring human and canine tumors. Starting with the most recurrent fusions, and then working our way out to lower frequency insertion events we will systematically look for orthologous aberrations in human and canine osteosarcoma tumor data. By this logic, SB fusions will tag candidate regions of interest for us. As a first pass, we will analyze RNA-SEQ and tumor normal exome data for transcript level, mutations, RNA-fusions and copy number changes. In addition to using traditional genome-wide bioinformatics methods, because we are focusing on small regions of the genome, this allows us to use methodology not feasible for genome-wide analyses to interrogate candidate driver regions.

Results: Using a systematic and statistically rigorous approach, we show that we can identify mutations, fusions and copy number changes in the majority of Human and Canine OS tumors that correspond with sites implicated by the mouse transposon screens. Further we show relationships between these driver events. Additionally, we identify endogenous cooperating driver events in predisposed mice that lack SB acceleration and show that these are also simultaneously occurring in the SB accelerated mice. We show that some naturally occurring driver events are conserved between humans and dogs, while other types appear to be occurring at high rate of incidence only in canine osteosarcoma. The widespread utilization of a specific driver event in canines, may explain the increased incidence of Osteosarcoma in dogs relative to Humans.

Conclusion: From this work we conclude that driver events associated with Osteosarcoma are generally conserved across species, and that deviations from conservation may underlay increased risk for tumor formation observed with the canine genome. From these results we speculate that differential cancer risk across species may be associated with changes in the relative genomic positions and gene context of oncogenes and tumor suppressor.

Paper 028 #2804871

AUTOPHAGY IN ALVEOLAR SOFT PART SARCOMA CONFERS MECHANISMS OF RESISTANCE TO CHEMOTHERAPY

Jared J. Barrott, PhD; ***Kevin B. Jones***
Orthopaedics, University of Utah, Salt Lake City, UT, USA

Objective: Altered metabolism is considered to be one of the new hallmarks of cancer. Autophagy is one major avenue of altered cancer metabolism, enabling cell survival under metabolic stress and promoting chemoresistance. The nuclear localization of MiTF/TFE3 family transcription factors has associated with upregulated transcription of autophagy genes in pancreatic cancer. Alveolar soft part sarcoma is a rare but deadly soft-tissue sarcoma, with a predilection for adolescent and young adult victims. Alveolar soft part sarcoma is noteworthy for its resistance to traditional cytotoxic chemotherapies. It consistently associates with a t(X;17) chromosomal translocation that produces the ASPSCR1-TFE3 target gene, bearing the DNA-binding domain from TFE3 and protein interaction domains from ASPSCR1. We have demonstrated that conditional expression of ASPSCR1-TFE3 is sufficient to drive alveolar soft part sarcomagenesis in the mouse with complete penetrance. Mouse tumors recapitulate human alveolar soft part sarcoma histology and transcriptomes faithfully. While the direct targets of ASPSCR1-TFE3 have been studied in a renal cell carcinoma cell line, they have not been studied in alveolar soft part sarcoma. Our objective was to identify the direct targets of ASPSCR1-TFE3 and how these targets confer resistance to doxorubicin.

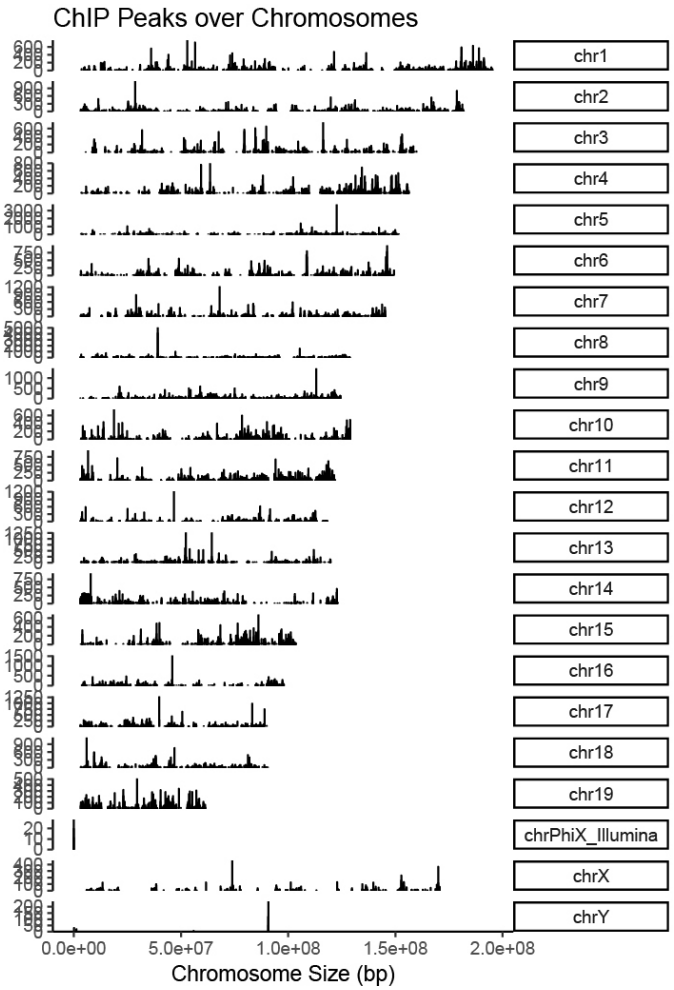
Methods: The human cell lines expressing ASP-

SCR1-TFE3, ASPS-1 and FUUR-1, as well as mouse tumors driven by expression of ASPSCR1-TFE3 were subjected to nuclear fractionation and chromatin immunoprecipitation using antibodies against ASPSCR1 and RNAPol2. Cells and tumors were further characterized for their presnce of auotphagic flux by detection of LC3-II and abundance of lysosomal proteins LAMP1 and CTSD.

Cell lines were treated with combination therapy using the autophagy inhibitor, chloroquine, and doxorubicin and compared to monotherapy and controls. Viability was assesed as well as changes in mitochondria, ROS production, and apoptosis. Furthermore cells were analyzed by gas-chromatography mass spectrometry (GC-MS) for metabolites involved in cellular respiration and glycolysis. Lastly, mice were treated with either control, monotherapy of chloroquine (15 mg/kg) or doxorubicin (10 mg/kg), or combination therapy for up to 5 months. Mice on combination therapy showed a stastical improvement in survival of 3 months over control and doxorubicin treatments.

Results: We report not only the first genome-wide localization of the ASPSCR1-TFE3 oncoprotein on chromatin from alveolar soft part sarcoma cell lines and mouse tumors, but also its association with actively transcribed genes. Among these are found many genes related to autophagy, especially those related specifically to the nutrient responsive pathways that drive autophagy. We demonstrate high expression of autophagy-related lysosomes and proteins at baseline conditions in human tumors and cell lines and mouse tumors. We also demonstrate active autophagic flux even in the absence of stress conditions. Inhibition of autophagy has no apparent impact on survival of alveolar soft part sarcoma cells alone, but profoundly impacts their protein degradation pathways and the availability of amino acids for protein assembly in stress. Inhibition of autophagy strongly synergizes with chemotherapy to kill alveolar soft part sarcoma cells, suggesting it was a source mechanism for resistance. Furthermore, mice treated with combination therapy of autophagy inhibition and chemotherapy significantly extends life 3 months beyond control and single agents alone.

Conclusion: We have therefore demonstrated the direct targets of ASPSCR1-TFE3 in alveolar soft part sarcomas, including a number of autophagy genes that are expressed in these tumors, independently from nutrient deprivation or stress, rendering cells particularly resistant to many therapy-induced stresses. Inhibition of autophagy in alveolar soft part sarcoma causes the tumor cells to be more susceptible to chemotherapeutic stress.



Genomic characterization of ChIPseq peaks for ASPSCR1-TFE3 in a mouse model of alveolar soft part sarcoma.

5:15 pm – 5:45 pm

Young Investigator Award Winners

Paper 029 #2739815

SEVERITY CLASSIFICATION ON MRI IN TENOSYNOVIAL GIANT CELL TUMOURS

Monique Mastboom, Drs.[1]*; Floortje Verspoor*[2]*; David Hanff*[3]*; Maaike Gademan*[4]*; P.D.Sander Dijkstra*[1]*; Bart Schreuder*[2]*; Hans Bloem*[1]*; Robert van der Wal*[1]*; Michiel V. Sande*[1]

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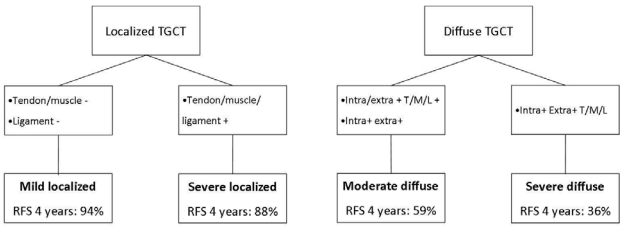
Objective: Available literature on Tenosynovial Giant Cell Tumours (TGCT) at best compares localized- to dif-

fuse-disease. Only sub-classifying TGCT into two types seems to be an oversimplification of disease stages and fails to predict differences in recurrent disease for individual patients. This study aims to establish objective MRI-scoring items and subsequently a radiology-based severity classification for patients with TGCT affecting large joints, that is able to differentiate between severity stages of TGCT.

Methods: MRI-scoring items were evaluated by field experts (radiologists/orthopaedic oncologists), deduced from clinically important parameters. Four MRI scoring items showed moderate to good inter- and intra-observer agreement: TGCT-type, intra- and/or extra-articular involvement, tendon/muscle involvement and ligament involvement.

Inclusion criteria were: histologically proven TGCT, adequate MRI quality to assess scoring items between 2006 and 2015 and primary treated with open resection in a Dutch tertiary oncology centre. To assess effect of MRI scoring items on recurrent disease, four severity stages were defined (Figure 1). Following predictors were proposed: gender, localisation (knee versus other joints) and age at MRI. Cox-regression survival analyses were performed.

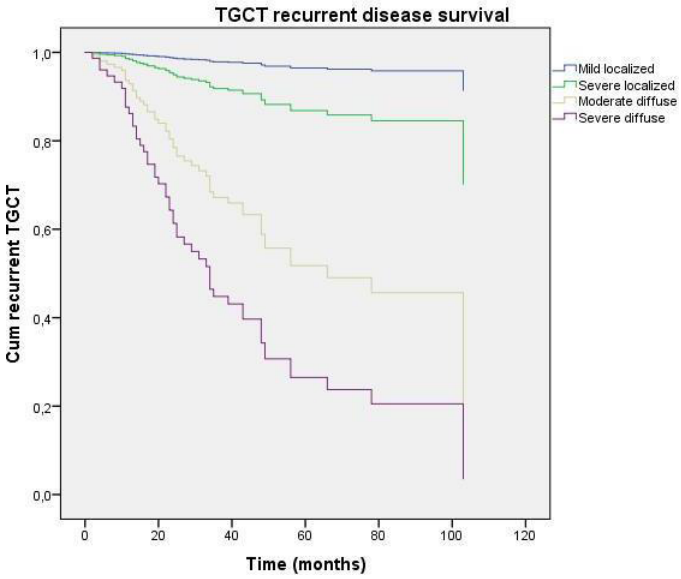
Results: Fifty out of 174 patients showed recurrent disease, after median follow-up of 40 months. 50% of patients had diffuse-TGCT. Univariate analysis for recurrent disease yielded no significant associations for gender, localisation and age (p>0.53). Covariate severity stage showed significant association (p<0.000).
Recurrence free survival at 4 years (close to median follow-up) was 94% in mild localized (n56, 1event), 88% severe localized (n31, 3events), 59% moderate diffuse (n32, 12events), 36% severe diffuse (n55, 34events).
Compared to severe diffuse, Hazard Ratios were 0.03(95%CI 0.00-0.20), 0.11(95%CI 0.03-0.36), 0.50(95%CI 0.26-0.97) for moderate diffuse, severe localized and mild localized, respectively. Cox regression estimates show the discriminatory ability for recurrence of our novel TGCT severity classification (Figure 2).



TGCT severity classification

- no involvement of mentioned structure; + involvement of mentioned structure.

Tendon/muscle or T/M, Tendon muscle involvement; Ligament or L, Ligament involvement; intra, intra-articular; extra, extra-articular.



Conclusion: It is possible to distinguish four well-defined objective MRI-scoring items for TGCT affecting large joints. TGCT severity classification on MRI, composed of four severity stages, is able to differentiate in disease severity. Future TGCT-studies should take this classification into account, to describe disease severity and improve study comparability.

Paper 030 #2803705

HOW LONG AND HOW OFTEN SHOULD WE FOLLOW-UP PATIENTS WITH LOCALIZED SOFT TISSUE SARCOMA AFTER CURATIVE RESECTION? EVIDENCE FOR A TIME- AND RISK-ADAPTED APPROACH TO AFTERCARE FROM A MULTICENTER ANALYSIS OF 835 CASES

Florian Posch, MD, MSc[1]*; Maria Smolle*[2]*; Madeleine Willegger*[3]*; Per-Ulf Tunn*[5]*; Elisabeth Goldenitsch*[4]*; Jakob M. Riedl*[1]*; Bernadette Liegl-Atzwanger*[6]*; Armin Gerger*[1]*; Martin Pichler*[1]*; Joannis Panotopoulos*[3]*; Carmen Döller*[7]*; Herbert Stöger*[1]*; Reinhard Windhager*[3]*; Andreas Leithner*[2]*; Joanna Szkandera*[1]
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Objective: Post-surgical follow-up of patients with localized soft tissue sarcoma (STS) is a commonly practiced strategy for early detection of local recurrence (LR) and distant metastasis (DM). However, in this setting the opti-

mal timing and length of follow-up is unclear. In this study, we use flexible parametric modeling to study time-dependent patterns of recurrence to obtain guidance for a rational duration and intensity of aftercare for STS.

Methods: In this ambispective cohort study, 835 patients with localized STS (AJCC stages I-III) who were treated with surgery in curative intent between 1994 and 2016 at 4 centers in Austria and Germany were followed-up (Table 1). Co-primary endpoints were the time-dependent rates of LR and DM, as analyzed by flexible parametric models.

Results: During a median follow-up of 5.4 years (25th-75th percentile: 2.8-8.3), we observed 107 LR and 179 occurrences of DM (Figure 1A). In flexible parametric modeling, the rates of LR and DM showed a highly non-constant pattern, with both LR and DM having a peak at around 1 year after surgery, followed by a sharp decline (Figure 1B). Importantly, patterns of LR and DM rates strongly differed according to tumor characteristics, such as tumor grade and histologic subtype. Patients with G3 tumors had the highest peak rate of LR, but the LR rate in G2 tumors exceeded the LR rate of G3 tumors at around 2 years after surgery (Figure 2A). Patients with malignant peripheral nerve sheath tumors (MPNST) and myxofibrosarcoma featured constantly higher LR rates than patients with liposarcoma (Figure 2B). Moreover, strongly differential recurrence rate patterns according to grade and histology were also seen for DM (Figure 3). Data for other clinical covariates and a proposed personalized follow-up protocol for STS patients will be presented at the meeting.

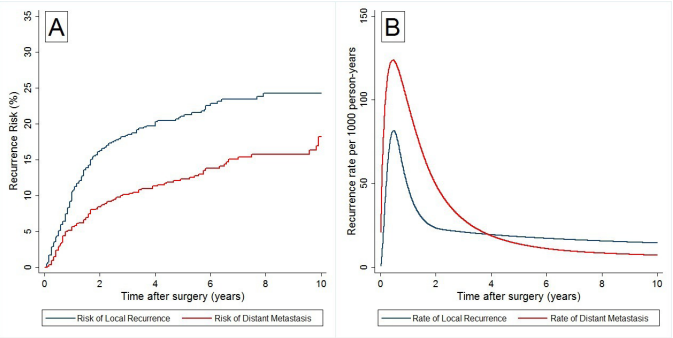


Figure 1. Risks and rates of local recurrence and distant metastasis in patients with soft tissue sarcoma after surgery in curative intent. Recurrence risk (Panel A) was estimated with competing risk cumulative incidence estimators, treating death-from-any-cause as the competing event of interest. Recurrence rates (Panel B) were estimated with flexible parametric models. The local recurrence and distant metastasis rates are highly non-constant over time, with a strong peak at 1 year after surgery, followed by a strong decline. This clearly suggests that follow-up measures local recurrence and distant metastasis should be intense for 2 and 4 years after surgery, respectively. After 5 years, the distant metastasis rate continuously declines further, while the local recurrence rate prevails to be elevated.

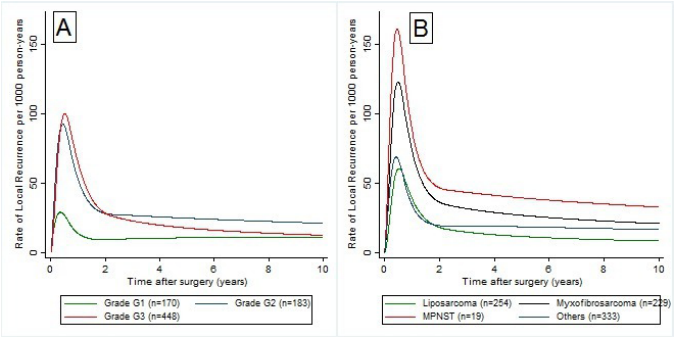


Figure 2. Rates of local recurrence in patients with soft tissue sarcoma according to tumor grade (Panel A) and selected histologic subtypes (Panel B). The local recurrence rate remains elevated in G2 tumors beyond 5 years after surgery, whereas G3 tumor develop local recurrence early-on but show a continuously declining local recurrence rate which reaches G1 tumors after around 8 years of follow-up. This suggests that patients with G2 tumor may benefit from follow-up for local recurrence beyond 5 years. Patients with MPNST and myxofibrosarcoma have not only higher local recurrence rate peaks after around 1 year, but these rates also prevail beyond 5 years. In contrast, patients with liposarcoma have not only lower peak local recurrence rates, but also very low local recurrence rates beyond 5 years. This supports the concept that follow-up should be informed by histologic subtype. Specifically, patients with MPNST may benefit from a follow-up for local recurrence beyond 5 years.

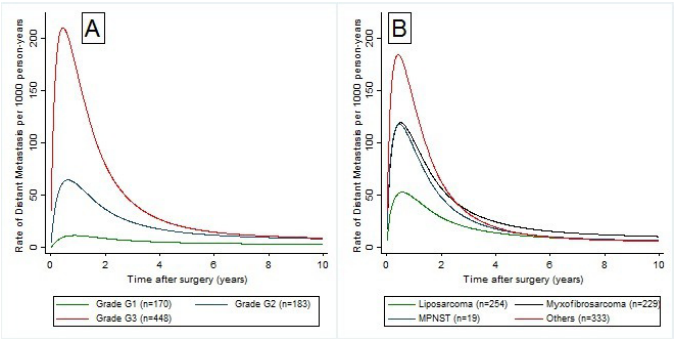


Figure 3. Rates of distant metastasis in patients with soft tissue sarcoma according to tumor grade (Panel A) and selected histologic subtypes (Panel B). The distant metastasis rate has a strikingly higher peak in G3 tumors than in G2 and G1 tumors, suggesting that these patients should be followed-up with chest computed tomography intensively during the first 3 years of follow-up. In contrast, the distant metastasis rate has only a minimal peak in patients with G1 tumors at 1 year, and declines to negligible levels thereafter. Thus, it appears reasonable to discontinue follow-up for distant metastasis after 1 year in patients with liposarcoma. Beyond 5 years, distant metastasis rates are low for all tumor grades and all investigated histologic subtypes, which supports the concept of discontinuing follow-up for distant metastasis after 5 years in patients with soft tissue sarcoma.

Baseline characteristics of the multicenter cohort (n=835)

Variable	Summary measure
Age at surgery (years)	60 [46-71]
Female sex	408 (49%)
Center #1: Graz, Austria	370 (44%)
Center #2: AKH Vienna, Austria	201 (24%)
Center #3: Berlin, Germany	188 (23%)
Center #4: Gersthof Vienna, Austria	76 (9%)
Tumor Grade G1	170 (21%)
Tumor Grade G2	183 (23%)
Tumor Grade G3	448 (56%)
AJCC tumor stage I	169 (21%)
AJCC tumor stage II	285 (36%)
AJCC tumor stage III	347 (43%)
Histology: Liposarcoma	254 (30%)
Histology: Myxofibrosarcoma	229 (27%)
Histology: MPNST	19 (2%)
Histology: Others	333 (40%)
Adjuvant radiotherapy	491 (59%)

Summary measures are medians [25th-75th percentile] for continuous variable such as age, and absolute counts (percentages) for categorical data. Abbreviations: AJCC - American Joint Committee on Cancer, MPNST: Malignant Peripheral Nerve Sheath Tumor

Conclusion: In patients with localized STS after curative surgery, rates of LR and DM are highly non-constant over time and are strongly modified by tumor characteristics. These findings contradict a “one-size-fits-all” aftercare policy, but rather support the concept of a time- and risk-adapted strategy for personalized post-surgical follow-up. Follow-up for LR should be intense during the first 2 years after surgery for all G2 and G3 tumors, and extended beyond 5 years for selected high-risk histologic subtypes. Follow-up for DM should be intense during the first 3 years for G2 and G3 tumors, but may be ceased after 1 year for G1 tumors and after 5 years for all tumors.

8:00 am – 9:45 am
– SPECIAL SESSION 2 –
Trials/Approaches in Rarer Sarcomas, Desmoid Tumor

Paper 031 #2774046

CASPS (CEDIRANIB IN ALVEOLAR SOFT PART SARCOMA), AN INTERNATIONAL RANDOMISED PHASE II TRIAL

Ian Judson, MD[1]; *James Morden*[3]; *Michael Leahy*[2]; *Vivek Bhadri*[4]; *Quentin Campbell-Hewson*[5]; *Ricardo Cubedo*[6]; *Adam Dangoor*[7]; *Ivo Hennig*[8]; *Warren Joubert*[9]; *Antonio López Pousa*[10]; *Beatrice Seddon*[12]; *Claire Snowdon*[3]; *Martin Tattersall*[4]; *Javier Martinez Trufero*[11]; *Judith Bliss*[3]

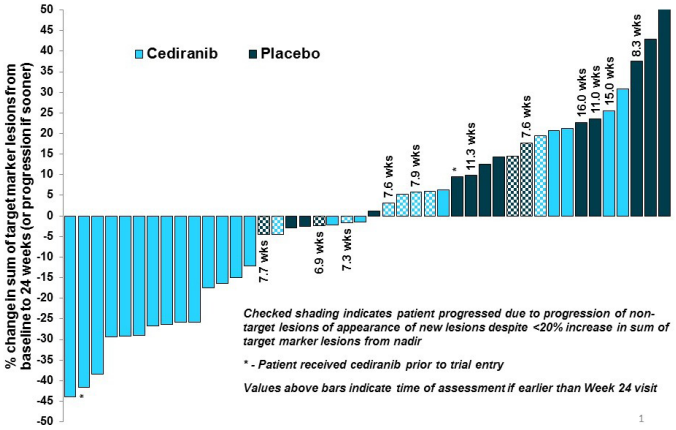
[1]Royal Marsden Hospital, London, United Kingdom; [2]The Christie NHS Foundation Trust, Manchester, United Kingdom; [3]Institute of Cancer Research Clinical Trials & Statistics Unit (ICR-CTSU), London, United Kingdom; [4]Chris O'Brien Lifehouse, Sydney, NSW, Australia; [5]Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom; [6]Hospital Puerta de Hierro, Madrid, Spain; [7]University Hospitals Bristol NHS Foundation Trust, Bristol, United Kingdom; [8]Nottingham University Hospitals NHS Trust, Nottingham, United Kingdom; [9]Princess Alexandra Hospital, Brisbane, QLD, Australia; [10]Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; [11]Hospital Miguel Servet, Zaragoza, Spain; [12]University College London Hospitals NHS Foundation Trust, London, United Kingdom

Objective: ASPS is rare (0.5-1% of soft tissue sarcomas), mainly affects young people and is unresponsive to conventional chemotherapy. Cediranib (C), a tyrosine kinase inhibitor (TKI), including vascular endothelial growth factor receptors, has shown significant activity in ASPS in single arm phase II trials. CASPS was designed to discriminate between the impact of C and the intrinsically indolent nature of ASPS.

Methods: CASPS compared C (30mg od) with placebo (P) in a 2:1 double blind randomisation in pts age ≥16yrs with metastatic ASPS progressive in the previous 6mths. Pts were unblinded at wk24 or progression if sooner when those on P crossed over to C. The primary endpoint of % change in the sum of target marker lesions (TMLsum) between baseline and wk24 or progression if sooner was compared between groups by Mann-Whitney test. Secondary endpoints were progression-free survival (PFS), wk24 response rate (RR) and best response (RECIST v1.1), safety/tolerability, overall survival (OS). One-sided p-values and two-sided 90% confidence intervals are reported.

Results: 48 pts were recruited between 07/2011 and 07/2016 from 12 sites (UK, Australia & Spain). 52% pts were female, median age 31. Most common grade ≥3 AEs on C were hypertension (19.4%), raised gamma GT (6.5%), diarrhoea (6.5%), asthenia (3.2%) and fatigue (3.2%), which were manageable by dose reduction. In the evaluable population (N=44) median change in TMLsum on C was −8.3% (IQR −26.5% to +5.9%) vs P: +13.4% (IQR −0.6% to +23.1%), one-sided p=0.0010. Best response by wk24 was partial response (PR) in 6/28 (21%) pts on C vs 0/16 on P (one-sided p=0.053), giving a RR of 21%. At wk24 3 pts were still in PR and 14 had stable disease, giving a 6mth clinical benefit rate (CBR) of 61%. At the time of analysis 3 pts remained in PR with median response duration of 26+mths. The HR for PFS (C vs P) was 0.58 (90%CI 0.33-1.03, one-sided p=0.059), median PFS was 10.8mths on C vs 3.7mths on P. The HR for OS was 0.66 (95%CI 0.25-1.75) p=0.41. OS at 12mths was C: 94%; P: 66%, in spite of crossover. 12 C pts had received a prior TKI; this had no major impact on PFS.

%change sum TMLs at 24 wks / progression



Conclusion: CASPS confirms the activity of C in ASPS shown in previous trials. CASPS met its primary endpoint of a significant change in TMLsum at wk24 for C compared with P. There was a 7mth improvement in median PFS. Tumour tissue and serial blood samples will be analysed for predictive and prognostic biomarkers.

Paper 032 #2762187

THE USE OF LAROTRECTENIB IN THE MANAGEMENT OF LOCALLY ADVANCED PEDIATRIC *NTRK*-FUSION SARCOMA

Steven G. DuBois[1]*; Theodore W. Laetsch, MD*[2]*; Noah Federman*[3]*; Catherine M. Albert*[4]*; Brian Turpin*[5]*; Ramamoorthy Nagasubramanian*[6]*; Mark Reynolds*[7]*; Scott Cruickshank*[7]*; Michael C. Cox*[7]*; Douglas S. Hawkins*[4]*; Leo Mascarenhas*[8]*; Alberto S. Pappo*[9]

[1]Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, MA, USA; [2]University of Texas Southwestern Medical Center/Children's Health, Dallas, TX, USA; [3]University of California, Los Angeles, Los Angeles, CA, USA; [4]Seattle Children's Hospital, University of Washington, Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [5]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA; [6]Nemours Children's Hospital, Orlando, FL, USA; [7]Loxo Oncology, South San Francisco, CA, USA; [8]Children's Hospital Los Angeles, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA; [9]St Jude Children's Research Hospital, Memphis, TN, USA

Objective: NTRK fusions have been described in infantile fibrosarcoma (IFS) and other pediatric sarcomas. Systemic therapy may be used to cytoreduce locally advanced tumors prior to en bloc resection when limb preservation or limb function is threatened. Larotrectenib (laro) is a selective oral TRK inhibitor that has demonstrated significant activity in diverse adult and pediatric NTRK fusion cancers. A taste-masked liquid formulation of laro is available for children unable to swallow capules. This report describes clinical and anatomic pathology outcomes for children who received laro in the setting of an NTRK-fusion sarcoma and were subsequently referred for attempted definitive surgical resection.

Methods: This report highlights patients from the ongoing Phase 1 / 2 pediatric trial of laro (NCT02637687) who had a documented NTRK-fusion sarcoma and underwent an attempted definitive surgical resection. Tumor response (RECIST v1.1) and surgical outcomes were prospectively collected.

Results: Eleven patients with locally advanced NTRK-fusion sarcomas had been enrolled, as of a data cutoff of 14 April 2017. 7 had IFS and 4 had other sarcoma diagnoses. 8 tumors were in the extremities and 3 tumors were in other locations. 10 of 11 (91%) patients exhibited partial responses by RECIST. 3 patients had been referred to surgery after a median of 5 cycles (range 4 – 6) of laro. Two patients achieved pathological complete responses (CRs), have discontinued laro and remain disease free after 4 months median follow up. One patient with positive margins exhibited tumor growth post-operatively, resumed laro and remains on study. No patients have experienced postoperative complications or wound healing issues. In addition, one patient with IFS had a significant response and discontinued laro in order to establish whether the response could be maintained without surgery or drug. Results for additional patients undergoing surgical resection after the referenced interim data cutoff will be included in the final presentation.

Conclusion: Pediatric patients with NTRK-fusion advanced sarcomas are able to proceed to surgical resection following pre-surgical laro without postoperative complications or wound healing issues. Patients have achieved pathologic CRs following pre-surgical laro, avoiding highly morbid surgeries. These results support the continued evaluation of laro as pre-surgical therapy in children with newly diagnosed NTRK-fusion sarcomas.

Paper 033 #2803531

AXITINIB IN PROGRESSIVE ADVANCED SOLITARY FIBROUS TUMOR: RESULTS FROM AN EXPLORATORY ITALIAN PHASE 2 CLINICAL STUDY

Silvia Stacchiotti, MD[1]*; Carlo Morosi*[2]*; Anna Maria Frezza*[1]*; Alessandra Casale*[2]*; Elena Palassini*[1]*; Alessandro Gronchi*[3]*; Silvana Pilotti*[4]*; Paola Collini*[4]*; Salvatore Renne*[4]*; GianPaolo Dagrada*[5]*; Paolo G. Casali*[1]

[1]Cancer Medicine, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [2]Radiology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [3]Surgery, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [4]Pathology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [5]Molecular Biology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Objective: To explore the activity of axitinib (A) in patients (pts) with advanced solitary fibrous tumor (SFT).

Methods: An Italian investigator-driven exploratory prospective Phase II clinical study was started in April 2015 to evaluate the antitumor effect of A in adult pts with advanced SFT, at the starting oral dose of 5 mg BID, until progression or limiting toxicity. The target sample size was 16 evaluable pts. Eligible pts had to have evidence of progression in the 6 months prior to study entry. Pts pretreated with antiangiogenics were allowed. Pathologic diagnosis was centrally reviewed, distinguishing malignant (M-SFT) and dedifferentiated (D-SFT) subtypes. The primary endpoint was overall tumor response rate (ORR), defined by Choi criteria extended to MRI. Secondary endpoints were RECIST response rate, progression-free survival (PFS), overall survival (OS).

Results: Enrolment was completed in June 2017. Three of 16 pts had a D-SFT, 13 a M-SFT (at the time of the last path assessment); 8 were pretreated with antiangiogenics (3 sunitinib, 7 pazopanib), 4 with cytotoxic agents. Ten pts completed their treatment (all for progression), 4 are ongoing, while 2 are starting A. At the time of the present analysis, among 13/16 patients evaluable by Choi criteria (3 pts, too early), the best response was: 5 partial

response (PR) (ORR, 38%), 3 stable disease and 5 progression. Three/5 responsive pts were already pretreated with pazopanib. All D-SFT cases had a PD as their best response. Thirteen/16 pts were evaluable by RECIST with 1 PR, 11 SD and 1 progression. Toxicity was as expected. Median PFS by Choi criteria was 4 (range, 95% CI 3-5) months, with only one patient disease-free at >12 months. At a median follow-up of 10 months, median OS was 14 (range, 95% CI 10-16) months.

Conclusion: This exploratory Phase 2 study shows that axitinib can be active in M-SFT, though major dimensional responses were uncommon and the duration of response was limited. Responses were observed also in pts with M-SFT progressing after pazopanib, thus confirming in SFT the lack of cross-resistance to antiangiogenics. By contrast, this study does not support the use of axitinib in D-SFT.

Paper 034 #2804367

PRELIMINARY DATA ON SYSTEMIC THERAPY IN A MULTICENTER CASES SERIES OF PERIVASCULAR EPITHELIOID CELL TUMOURS (PECOMA)

Roberta Sanfilippo[1]*; Salvatore Provenzano*[1]*; Robin L. Jones*[2]*; Georgios Antoniou*[2]*; Vittoria Colia*[1]*; Elena Fumagalli*[1]*; Rossella Bertulli*[1]*; Jean-Yves Blay*[3]*; Axel Lecesne*[4]*; Mehdi Brahmi*[3]*; Armelle Dufresne*[3]*; Nadia Hindi MD, MSc*[5]*; Alessandro Gronchi*[1]*; Angelo Paolo Dei Tos*[6]*; Paolo G. Casali*[1]

[1]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [2]Royal Marsden Hospital, London, United Kingdom; [3]Centre Léon Bérard, Lyon, France; [4]Institut Gustave Roussy, Villejuif, France; [5]Virgen del Rocìo University Hospital, Seville, Spain; [6]Treviso Hospital, Treviso, Italy

Objective: Perivascular epithelioid cell tumors (PEComa) is a rare mesenchymal neoplasm with a variable biological behavior. Surgical resection is the mainstay of therapy. However, approximately one third of pts have an advanced disease d'emblée or develop metastases later on. The role of chemotherapy is controversial, with anecdotal responses reported, including some with mTOR inhibitors. The aim of this multicenter retrospective case series analysis was to describe the activity of systemic therapies in this disease.

Methods: We retrospectively identified all pts with advanced PEComa treated with medical therapy since January 2002 at Fondazione IRCCS Istituto Nazionale dei Tumori, Milan - Italy, and within the Italian Rare Cancer Network (RTR); at Royal Marsden Hospital, London – UK; within centres of the French Sarcoma Group and the Spanish Sarcoma Group. Clinical and histopathological characteristics, staging ,systemic treatments, and survival data were collected and analyzed.

Results: We preliminary analyzed 33 pts (M/F = 12/21, median age 54 years, range = 28 - 76) with advanced PEComa treated with medical therapy. Site of primary tumour was soft-tissues in 6/33 pts (18%), retroperitoneum in 6/33 pts (18%), kidney in 5/33 pts (15%), uterus in 5/33 (15%). Ten pts received gemcitabine-based chemotherapy and were evaluable for response: 2 had a PR (20%) and 1 a SD (10%); median PFS was 3 mos (1-6). Fifteen pts received an antracycline-based combination and were evaluable for response: 1 had PR (0,6%) and 5 a SD (33%); median PFS was 2 mos (0.9-15.6). Twenty-six pts received a mTOR inhibitor and were evaluable for response: 9 had a PR (35%), 10 a SD (38%); median PFS was 8.5 mos (0.4-68). Five patients received an antiangiogenic therapy (pazopanib or sunitinib), obtaining 1 PR and 2 SD, with a median PFS 6 mos (3.2-9.6).

Patients' characteristics - n(%)a

Total	33 (100)
Female	21 (64)
Males	12 (36)
Mean age at the diagnosis (years)	52
Site of the primary tumor	
Kidney	5 (15)
Soft-tissue	6 (18)
Retroperitoneum	6 (18)
Uterus	5 (15)
Other	11 (33)
Stage at the diagnosis	
Localized	19 (58)
Metastatic	14 (42)
Surgery of the primary tumor	
Yes	28 (85)
No	5 (15)
Disease stage at the time of medical treatment	
Locally advanced	1(1)
Metastatic	32 (99)
Median number of systemic therapy lines	2

Response to medical treatment (all lines)

Regimen	Total	PR	SD	PD	Median PFS in months (range)
Anthracycline-based	15	1	5	9	2.1 (0.9 - 15.6)
Gemcitabine-based	10	2	1	7	3.1 (1 - 6)
mTOR inhibitors	26	9	10	7	8.5 (0.4 - 67.9+)
Antiangiogenics	5	1	1	3	5.9 (3.2 - 9.6)

Conclusion: In this series, chemotherapy played a limited role. Poor activity was observed with anthracycline-based regimens, with only one long lasting stabilization. Gemcitabine-based regimens obtained some objective responses, although their duration was short. Antiangiogenics and mTOR inhibitors showed some activity, with a few

long-lasting responses. An effort to collect all cases of advanced PEComa treated with systemic therapy is ongoing, and a final analysis is foreseen.

Paper 035 #2797930

PROGNOSIS OF DESMOID TUMOURS INITIALLY MANAGED WITH SURVEILLANCE ONLY AT ALL ANATOMICAL LOCATIONS

Winan J. van Houdt, MD, PhD, MSc[1]*; Alisha Patel*[1]*; Robin L. Jones*[2]*; Myles J. Smith*[1]*; Aisha Miah*[3]*; Charlotte Benson*[2]*; Shane Zaidi*[3]*; Christina Messiou*[4]*; Eleanor Moskovic*[4]*; Dirk C. Strauss*[1]*; Andrew J. Hayes*[1]*; Olga Husson*[2]*; Winette van der Graaf*[2]

[1]Department of Surgical Oncology, The Royal Marsden Hospital, London, United Kingdom; [2]Department of Medical Oncology, the Royal Marsden Hospital, London, United Kingdom; [3]Department of Clinical Oncology, the Royal Marsden Hospital, London, United Kingdom; [4]Department of Radiology, the Royal Marsden Hospital, London, United Kingdom

Objective: Desmoid tumours are locally aggressive mesenchymal tumours that lack metastatic potential. Tumour behaviour is unpredictable and varies along a spectrum from remission to growth. Recently, active surveillance has been increasingly adopted as initial management. The aim of this study is to analyse the need and indications for treatment in desmoid patients initially managed with surveillance only.

Methods: Patients with a desmoid tumour at any anatomical location diagnosed between 1998 and 2016 were selected from a prospectively maintained database. Differences between patient groups were analysed with independent t-tests or Chi-square tests. Inverse univariate cox proportional hazard regression analyses were conducted to assess factors associated with start of treatment, tumour behaviour and pain.

Results: A total of 168 patients initially managed with surveillance only were identified. The tumours were located in an extremity (51), in the abdominal wall (61), intra-abdominally (15), chest wall (30) or other locations (11). From these patients, 33% (n=55) developed progressive disease, 38% (n=64) had stable disease and 28% (n=47) had a remission. Tumours in patients <50 years old were more likely to show progressive disease after surveillance in univariate analysis (p= 0.046). A total of 78 patients (46%) eventually had some form of treatment, while 90 patients (54%) continued on surveillance only. Median time to treatment was 31 months. Patients with tumours >5 cm were more likely to undergo treatment (p<0.01), while no significant differences were found between the different anatomical locations. Treatment consisted mainly of surgery (n=40, 44%) or systemic therapy (n=36, 40%). The indications to start treatment were pain (32%), growth (31%) or both (13%). Tumours located in the chest wall or upper extremity caused significantly more pain when compared to other locations (p=0.01), while pregnancy-associated desmoid tumours caused significantly less pain (p=0.04).

Conclusion: Patients with desmoid tumours can be managed with surveillance only, but a large minority still needs treatment after an initial period of surveillance. Pain and tumour growth are the most common indications to start treatment after initial surveillance.

Paper 036 #2762720

AN UPDATE ON THE MANAGEMENT OF SPORADIC DESMOID-TYPE FIBROMATOSIS: A EUROPEAN CONSENSUS INITIATIVE BETWEEN SARCOMA PATIENTS EURONET (SPAEN) AND EUROPEAN ORGANISATION FOR RESEARCH AND TREATMENT OF CANCER (EORTC) / SOFT TISSUE AND BONE SARCOMA GROUP (STBSG)

Bernd Kasper, MD, PhD[1]*; Christina Baumgarten*[2]*; Jesica Garcia*[2]*; Sylvie Bonvalot*[3]*; Rick Haas, MD, PhD*[4]*; Florian Haller*[5]*; Peter Hohenberger*[1]*; Nicolas Penel*[6]*; Christina Messiou*[7]*; Winette van der Graaf*[8]*; Alessandro Gronchi*[9]

[1]Interdisciplinary Tumor Center, Mannheim University Medical Center, Mannheim, Germany; [2]Sarcoma Patients EuroNet (SPAEN), Wölfersheim, Germany; [3]Department of Surgical Oncology, Institut Curie, PSL University, Paris, France; [4]Department of Radiotherapy, The Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands; [5]Institute of Pathology, Friedrich Alexander University Erlangen, Erlangen, Germany; [6]Department of Medical Oncology, Centre Oscar Lambret, Lille, France; [7]Radiology, The Royal Marsden Hospital, London, United Kingdom; [8]Division of Clinical Studies, The Institute of Cancer Research, London, United Kingdom; [9]Department of Surgery, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Objective: Desmoid-type fibromatosis (DF) is a rare and locally aggressive monoclonal, fibroblastic proliferation characterized by a variable and often unpredictable clinical course. In attempt to establish an evidence-based treatment approach for DF the European Desmoid Working Group published a position paper in 2015 with treatment practice recommendations. Here, we present an update of this consensus approach based on professionals' and patients' expertise following a 2nd Round Table Meeting on the 23rd of February 2017 bringing together soft tissue tumor experts from the EORTC / STBSG with patients and patient advocates from SPAEN. We focus on new findings regarding the prognostic value of the mutational analysis in DF patients and an update on systemic treatment options.

Methods: This position paper adheres to the EORTC Policy 19 on "Guidelines, Expert Opinions, and the use of EORTC Results in Promotional Material on Cancer Care"

and has formal EORTC Board approval.

Results: The key points of the position paper can be summarized as follows: (1) There is no level I or II evidence for the treatment approach for DF available, however, there are prospectively conducted studies and meta-analysis / systematic reviews; (2) There is agreement that an initial watchful waiting strategy is useful to document actual tumor progression before any treatment is started; (3) There is lack of correlation between surgical margins and recurrence rates, thus, aggressive and function-threatening (re-)surgery is not recommended; (4) The use of radiation therapy should be carefully weighed against side effects and long-term risk of secondary cancers; (5) CTNNB1 mutation status may be used in guiding diagnostic and treatment decisions; (6) Optimal systemic treatment is not standardized and needs to be individualized on a multidisciplinary basis for patients with clear progressing disease.

Conclusion: We believe that this unique initiative will become the reference for the management of this disease and the basis to put in perspective any further research.

Paper 037 #2794088

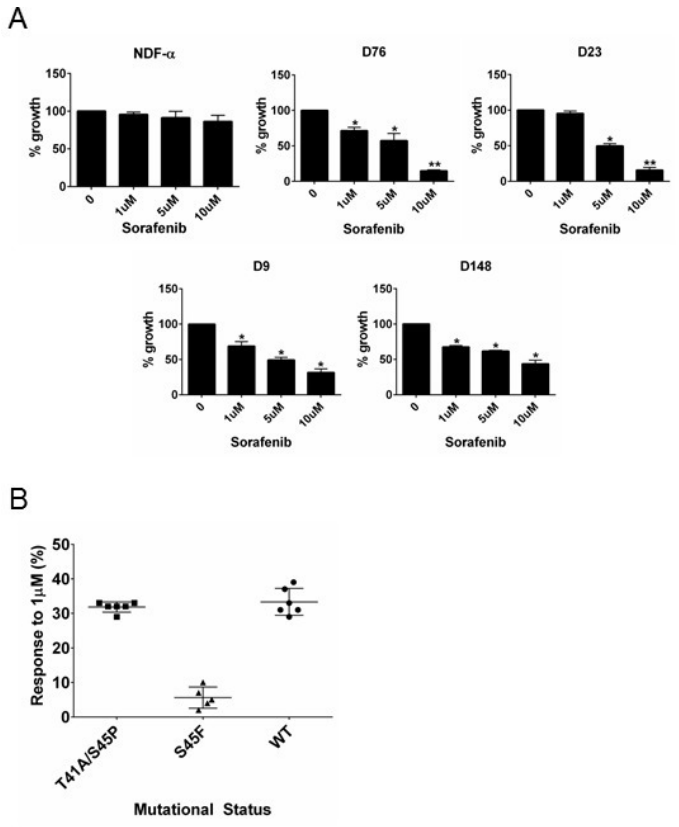
AUTOPHAGY INHIBITION OVERCOMES SORAFENIB RESISTANCE IN *CTNNB1* MUTANT S45F DESMOID TUMORS

Danielle Braggio, PhD[1]*; David Koller*[2]*; Feng Jin*[3]*; Nanda Siva*[4]*; Abeba Zewdu*[1]*; Gonzalo Lopez*[1]*; Kara Batte*[1]*; Lucia Casadei, PhD*[1]*; Meng Welliver*[3]*; Anne Strohecker*[1]*; Raphael Pollock*[2]*; Dina Lev*[5]
[1]Comprehensive Cancer Center, The Ohio State University, Columbus, OH, USA; [2]Department of Surgery, The Ohio State University, Columbus, OH, USA; [3]Radiation Oncology Department, The Ohio State University, Columbus, OH, USA; [4]Department of Chemical and Biomedical Engineering, West Virginia University Statler College of Engineering and Mineral Resources, Morgantown, WV, USA; [5]Surgery B, Sheba Medical Center, Tel Aviv, Israel

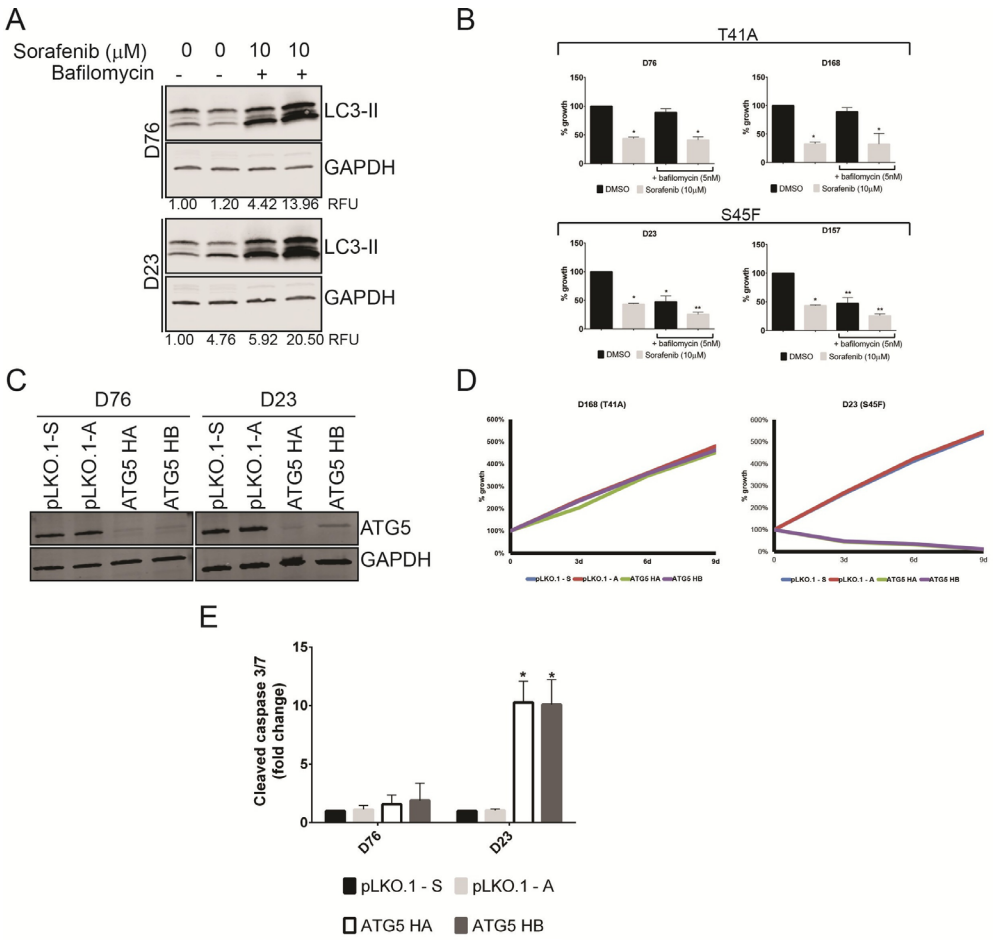
Objective: To conduct a comprehensive analysis of sorafenib efficacy in a large panel of desmoid cell strains to probe for response mechanism.

Methods: A panel of DT cell strains was exposed to increasing concentrations of sorafenib or combination of drugs in vitro and evaluated for cell growth, colony formation, migration, invasion, cell cycle, and apoptosis. Explant cultures were also exposed to sorafenib or combination of drugs and evaluated for cell viability and apoptosis. To assess autophagic dynamics, autophagy flux was measured with bafilomycin, an inhibitor of late phase autophagy. The autophagic responsiveness between DTs harboring different CTNNB1 mutations was compared under autophagy enhancing conditions.

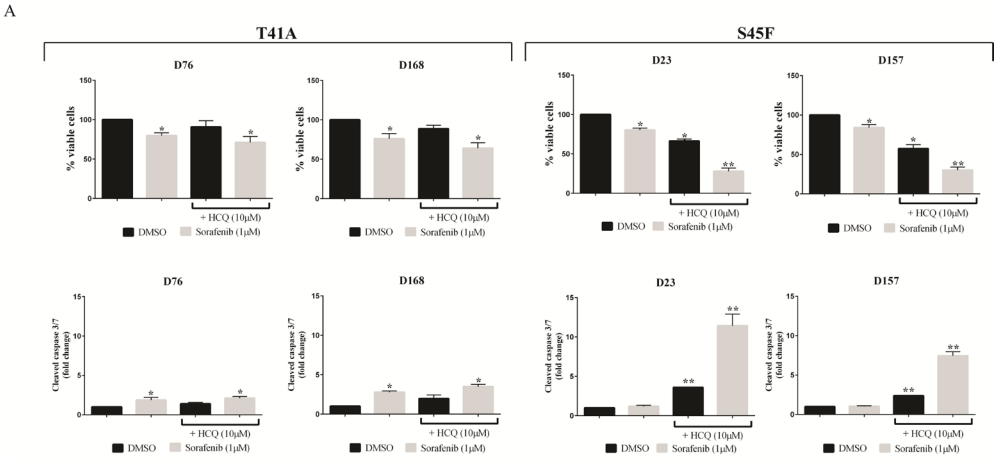
Results: Within all desmoid cells tested, we found a distinctive group of responders and non-responders. When we clustered the non-responder group, surprisingly, we observed that all cells were S45F mutants. Several studies have shown that the mutation S45F correlates with a higher risk of DT recurrence and to a lack of response to meloxicam, suggesting the more aggressive behavior of desmoid tumors so mutated. Autophagy is a well-established mechanism of cell stress response that is often activated in response to anti-cancer regimens. Thus we assessed basal autophagy in the responders and non-responders. When autophagy was inhibited genetically or pharmacologically in the S45F mutant cell strains, sensitivity to sorafenib was restored.



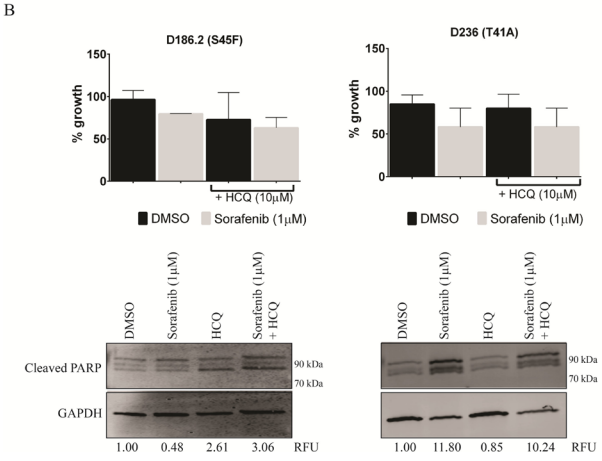
Sorafenib efficacy in desmoid cell strains



CTNNB1 S45F mutated cells are highly dependent on autophagy for survival.



Combination of sorafenib and chloroquine enhances the anti-proliferative and pro-apoptotic effects on S45F mutated DTs *in vitro* and *ex vivo*



Conclusion: Our findings suggest that the cell death response to sorafenib differs when comparing DTs harboring the CTNNB1 S45F mutation and T41A mutated or wild-type DTs. Furthermore, combination of HCQ and sorafenib enhances the anti-proliferative and pro-apoptotic effects on S45F mutated DT cells, suggesting that profiling β-catenin status could guide clinical trial management of desmoid patients considering sorafenib treatment.

9:45 am – 10:30 am
– SESSION 5 –
GIST

Paper 038 #2803523

CLINICAL ACTIVITY OF BLU-285 A HIGHLY POTENT AND SELECTIVE KIT/PDGFRα INHIBITOR DESIGNED TO TREAT GASTROINTESTINAL STROMAL TUMOR (GIST)

Michael Heinrich[1]*; Robin L. Jones*[2]*; Margaret von Mehren*[3]*; Patrick Schoffski*[4]*; Sebastian Bauer*[5]*; Olivier Mir*[6]*; Philippe A. Cassier*[7]*; Ferry Eskens*[9]*; Hongliang Shi*[8]*; Terri Alvarez-Diez*[8]*; Oleg Schmidt-Kittler*[8]*; Mary Ellen Healy*[8]*; Beni B. Wolf*[8]*; Suzanne George*[10]

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Objective: Activating mutations in KIT or PDGFRα drive >85% of GIST. However, primary and acquired resistance mutations are not effectively treated by approved therapies. A phase 1 study (NCT02508532) was initiated in advanced GIST to assess the safety and clinical activity of BLU-285, a potent, highly-selective oral inhibitor that targets GIST resistance mutants including KIT Exon 17/18 and PDGFRa D842 activation loop mutants.

Methods: Adult patients (pts) with unresectable GIST, who had received ≥2 kinase inhibitors including imatinib or who had a primary PDGFRα D842 mutation regardless of prior therapy, were given BLU-285 once daily on a 4-week cycle following a 3+3 escalation/MTD expansion design. Adverse events (AEs) per CTCAE v4.03, PK and plasma/tumor mutant DNA levels were assessed. Response was determined by RECIST 1.1 every 8 weeks and confirmed via central radiology review.

Results: At a 28APR17 cutoff, 72 pts (32 PDGFRa/40 KIT) have been treated with BLU-285 at doses of 30-600 mg (46 dose escalation; 26 in the ongoing dose expansion). Median number of prior kinase inhibitor regimens was 4 (2-11) KIT/1.5 (0-6) PDGFRa. Based on safety, PK, and anti-tumor activity, 400 mg was the MTD and RP2D. RECIST 1.1 responses were seen across all dose levels for PDGFRa GIST and at higher dose levels for KIT GIST. Of 25 PDGFRa D842-mutant pts with ≥1 central radiographic assessment, 15 had PR (12 confirmed; ORR 60%) and 10 had SD. mPFS was not reached and the estimated 9 mo. PFS was 87%. Of 25 evaluable KIT pts, 2 had PR (1 confirmed; ORR 8%) and 12 SD. mPFS for KIT pts treated at doses ≥ 300 mg was 9.3 mo and 2 mo for pts treated at doses of 30-200 mg. Tumor reductions and SD were observed across multiple KIT genotypes. Most AEs were grade 1 or 2, most commonly nausea (60%), fatigue (53%), vomiting (42%), periorbital edema (36%), diarrhea (33%), and peripheral edema (31%). There were no grade 4 or 5 BLU-285-related AEs and fatigue (8%) and hypophosphatemia (6%) were the only treatment-related Gr 3 AEs occurring in ≥ 5% of pts. 2 pts experienced DLT (1 Gr 2 hyperbilirubinemia; 1 Gr 2 rash, hypertension, memory impairment) at 600 mg. 51 pts remain on treatment (duration 1-18 mo). Updated results including ct-DNA and preliminary anti-tumor activity for the dose expansion cohorts will be presented.

Conclusion: Precision targeted therapy with BLU-285 demonstrates important clinical activity in pts with both PDGFRa- and KIT-mutant GIST that is resistant to available therapies.

Paper 039 #2804377

DCC-2618, A NOVEL PAN-KIT AND PDGFRA KINASE SWITCH CONTROL INHIBITOR DEMONSTRATES ENCOURAGING ACTIVITY IN PATIENTS (PTS) WITH GASTROINTESTINAL STROMAL TUMORS (GIST)

Neeta Somaiah, MD[1]*; Albiruni Razak*[2]*; Michael Gordon*[3]*; Filip Janku*[4]*; Sharon Friedlander*[5]*; Daniel Flynn*[5]*; Michael Kaufman*[5]*; Jama PItman*[5]*; Rodrigo Ruiz-Soto*[5]*; Bryan Smith*[5]*; Deborah Westwood*[5]*; Julia Jennings*[6]*; Jerilynn Jacobson*[5]*; Oliver Rosen*[5]*; Suzanne George*[6]

[1]Sarcoma Medical Oncology, MD Anderson Cancer Center, Houston, TX, USA; [2]Princess Margaret Cancer Centre, Toronto, ON, Canada; [3]Pinnacle Oncology Hematology, Scottsdale, AZ, USA; [4]Phase I, University of Texas MD Anderson, Houston, TX, USA; [5]Clinical Research, Deciphera Pharmaceuticals, Waltham, MA, USA; [6]Center for Sarcoma and Bone Oncology, Dana-Farber Cancer Institute, Boston, MA, USA

Objective: TKIs currently approved for the treatment of GIST inhibit either mutations in the KIT ATP binding pocket region or the activation loop but do not demonstrate comprehensive activity across both regions known to cause imatinib resistance. DCC-2618 was designed to potently inhibit the broadest range of mutations in KIT & PDGFRα kinases including those that emerge on treatment with approved TKIs.

Methods: This is a dose-escalation study of oral DCC-2618 (QD or BID q28 days) followed by an expansion cohort in pre-treated TKI resistant GIST. During the escalation phase, FDG-PET scans were performed at baseline and after 3 wks of therapy; CT scans were performed every 2 cycles. Next generation sequencing (NGS) of plasma cell-free (cf) DNA was performed throughout the study

to quantify KIT, PDGFRα and other molecular alterations. Concordance of mutational status between plasma cfDNA and tumor tissue (collected at baseline and after 2 cycles) was assessed.

Results: 37/48 enrolled pts had KIT (33) or PDGFRα (4) driven GIST and received daily doses ranging from 40-400 mg. Median number of prior agents was 3. The dose selected for expansion was 150 mg QD. Of 23 pts with KIT mutant GIST assessed by FDG PET, 18 (78%) had a partial metabolic response per EORTC criteria. Three of 25 evaluable patients showed RECIST partial responses. Disease Control Rate for KIT and PDGFRα GIST patients for doses of ≥100 mg daily at 12 weeks was 78% (18/23 pts) and 24 weeks was 60% (9/15 pts). One pt remains on study free of PD for >1 year. NGS of cfDNA revealed a reduction of mutation allele frequency (MAF) in exons 9, 11, 13, 14, 17 and 18. Several patients harbored multiple KIT resistance mutations. Safety for all 48 pts was as follows: grade (G) 3 /4 adverse effects [regardless of attribution, incidence of >1 pt] included anemia (7), asymptomatic lipase increase (↑) (6), hypertension (3), creatine phosphokinase (CPK) ↑ (2). Two of the G3 lipase ↑ (at 100 mg BID and 200 mg BID) and 1 G4 CPK ↑ at 150 mg QD were DLTs.

Conclusion: DCC-2618 was well tolerated up to 200 mg BID and all DLTs were not clinically significant. DCC-2618 showed encouraging disease control with objective responses and prolonged stable disease in heavily pre-treated GIST patients. The notable decreases in MAF of resistance mutations across all exons supports the use of DCC-2618 beyond imatinib resistance and warrants testing in a randomized phase 3. (NCT# 02571036)

Paper 040 #2760542

KIT MUTATION ZYGOSITY IMPACTS TKI SENSITIVITY IN GIST

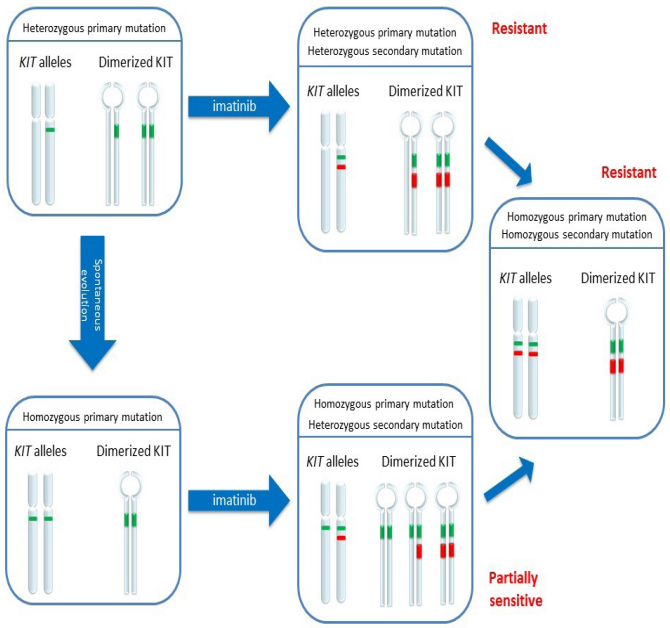
Armelle Dufresne[1]*; Nacef Bahri*[2]*; Alexandra Lauria*[2]*; Inga Marie Schaefer*[2]*; Adrian Marino Enriquez*[2]*; Jonathan Fletcher*[2]

[1]*Centre Leon Berard, Lyon, France;* [2]*Brigham and Women's Hospital, Boston, MA, USA*

Objective: Most GISTs result from gain-of-function mutations in genes encoding the KIT or PDGFRA receptor tyrosine kinases. Despite initial disease control by imatinib, most patients with advanced GIST experience eventual disease progression, due to secondary KIT/PDGFRA TKI-resistance mutations. These secondary mutations can be heterozygous or homozygous, and in the present studies we evaluated the impact of zygosity on TKI-resistance.

Methods: We developed isogenic GIST48 in vitro models with a homozygous primary KIT mutation (KIT exon 11 V560D) coupled in cis with either heterozygous or homozygous secondary KIT exon 17 D820A mutations. These sublines were designated GIST48/820-het and GIST48/820-hom, respectively. Western blotting, cell viability and migration assays were performed with and without imatinib treatment to compare TKI resistance in these sublines.

Results: Using cross-linking studies, we showed that mutant KIT oligomers in GIST were expressed in dimeric form. These studies predicted that GIST48/820-het cells express a mix of imatinib-sensitive and imatinib-resistant KIT dimers, whereas GIST48/820-hom express only imatinib-resistant KIT dimers (Figure). In keeping with these models, western blot studies showed greater imatinib-resistance in GIST48/820-hom cells, with less inhibition of phospho-KIT, phospho-AKT and phospho-MAPK. Cell viability assays also demonstrated dramatically greater imatinib-resistance in GIST48/820-hom (IC50 1524nM) than in GIST48/820-het (IC50 80). Likewise, cell migration was more resistant to imatinib in GIST48/820-hom than in GIST48/820-het.



Conclusion: These results demonstrate that zygosity of primary and secondary KIT mutations impacts GIST resistance to TKI. Namely, GISTs with homozygous primary and secondary mutations are more TKI-resistant than GISTs with homozygous primary and heterozygous secondary mutations. These findings reveal nuanced and incremental mechanisms of imatinib-resistance, and are clinically relevant because they demonstrate persistence of partial imatinib-sensitivity, even after GIST cells acquire secondary TKI-resistance mutations. In sum, there are two reasons that GIST patients should continue to receive KIT/PDGFRA-inhibitors after clinical progression. First, as is well known, most GIST patients with secondary TKI-resistance have some burden of disease with only the primary TKI-sensitive mutation. Second, some progressing GISTs have homozygous primary mutations and heterozygous secondary resistance mutations, in which a subset of the oncogenic kinase dimers remain TKI-sensitive.

1:00 pm – 2:00 pm
– SESSION 6 –
Osteosarcoma & Chondrosarcoma

Paper 041 #2784460
PERIOPERATIVE RH-ENDOSTATIN WITH CHEMOTHERAPY IMPROVES THE SURVIVAL OF OSTEOSARCOMA PATIENTS
***Xiaohui Niu**; Hairong Xu, MD; Zhen Huang*
Department of Orthopaedic Oncology, Beijing Ji Shui Tan Hospital, Peking Universtiy, Beijing, China

Objective: The anti-angiogenic strategy is an emerging treatment against malignant tumors. Rh-Endostatin is an anti-angiogenic agent has been widely used against non-small lung cancer. This object of this research is to investigate the efficacy and safety of perioperative use of Rh-Endostatin against stage IIB osteosarcoma.

Methods: This is a controlled non-randomized clinical research. There were 388 patients enrolled in Beijing Ji Shui Tan Hospital from January 2008 to April 2012. Fifty-eight cases were excluded in the final analysis. The control treatment group has 272 cases with 180 males and 92 females with a median age of 17 years old. The treatment group has 58 patients with 36 males and 22 females with a median age of 16 years old. Control treatment group received preoperative chemotherapy- surgery-postoperative chemotherapy treatment. The Rh-Endostatin treatment group was given 4 cycles of Rh-Endostatin in the perioperative period on the basis of the control treatment. Patients were followed up from 6-101 months with a median period of 50.2 months.

Results: In the control treatment group, the 5-year distant metastasis-free survival (DMFS) was 61%, while the Rh-Endostatin treatment group were 79% with statistically significant difference (P = 0.009). In the control treatment group, the 5-year disease progression-free survival (PFS) was 60%, while the Rh-Endostatin treatment group were 78% with statistically significant difference (P = 0.015). In the control treatment group, the 5-year overall survival (OS) was 75%, while the Rh-Endostatin treatment group was 86%, with statistically significant difference (P = 0.028). No difference in adverse drug reactions was found in these two groups.

Conclusion: Perioperative administration of Rh-Endostatin with traditional chemotherapy could significantly improve the distant metastasis-free survival, disease progression-free survival, and overall survival in osteosarcoma patients. It is safe and worthy for further clinical application.

Paper 042 #2753015
PHASE 2 TRIAL OF THE GPNMB-TARGETED ANTIBODY-DRUG CONJUGATE, CDX-011 (GLEMBATUMUMAB VEDOTIN) IN RECURRENT/ REFRACTORY OSTEOSARCOMA (OS): A REPORT FROM THE CHILDREN'S ONCOLOGY GROUP (COG)
***Lisa M. Kopp**[1]; Suman Malemati[4]; Mark Karilo[5]; Brenda Weigel[3]; Yun Gao, MS[5]; Lisa A. Teot[2]; Justin Cates[8]; Amy R. Newman[10]; Victor M. Villalobos[7]; Robert L. Randall[9]; Joel M. Reid[11]; Grace Lin[12]; Alisa Eicher[4]; Justin Davis[5]; Richard Gorlick[6]; Katherine Janeway[2]*
[1]University of Arizona, Tucson, AZ, USA; [2]Dana Farber Cancer Institute, Boston, MA, USA; [3]University of Minnesota/Masonic Cancer Center, Minneapolis, MN, USA; [4]Oregon Health and Science University, Portland, OR, USA; [5]Children's Oncology Group, Monrovia, CA, USA; [6]MD Anderson Cancer Center, Houston, TX, USA; [7]University of Colorado Denver, Aurora, CO, USA; [8]Vanderbilt University/Ingram Cancer Center, Nashville, TN, USA; [9]Primary Children's Hosptial, Salt Lake City, UT, USA; [10]Midwest Children's Cancer Center, Milwaukee, WI, USA; [11]Mayo Clinic, Rochester, MN, USA; [12]Lucile Packard Children's Hospital Stanford University, Palo Alto, CA, USA

Objective: In Osteosarcoma (OS) few treatment advances have been made in over 30 years. Only 12% of patients with recurrent OS enrolled on COG phase 2 trials remain progression-free at 4 months. Glycoprotein non-metastatic B (GPNMB) is a type I transmembrane glycoprotein that is highly expressed on the plasma membranes of OS cells. CDX–011 consists of a fully human IgG2 monoclonal antibody (CR011) conjugated to the potent microtubule inhibitor, monomethyl auristatin E (MMAE). In pre-clinical testing, CDX–011 induced cytotoxic effects in 74% of OS cell lines and GPNMB protein levels correlated with CDX–011 in vitro cytotoxicity. To evaluate whether CDX–011 has clinical activity in OS, we conducted a single arm phase 2 trial in patients with recurrent / refractory OS.

Methods: Patients > 12 yrs and < 50 yrs with relapsed or refractory histologically verified OS and measurable disease according to RECIST 1.1 were eligible. Cohorts were divided by age and prior Eribulin therapy. CDX–011 1.9 mg/kg/dose was administered intravenously on Day 1 of each 21-day cycle. GPNMB expression was measured in tumor specimens by immunohistochemistry (IHC). The primary endpoint was disease control at 4 months and RECIST response. Disease control was defined as stable disease at four months of therapy or six cycles, whichever occurred first. Secondary aims included determining the feasibility, toxicity profile, pharmacokinetics (PK) and pharmacodynamics of CDX–011, and relationship of GPNMB expression to response. The 2 stage design used provided at least 90% chance of identifying CDX–011 as effective when the probability of RECIST response

was 0.22 or the probability of disease control was 0.42.

Results: 22 patients were enrolled (3 with prior Eribulin). All were evaluable for disease response. CDX–011 was tolerated well and there were no unexpected toxicities. The most frequent Grade 3 AE was rash. There was one death from end organ failure due to multiple toxicities, which were determined to not be solely related to CDX–011. Of 19 patients considered for CDX–011 efficacy, 1 evaluation is not complete, 1 had a partial response and 2 had stable disease at 4 months. GPNMB by IHC was completed on available specimens (P=0.19) Figure 1. PK results are in process.

Relation of GPNMB Maximum Staining Intensity to Disease Control Success

Max Staining Intensity	Disease Control Success			
Frequency	Indeterminate	No	Yes	Total
Missing	0	4	0	4
0	0	1	0	1
1	1	1	1	3
2	0	2	0	2
3	0	10	2	12
Total*	1	18	3	22

Fisher's Exact Test	
Table Probability (P)	0.19
Pr <= P	0.68

*Evaluation of effective sample size = 17. Missing data = 5 (1 indeterminate response and 4 missing samples)

Conclusion: CDX–011 was well tolerated in this population. Although there was some antitumor activity, there was not sufficient disease control in Stage 1 to warrant proceeding to Stage 2.

Paper 043 #2758475

TAS-115, A NOVEL ORAL MET/VEGFR/CSF1R INHIBITOR, REVEALED THE PRELIMINARY ANTI-TUMOR ACTIVITY AGAINST OSTEOSARCOMA AND RARE SUBTYPES OF SOFT TISSUE SARCOMA IN THE PHASE I STUDY

Yoichi Naito[1]*; Kenji Nakano*[2]*; Shigehisa Kitano*[3]*; Takahiro Kogawa*[1]*; Akihiko Shimomura*[3]*; Kan Yonemori*[3]*; Mai Onomura*[2]*; Toshihiko Doi*[1]*; Noboru Yamamoto*[3]*; Shunji Takahashi*[2]*; Uemura Hiroji*[4]*; Nobuhito Araki*[5]*; Akira Kawai*[3]

[1]National Cancer Center Hospital East, Kashiwa, Japan; [2]Cancer Institute Hospital of JFCR, Tokyo, Japan; [3]National Cancer Center Hospital, Tokyo, Japan; [4]Yokohama City University Medical Center, Yokohama, Japan; [5]Osaka International Cancer Institute, Osaka, Japan

Objective: TAS-115 is a novel multi-targeted kinase inhibitor mainly targeting hepatocyte growth factor receptor (MET), vascular endothelial growth factor receptor (VEGFR) and macrophage colony-stimulating factor 1 receptor (CSF1R), essential for the differentiation of osteoclasts. In the expansion cohort of the phase I study, the tolerability at recommended dose and the preliminary efficacy of TAS-115 in patients (pts) with various cancer types including osteosarcoma (OS) and rare subtypes of soft tissue sarcoma (STS) which have been reported to overexpress MET were evaluated.

Methods: In the OS and STS cohort, target population was pts with histologically proven OS and rare subtypes of STS including alveolar soft part sarcoma, clear cell sarcoma and epithelioid sarcoma. Eligible pts (ECOG PS ≤1, aged ≥15 years in OS, or ≥20 years in STS) who were refractory to standard treatment were enrolled. The dose of TAS-115 was 650 mg/day determined in dose escalation cohort of the phase I study. Pts received TAS-115 orally with a 5-days-on/2-days-off schedule for up to 21 days per cycle. Efficacy and safety were evaluated based on the RECIST ver 1.1 and the CTCAE ver 4.03, respectively.

Results: A total of 17 pts received TAS-115 as of Apr 2017. There were 8 pts with OS, 4 pts with epithelioid sarcoma, 3 pts with alveolar soft part sarcoma and 2 pts with clear cell sarcoma. The best overall response per RECIST criteria was stable disease in 5 of 17 pts (29.4%). A patient with epithelioid sarcoma experienced significant response by bone scintigraphy. Efficacy against bone metastases had also been confirmed in another patient with OS; that was marked reduction of 18F-fluorodeoxyglucose uptake on bone metastases by PET scan imaging. In addition, another patient with OS had a durable disease stabilization exceeding to 10 months, as compared with prior chemotherapy (3.2 months with Gemcitabine+Docetaxel). The most common (all grade ≥30%) adverse drug reactions (ADRs) were AST increased, anorexia, fatigue, nausea, ALT increased, hypophosphatemia and leukopenia. The rate of grade ≥3 ADRs was 20.2%. Although 82.4 % of pts required interruption of TAS-115, these ADRs were resolving by interruption of TAS-115.

Conclusion: Toxicities of TAS-115 were acceptable and preliminary anti-tumor activity was observed in pts with OS and rare subtypes of STS. The ongoing expansion cohort of this phase I study is still under evaluation. Clinical trial information: JapicCTI-132333.

Paper 044 #2795749

GRM4 AND IL23 ARE NOVEL THERAPEUTIC TARGETS IMPLICATED IN OSTEOSARCOMA SUSCEPTIBILITY AND PROGRESSION

David Thomas, FRACP, PhD*; Maya Kansara*

Cancer, Garvan Institute of Medical Research, Sydney, NSW, Australia

Objective: There is a need for novel therapies for osteosarcoma. Multiple lines of evidence support the role of

immunotherapy in bone cancer. Genome-wide association studies have identified the GRM4 (glutamate metabotropic recptor 4) locus as the strongest assocaition with susceptibility to osteosarcoma. Although the mechanisms are not known, emerging evidence suggests a link to immune regulatory functions. Here we use genetic models to demonstrate that Grm4 and Il23 are epistatically linked and rate-limiting to spontaneous osteosarcoma development in mice. Because there are emerging and established drugs that target both IL23 and GRM4, we use our model systems to study pharmacologic interdiction of the GRM4-IL23 axis on tumor development in vivo.

Methods: We have used a radiocarcinogen-induced osteosarcoma model to study the dependence of tumor development on Grm4 and Il23 in mice. The relationship between activation of GRM4 and expression of IL23 was studied in mouse and human monocytic cells. A panel of human osteosarcomas was studied for expressiom of IL23A. Finally, we conducted therapeutic studies using syngenic murine osteosarcoma cell lines, using an agonist for GRM$ (PHCCC) and an antagonist of IL23.

Results: In both human and murine monocytes, activation of Grm4 suppressed expression of Il23, while murine Grm4 -/- dendritic cells expressed markedly increased amounts of Il23 transcript and protein. Interestingly, the levels of Il12, a tumor suppressor cytokine linked to Il23, were reciprocally increased by activation of Grm4. These data suggest that GRM4 promotes an effective immune suppressor response by activating IL12 and suppressing IL23. Consistent with opposing roles in tumor development, the Grm4 -/- mice appear predisposed to earlier onset osteosarcoma development, while Il23 -/- mice were strikingly protected from the development of osteosarcomas (P<0.0001). In both mouse and human osteosarcomas, IL23 was expressed by infiltrating macrophages and dendritic cells. Using either an agonist for GRM4 (PHCCC) or an antagonist of IL23, we show that we can suppress tumour growth, an effect which appears synergistic with doxorubicin-based chemotherapy.

Conclusion: Taken together, these data provide a mechanistic basis for the genetic association between GRM4 and human osteosarcoma via IL12/IL23. More importantly, as agents targeting both GRM4 and IL23 are in clinical development, these genes represent promisign novel therapeutic targets for patients with osteosarcoma.

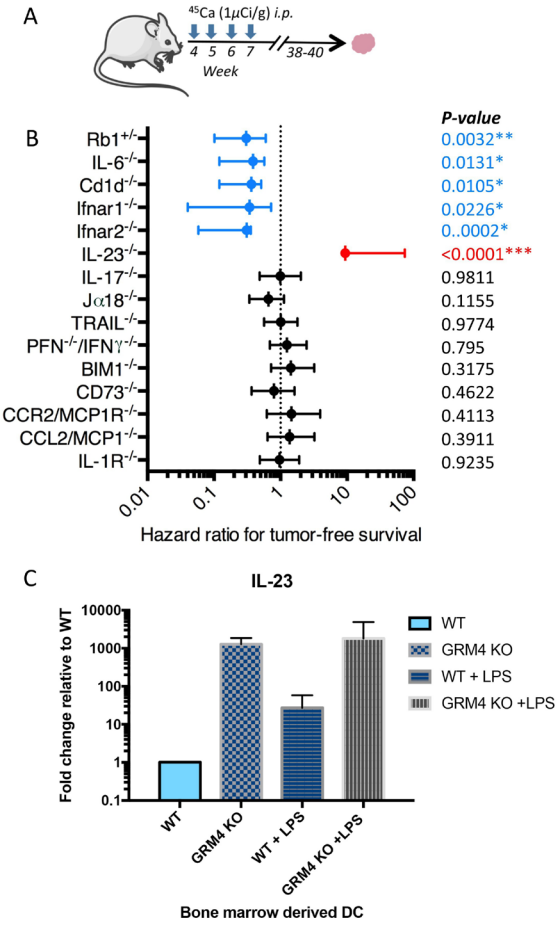


Figure 1 IL-23 knockout- mice are protected from the development of radiation induced osteosarcoma. Link between GRM4 and IL23 expression A) Schematic of radiation-induced mouse model of osteosarcoma. Mice at 28 days of age were injected with 1 μCi/g ^{45}Ca intraperitoneally once weekly for 4 consecutive weeks and monitored for the growth of tumors.1 B) Use of radiocarcinogen model to identify genotypes that modify the development of osteosarcoma. Hazard ratio (log rank) 95% confidence interval, Mantel-Cox test for significance compared to control C57/Bl6 mice. Knockout genotypes compared to wildtype C57BL/6 mice (25-30 mice per cohort). C) Dendritic cells (Dcs) isolated from GRM4 knockout mice have upregulated IL23 expression compared to Dcs derived from control animals. Lipopolysaccharide up regulates expression further in Dcs from control mice. Experiments in triplicate mean ± SEM.

2:00 pm – 3:00 pm
– SESSION 7 –
Ewing Sarcoma

Paper 045 #2783571

THE INFLUENCE OF LOCAL TREATMENT ON OUTCOME OF LOCALIZED PELVIC EWING SARCOMA - A RETROSPECTIVE ANALYSIS OF THE EURO-EWING99 TRIAL

Dimosthenis Andreou, MD[1]*; Andreas Ranft*[2]*; Daniel Baumhoer*[3]*; Henk van den Berg*[4]*; P.D. Sander Dijkstra*[5]*; Georg Gosheger*[1]*; Jendrik Hardes*[1]*; Ruth Ladenstein*[6]*; Andreas Leithner*[7]*; Sergiu Scobioala*[2]*; Arne Streitbuerger*[1]*; Per-Ulf Tunn*[8]*; Eva Wardelmann*[2]*; Heribert Juergens*[2]*; Uta Dirksen*[9]

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Objective: Approximately 20% of all Ewing sarcoma (ES) are localized in the pelvis. Due to the specific features of pelvic anatomy, local treatment can be challenging. We sought to identify factors associated with local recurrence (LR) and overall survival (OS) in patients undergoing multimodal treatment.

Methods: We performed a retrospective analysis of the files of 180 patients with previously untreated localized ES of the pelvis registered in the Euro-EWING99 trial (NCT00020566) from centers in D, A, B, CH, CZ und NL between 1998 and 2009. Median follow-up was 54 months for all patients and 84 months for survivors.

Results: The probability of LR at 5 years amounted to 24%, while OS was 59%. Sacral tumors were associated with an improved LR (p=0.032) and OS (p=0.025) compared to non-sacral tumors.
Tumor volume, with a cutoff at 200ml, had no influence on LR and OS in this selected group of patients (p=0.176). Both a poor histological response to induction chemotherapy (p=0.014) and the development of surgical complications after tumor resection in non-sacral tumors (p=0.004) were associated with a poorer OS, while performing the tumor biopsy and resection at the same institution was associated with a lower LR (p=0.035).

Definitive radiotherapy in sacral tumors was comparable to combined surgery and radiotherapy in terms of LR (p=0.125) and OS (p=0.764), while the combined local treatment in non-sacral tumors was associated with an improved LR (p=0.015) and OS (p=0.024) compared to surgery alone, with a OS benefit even in the subgroup of patients with wide surgical margins and a good histological tumor response to induction treatment (p=0.009).
A persisting soft tissue infiltration after induction treatment in patients with non-sacral bone tumors who underwent surgical treatment was associated with a poorer LR (p=0.026) and OS (p=0.005). Finally, the complete removal of the affected bone was associated with an improved LR (p=0.001) and OS (p<0.0001) in non-sacral tumors.

Conclusion: Definitive radiotherapy appears to be an adequate local treatment for patients with sacral ES, while combined surgery and radiotherapy appears to be superior to surgery alone in patients with non-sacral pelvic tumors. A persisting soft tissue infiltration after induction treatment seems to be a simple but significant prognostic marker, while the complete removal of the involved bone in patients with non-sacral tumors was associated with a highly improved LR and OS in our analysis.

Paper 046 #2801616

GERMLINE ALTERATIONS AND FAMILY HISTORY CONTRIBUTE TO EWING SARCOMA SUSCEPTIBILITY, AN UPDATE FROM PROJECT GENESIS (GENETICS OF EWING SARCOMA INTERNATIONAL STUDY, CHILDREN'S ONCOLOGY GROUP AEPI10N5)

Erin Young, PhD[1]*; Schuyler O'Brien*[1]*; Trent Fowler*[1]*; Barry Moore*[5]*; Rosann Robinson*[1]*; Jamie Gardiner*[1]*; Nathan Pankratz*[2]*; Spencer Kelley*[2]*; Mark Yandell*[5]*; Gabor Marth*[4]*; Aaron Quinlan*[6]*; Wendy Kohlmann*[1]*; Stephen Lessnick*[3]*; Logan G. Spector, PhD*[2]*; Joshua D. Schiffman*[7]

[1]Huntsman Cancer Institute, University of Utah, SLC, UT, USA; [2]Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN, USA; [3]Center for Childhood Cancer and Blood Diseases, Nationwide Children's Hospital, Columbus, OH, USA; [4]Department of Pathology, University of Utah, Salt Lake City, UT, USA; [5]Department of Human Genetics, University of Utah, Salt Lake City, UT, USA; [6]Base2 Genomics, LLC, Salt Lake City, UT, USA; [7]Department of Pediatrics, University of Utah, Salt Lake City, UT, USA

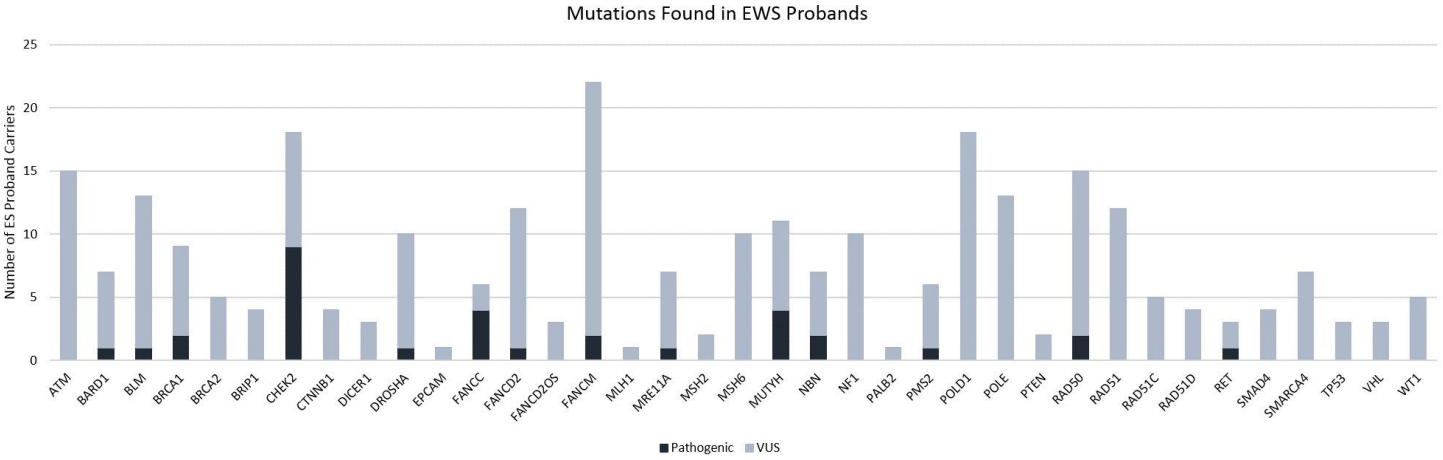
Objective: Ewing Sarcoma (ES) is the second most common bone tumor in children, characterized by EWS-FLI1 translocations. Evidence for genetic predisposition has been limited, despite increased Caucasian incidence, hernia association, and rare familial cases. Genome-wide Association Studies have pointed to SNPs linked to GGAA microsatellites (STRs) and a recent germline study on a small ES cohort found pathogenic variants in the DNA damage response pathway. Project GENESIS (Genetics of Ewing Sarcoma International Study, COG AEPPI10N5) began enrolling ES patients in 2013 to study the genetic epidemiology of ES, and recently completed whole ge-

nome sequencing (WGS) and family history collection. We present the results from the first analyses from the largest genetic epidemiology study of ES.

Methods: ES cases and parents (trios) were enrolled through Project GENESIS (N=485 probands), including self-reported family history (FHx) and saliva collection (including COG patients and self-referrals). Through the Gabriella Miller Kids First X01 mechanism, WGS was performed on 418 ES cases, including 304 trios. Genome-wide discovery of single nucleotide, insertion-deletion, structural, copy number, and STR variation was conducted using the cloud-based genome analysis platform from Base2 Genomics. STRs were analyzed in the WGS data set, as well as a targeted sequencing approach (>400 GGAA STRs) using Ion Torrent (read lengths >400 bp). Genetic counselors reviewed FHx to identify cases that met criteria for genetic testing.

Results: The initial analysis included 65 known DNA response genes and revealed 40 pathogenic and likely pathogenic (P/LP) germline mutations (7.7% carrier frequency), including: CHEK2 (2.2%), FANCM (2.2%) and FANCC (1.0%), BRCA1 (0.5%), BLM (0.2%). Also, 249 rare variants of uncertain significance (VUS) were identified (41.6% carrier frequency), including: FANCM (4.8%), ATM (3.6%), BLM (2.9%), FANCD2 (2.6%), CHEK2 (2.2%), BRCA1 (1.7%). GGAA STR analysis revealed 18% greater allele variation in our targeted approach vs. WGS calls, highlighting the challenge of interrogating STRs in context of next generation sequencing. Of 365 available pedigrees, 44 ES pedigrees (11.5%) had >1 first degree/second degree relative who met NCCN guidelines for genetic counseling/testing (22 Hereditary Breast Ovarian Cancer, 6 Li-Fraumeni, 5 Lynch Syndrome, 3 Hereditary Prostate, 2 Hereditary Melanoma, 1 PTEN), and 2 pedigrees had familial ES.

Conclusion: To our knowledge, this is the most extensive genetic epidemiology study in ES to date. Initial results confirm and expand variants in DNA repair genes, and increased FHx in patients with ES suggest both known and novel cancer syndromes associated with ES risk. Rare but definitive cases of familial ES also were identified. Further analysis of microsatellite and GWS results are ongoing, as well as combined analyses with FHx and other collected epidemiological variables including parental occupation, age, and geography. The data thus far suggests ES cases and family members could benefit from germline cancer predisposition testing.



The number of rare variants identified in ES probands in 65 DNA damage response genes broken down into gene categories. VUS = variants of uncertain significance

Paper 047 #2776419

A NOVEL ROLE FOR THE EWS PORTION OF EWS/FLI IN BINDING GGAA-MICROSATELLITES REQUIRED FOR ONCOGENIC TRANSFORMATION IN EWING SARCOMA

***Kirsten Johnson, BS**; Stephen Lessnick*
Center for Childhood Cancer & Blood Disorders, The Research Institute at Nationwide Children's Hospital, Columbus, OH, USA

Objective: The purpose of this study is to investigate the mechanism by which EWS/FLI transcriptionally activates gene targets via polymorphic GGAA microsatellites. Ewing sarcoma usually expresses the EWS/FLI fusion transcription factor oncoprotein. EWS/FLI regulates myriad genes required for Ewing sarcoma development. EWS/FLI binds GGAA-microsatellite sequences in vivo and in vitro. These sequences provide EWS/FLI-mediated activation to reporter constructs, suggesting that they function as EWS/FLI-response elements. Clinically, genomic GGAA-microsatellites are highly variable and polymorphic. Current data suggest that there is an optimal "sweet-spot" GGAA-microsatellite length (of 18-26 GGAA repeats) that confers maximal EWS/FLI-responsiveness to target genes, but the mechanistic basis for this remains unknown.

Methods: We explored the stoichiometry and binding affinity of EWS/FLI for different GGAA-repeat lengths through biochemical studies, including fluorescence polarization, ChIP-seq, and RNA-seq, combined with bioinformatics analysis. Additionally, use of mutant constructs of EWS/FLI has been critical for elucidating particular binding behavior of EWS/FLI at different microsatellite repeat lengths.

Results: Our biochemical studies, using recombinant Δ22 (a version of EWS/FLI containing only the FLI portion) demonstrate a stoichiometry of one Δ22-monomer binding to every two consecutive GGAA-repeats on shorter microsatellite sequences. Surprisingly, the affinity for Δ22 binding to GGAA-microsatellites significantly decreased, and ultimately became unmeasureable, when the size of the microsatellite was increased to the "sweet-spot" length. In contrast, a fully-functional EWS/FLI mutant (Mut9, which retains approximately half of the EWS portion of the fusion) showed low affinity for smaller GGAA-microsatellites, but instead significantly increased its affinity at "sweet-spot" microsatellite lengths. Single-gene ChIP and genome-wide ChIP-seq and RNA-seq studies extended these findings to the in vivo setting.

Conclusion: Together, these data reveal an unexpected novel role for the EWS portion of the EWS/FLI fusion in DNA-binding. Additionally, our data suggest a length-dependent biochemical mechanism for EWS/FLI binding and transcriptional regulation at GGAA-microsatellites.

Paper 048 #2768194

EFFICACY AND SAFETY OF LURBINECTEDIN (PM1183) IN EWING SARCOMA: RESULTS FROM A PHASE 2 STUDY

***Vivek Subbiah, MD**[1]; Kumar Sankhala[2]; Enrique Sanz-Garcia[3]; Valentina Boni[4]; Ahmad Awada[5]; Victor M. Villalobos[6]; Pilar Lardelli[7]; Mariano Siguero[7]; Carmen Kahatt[7]; Arturo Soto-Matos[7]; Stefano Ferrari[8]*
[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Sarcoma Oncology Center, Santa Monica, CA, USA; [3]Hospital Vall D'Hebron, Barcelona, Spain; [4]Hospital Universitario Madrid Sanchinarro, Madrid, Spain; [5]Institut Jules Bordet, Université Libre de Bruxelles, Bruxelles, Belgium; [6]University of Colorado Cancer Center, Denver, CO, USA; [7]PharmaMar, Madrid, Spain; [8]Istituti Ortopedici Rizzoli, Bologna, Italy

Objective: Patients (pts) with advanced/relapsed Ewing sarcoma (ES) have a poor outcome. New therapeutic agents with different mechanisms of action are needed. L is a new anticancer drug that blocks transactivated transcription and induces DNA double-strand breaks, leading to apoptosis. Moreover, in sarcomas associated with translocations, such as ES, in which the translocation produces a fusion protein that acts as a deregulated transcription factor, L might interfere with the binding of this protein to specific DNA promoters and thus with the synthesis of downstream proteins.

Methods: A multicenter phase 2 trial to assess the efficacy and safety of L in several types of advanced solid tumors (basket trial), including ES, is ongoing. In the ES cohort, 15 adult patients who had received no more than two prior chemotherapy-containing regimens in the advanced disease setting were first recruited. If at least one confirmed response was observed, recruitment was to be increased to 25 evaluable patients. The study intervention comprised lurbinectedin 3.2 mg/m2 in a 1-hour infusion every 3 weeks.

Results: 25 patients were enrolled. Median age was 30 years (range, 18-74) and 14 were males. 23 had an ECOG of 0/1. ES was extraosseous in 13 pts; 6 pts had ≥3 disease sites and 20 had received at least 1 line of prior chemotherapy. 23 pts received a median of 2 cycles of L (range, 1-9) and a median total dose of 6.6 mg/m2 (range, 3.2-28.2).

Of 17 evaluable pts, 3 (17.6%) had a partial response and 8 (47%) had disease stabilization, 4 of them for ≥3 months. Median duration of the response was 2.9 months (range, +1.5-5.5) and median progression-free survival was 4.1 months (CI 95% 1.4-5.1).

Most common adverse events were related to myelosuppression: 50% neutropenia grade (G) 3/4, 13% febrile neutropenia, and 13% thrombocytopenia G ¾; 5 pts had dose delay because of neutropenia G2-4 or thrombocytopenia G2, and 4 pts had dose reduced because of neu-

tropenia G4. G-CSF was given to 10 pts. There were no withdrawals or deaths due to toxicity.

Conclusion: L as a single agent has shown activity in pretreated pts with advanced ES, with an acceptable safety profile and tolerability. Myelotoxicity was well controlled with dose adjustments and G-CSF. Further and larger studies of L alone or in combination regimens are warranted for pts with advanced ES.

4:00 pm – 5:00 pm
– SYMPOSIUM 3 –
New Research Technologies

Paper 049 #2784070

DETECTION OF *EWSR1* FUSIONS IN CIRCULATING CELL FREE DNA IS ASSOCIATED WITH DISEASE FEATURES AND POOR OUTCOMES IN EWING SARCOMA (EWS): A REPORT FROM THE CHILDREN'S ONCOLOGY GROUP (COG)

D.S. Shulman[1]*; K. Klega*[1]*; A. Imamovic-Tuco*[1]*; A. Clapp*[6]*; A. Nag*[6]*; A. Thorner*[6]*; S. Lessnick*[2]*; R. Gorlick*[3]*; K. Janeway*[1]*; K.T. Vo*[4]*; D. Hall*[5]*; M. Krailo*[5]*; D. Barkauskas*[5]*; S.G. DuBois*[1]*; B. Crompton*[1]
[1]Pediatric Oncology, Dana-Farber / Boston Children's Cancer and Blood Disorders Center, Boston, Massachusetts, USA; [2]Center for Childhood Cancer and Blood Disorders, Nationwide Children's Hospital, Columbus, Ohio, USA; [3]Division of Pediatrics, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA; [4]Department of Pediatrics, UCSF Benioff Children's Hospital, San Francisco, California, USA; [5]Children's Oncology Group, Los Angeles, California, USA; [6]Cancer Genome Discovery, Dana-Farber Cancer Institute, Boston, Massachusetts, USA

Objective: Detection of circulating tumor DNA (ctDNA) in the peripheral blood of patients with EWS holds promise for assessing prognosis and disease response, and potentially improving risk stratification and disease surveillance. We sought to describe the incidence of detection of *EWSR1* fusions in ctDNA and the association between fusion detection with clinical features and outcome in a large cohort of patients with EWS.

Methods: A custom next generation sequencing hybrid capture assay was used to detect *EWSR1*, *CIC*, and *BCOR* gene fusions in the peripheral blood of 94 patients with a histopathologic diagnosis of EWS enrolled on COG AEWS07B1 biology study. One sample was analyzed for each patient either at diagnosis or relapse. Patients were coded as positive or negative for detectable fusion and this binary predictor variable ("ctDNA positivity") tested for association with clinical features (age, sex, primary site and stage) using Fisher exact tests. Event free survival (EFS) was estimated by Kaplan-Meier methods and association with ctDNA detection tested with log-rank tests.

Results: Samples from 94 patients with EWS were evaluated (82% from initial diagnosis). Of those with newly diagnosed disease, the median age was 14 [2-21] years, 55% were male, 22% had pelvic primary tumors, and 34% had metastatic disease. 53% of newly diagnosed patients and 47% of relapsed patients had detectable circulating *EWSR1* fusions, with a median of 11 (2-101) and 14 (6-101) reads, respectively. The 49 positive samples included *EWSR1/FLI1* (n=43), *EWSR1/ERG* (n=5), and one novel *EWSR1* fusion. No *CIC* or *BCOR* fusions were detected. Age and sex were not associated with ctDNA positivity. Patients with newly diagnosed disease were more likely to have detectable ctDNA if they had metastatic disease (69% positive vs. 44% positive if localized; p=0.053) or pelvic primary site compared other sites of disease (82% positive vs. 45% positive if non-pelvic; p=0.042). Among all newly diagnosed patients with available EFS data (n=51), detectable ctDNA was associated with inferior 5-year EFS (25% vs. 75%; p=0.0013). A similar association was seen in the subgroup with newly diagnosed localized disease (5-year EFS 25% if positive vs. 71% if negative; p=0.011).

Conclusion: *EWRS1* fusions are detectable in ctDNA in a substantial proportion of patients with EWS. The presence of detectable fusions is associated with stage, primary site, and inferior EFS. Evaluation of a validation cohort is ongoing.

Paper 050 #2772873

A NOVEL CHIMERIC ANTIGEN RECEPTOR (CAR) TARGETING B7-H3 MEDIATES REGRESSION OF ESTABLISHED TUMORS AND CURE OF LOCALIZED AND METASTATIC OSTEOSARCOMA XENOGRAFTS

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Objective: Osteosarcoma is the most common primary bone tumor in children. Although aggressive multi-modal therapy has resulted in improved patient outcomes for patients with localized disease, little progress has been made in treating patients with metastatic or relapsed disease. New modalities are needed to make progress. Chimeric antigen receptor (CAR) T cells represent a novel class of therapeutics that have shown unprecedented results in the treatment of leukemia. These advances have yet to be translated to sarcomas and other solid tumors. We aimed to create a novel CAR targeting B7-H3, a checkpoint molecule overexpressed on osteosarcoma as well as other pediatric solid tumors.

Methods: Pediatric tumor microarrays were stained for B7-H3 expression by immunohistochemistry (IHC) as a screen for antigen expression. Second generation CARs using the 41BB and CD3z signaling domains were generated from the single chain variable fragment (scFv) of MGA271, an anti-B7-H3 antibody currently in clinical trials, as well as nine fully human scFv's from a Fab library. These ten CARs were compared for their ability to lyse tumor cells and produce cytokine in response to co-culture with tumor. The most promising CAR was carried forward for in vivo studies of osteosarcoma.

Results: B7-H3 was highly expressed by IHC on pediatric sarcomas. Of the ten constructs screened, the CAR containing the binding regions from MGA271 had the strongest activity and was carried forward for in vivo studies. A single dose of intravenously administered B7-H3 CAR T cells mediated complete regression of established osteosarcoma xenografts (MG63.3) whereas irrelevant CD19 CAR T cells did not (Figure 1A). Additionally, the B7-H3 CAR was tested in a universally fatal metastatic model of osteosarcoma (hind limb amputation 30 days after establishment of tumors, death from lung metastasis occurs at 60 days post-amputation). Whereas all untreated mice died from lung metastases, 9/10 B7-H3 CAR treated mice survived for greater than six months (Figure 1B).

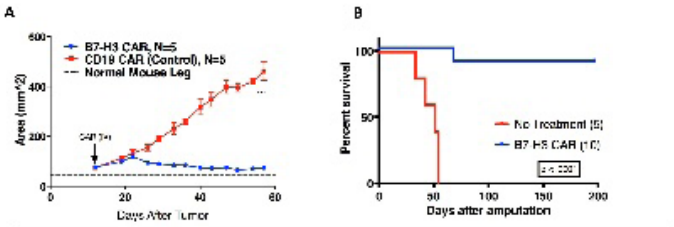


Figure 1. In vivo activity of the B7-H3 CAR: 10 million B7-H3 CAR+ T cells were injected intravenously into mice bearing xenograft MG63.3 tumors and caused complete regression of established tumors (A). In a universally fatal model of metastatic osteosarcoma, treatment with B7-H3 CAR T-cells prevented death in 9 out of 10 mice (B).

Conclusion: We have created an effective, novel therapeutic for osteosarcoma. This is the first reported CAR targeting B7-H3 to date and it has demonstrated impressive activity against osteosarcoma. This therapy could be transformative for patients with high risk disease who lack effective therapeutic options. Further studies are underway to broaden the applicability of this therapy to Ewing sarcoma and rhabdomyosarcoma.

Paper 051 #2766846

NEXT GENERATION SEQUENCING IDENTIFIES IMMUNOTHERAPY TARGETS IN SOFT TISSUE SARCOMA

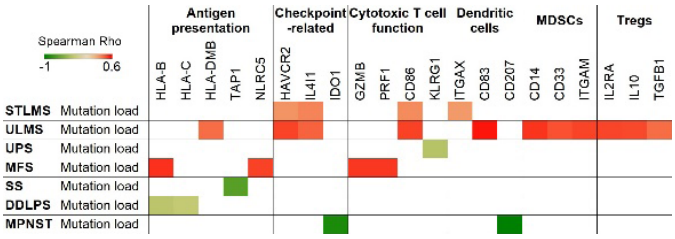
***J. Roszik**, V. Subbiah; J.A. Livingston; N. Somaiah; V. Ravi; W. Wang; C. Yee; P. Futreal; A. Lazar; A.P. Conley*

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

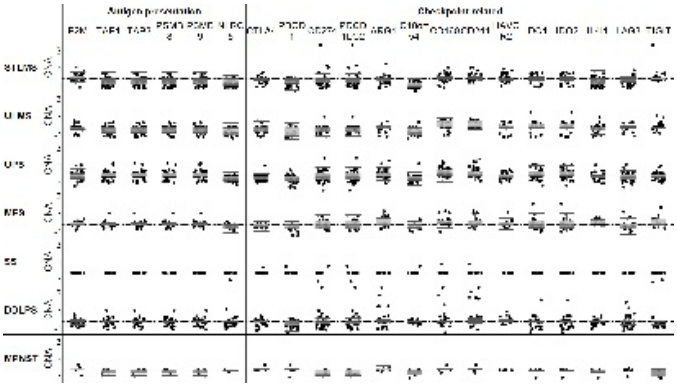
Objective: The early efficacy signals of single-agent pembrolizumab (anti-PD-1) antibody in the SARC028 trial in specific subsets of sarcoma indicates that immunotherapy may provide clinical benefit. Our aim was to determine whether specific genomic alterations, expression of infiltrating cytotoxic and suppressive cell type markers identified by next-generation sequencing (NGS) warrant further consideration of immunotherapy agents in soft tissue sarcoma.

Methods: We used sarcoma Cancer Genome Atlas (TCGA) mutation, mRNA expression, copy number, and clinical data to analyze mutation load, cytotoxic and suppressive cell activity, and relevance of checkpoint-related genes in dedifferentiated liposarcoma (DDLPS, n=50), soft tissue and uterine leiomyosarcoma (STLMS, n=53; ULMS, n=27), undifferentiated pleomorphic sarcoma (UPS, n=44), myxofibrosarcoma (MFS, n=17), synovial sarcoma (SS, n=10), and malignant peripheral nerve sheath tumors (MPNST, n=5).

Results: Expression of T cell markers of cytotoxic activity (IFNG, PRF1, and GZMA) was seen in sarcomas, and this was associated with a higher mutational burden and improved overall survival. However, increased mutation load also correlated with low expression of genes involved in antigen presentation, specifically HLA genes in DDLPS, and TAP1 transporter in SS ($p < 0.05$) (Figure 1). Mutational burden positively correlated with expression of HAVCR2 (TIM-3) and IL4I1 checkpoint genes in STLMS and ULMS ($p < 0.05$). Interestingly, higher MDSC and Treg marker expressions were associated with increased mutation load only in ULMS. Overall survival associations with antigen presentation and cytotoxic T cell markers were statistically significant ($p<0.05$) in UPS/MFS, and a trend ($p<0.1$) was noted for HLA-A, HLA-C, and TAP1 in the case of DDLPS. Copy number loss of antigen presentation-related genes was observed for STLMS and ULMS, and we also found NLRC5 loss in STLMS, ULMS, UPS, MFS, and DDLPS (Figure 2). In addition, copy number gains of checkpoint genes were also noted, including the metabolism-associated enzyme arginase 1 (ARG1) in MFS. Correlation analysis of mutation load and expression of genes involved in metabolism indicated a strong relationship in DDLPS and STLMS.



Mutation load associations in soft tissue sarcomas.



Copy number alterations in genes realted to antigen presentation and immune checkpoint mechanisms.

Conclusion: Genomic alterations in sarcoma subtypes may be exploited to develop effective immunotherapies.

Paper 052 #2804366

HARVESTING PATIENT-GENERATED INFORMATION FROM INTERNET DISCUSSION FORUMS

G. van Oortmerssen[1]*; H.J. Gelderblom*[2]

[1]Tilburg Center for Cognition and Communication, Tilburg University, Naarden, Netherlands; [2]Medical Oncology, Leiden University Medical Center, Leiden, Netherlands

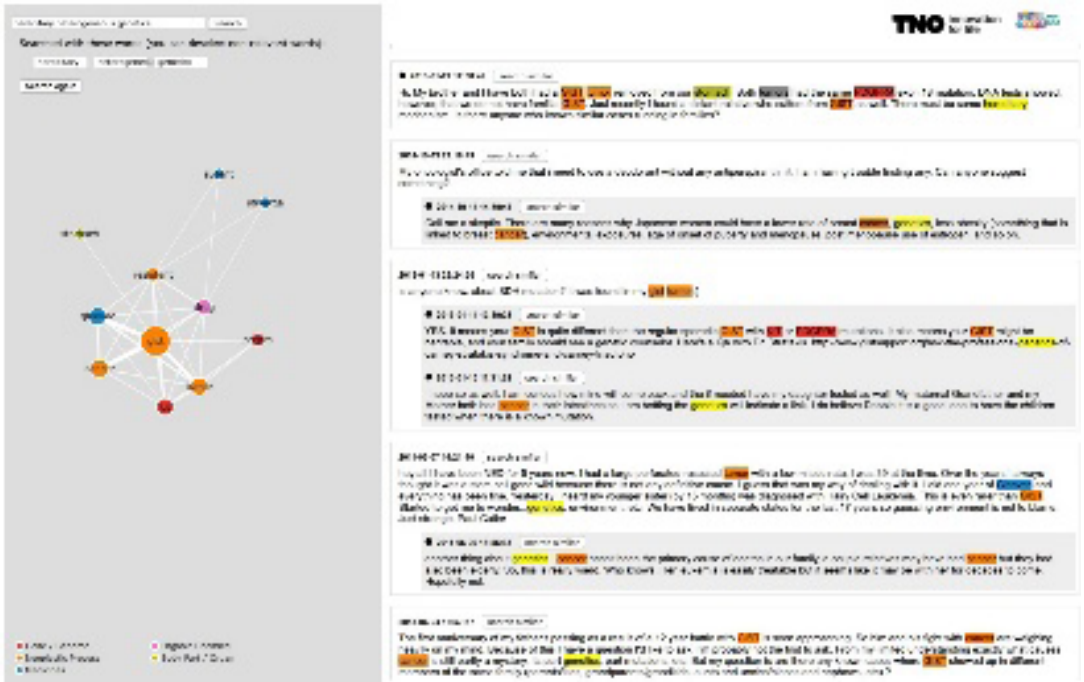
Objective: Sarcomas are rare and diverse, and consequently one of the challenges for oncologists and researchers is to gather information on patients outside of clinical trials. Internet discussion forums contain a wealth of data on patients, their disease history, experienced quality of life, and side effects of treatments. Often, patients develop strategies to cope with side effects and share these strategies with other patients. They use internet discussion forums to share information and experiences with other patients and to emotionally support other patients. Most oncologists are unaware of the existence of this information and of the potential benefit of patient generated information.

The objective of the project described in this paper is to harvest relevant data that subsequently can be used to by oncologists as input for research and for increased insight in patient experience.

Methods: The techniques that are used are based on computational linguistics and machine learning that can be used to analyse unstructured, informal text data. For tagging relevant entities in the text the UMLS ontology database (NIH) is used. Advanced search algorithms are being used to detect interesting information, which is presented in a graphical interface in order to reveal relationships among various entities. Relevant discussions are summarized automatically to allow fast perusal. The project is a unique multi-disciplinary collaboration between oncologists, computer scientists and patient organisations.

Results: The system will be demonstrated and specific results from an international discussion forum of Gastrointestinal Stromal Tumor patients are presented and discussed. Examples are given of how this information can impact clinical practice and feed research. Results have already provided new insights with respect to side effects of treatment. Patient generated information can provide new hypotheses that subsequently can be tested in clinical practice.

Conclusion: Text analysis of a GIST patient discussion forum leads to specific insights with respect to treatment of the disease. This approach has increased the interaction between oncologists and patients, and has already contributed to a joint agenda setting for research. There is great potential for using patient experiences as input for future research.



Sample screenshot of text mining system

2:00 pm – 3:00 pm
– SESSION 8 –
Population Sciences, Survivorships

Paper 053 #2783913

EXERCISE STRATEGIES IN A TUMOR MODEL TO DECREASE ACUTE AND LATE DOXORUBICIN-INDUCED CARDIOTOXICITY

***Eugenie S. Kleinerman, MD**; Fei Wang; Joya Chandra; Keri Schadler*
Pediatrics, M.D. Anderson Cancer Center, Houston, TX, USA

Objective: Determine whether exercise initiated during or after doxorubicin (Dox) therapy decreases the acute Dox-induced cardiotoxicity and late cardiac morbidity.

Methods: TC-71 Ewing's sarcoma cells were injected into the tibia of 4-wk old mice. When tumors reached 30-50 mm (5 days after injection) mice were divided into 4 treatment groups: A) control; B) Dox (2 mg/kg 2x/wk for 2 wks); C) Exercise (45 min/day treadmill walking, 5 days/wk on a motorized treadmill; D) Dox + Exercise. Tumor growth was monitored. Echos were performed before and at the end of therapy, evaluating ejection fraction (EF) fractional shortening (FS), & heart weight/tibia length (HW/TL). Heart sections were analyzed by H&E to assess histology and fibrosis; IHC to assess vessel morphology using CD31 and the pericyte markers NG2 and a-SMA; and electron microscopy (TEM) to assess vascular endothelial cells and pericytes, and the number of Dox-induced autophagosomes.

To determine if exercise initiated *during* Dox therapy affected the *late cardiac changes* induced by Dox, mice were treated as above for 2 weeks and analyzed before, immediately after Dox therapy, and then again, 90 days after Dox therapy.

To determine whether exercise initiated *after* Dox therapy affected cardiotoxicity, mice were treated for 2 wks with Dox. Exercise was initiated *after* therapy and mice were evaluated by echo 2, 4 and 6 wks later. Control mice received no treatment, exercise alone or Dox with no exercise.

Results: Tumor growth was inhibited in mice treated with Dox alone *or* Dox + exercise. Exercise did not inhibit Dox efficacy. There was a significant *decrease* in EF, FS and HW/TL following Dox therapy with *increased autophagosomes* in the hearts. This was **not** seen in mice treated with Dox + exercise (Fig 1,2). Intracellular ROS levels in PBMCs were significantly elevated in Dox-treated but not the Dox + exercise-treated mice. Heart vessels from Dox-treated mice had a decrease in a-SMA, the a-SMA/CD31 ratio and the number of open lumens, indicating that Dox therapy compromised cardiac vascular function via an effect on pericytes. This was confirmed by TEMs (Fig 3). Furthermore, exercise initiated *after* Dox and continued for 4 weeks reversed the Dox-induced effects on EF and FS.

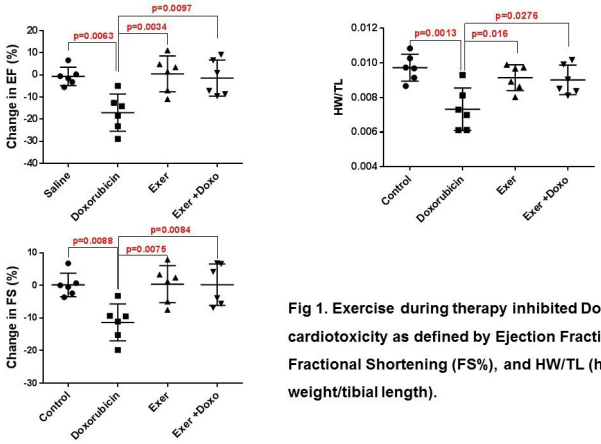


Fig 1. Exercise during therapy inhibited Dox-induced cardiotoxicity as defined by Ejection Fraction (EF%), Fractional Shortening (FS%), and HW/TL (heart weight/tibial length).

Fig 1. Exercise during therapy inhibited Dox-induced cardiotoxicity as defined by Ejection Fraction (EF%), Fractional Shortening (FS%), and heart weight/tibia length (HW/TL).

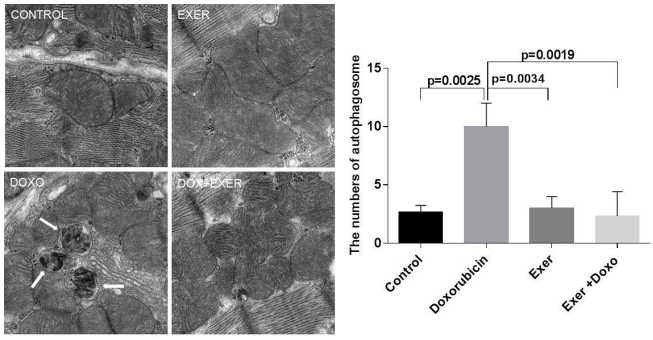
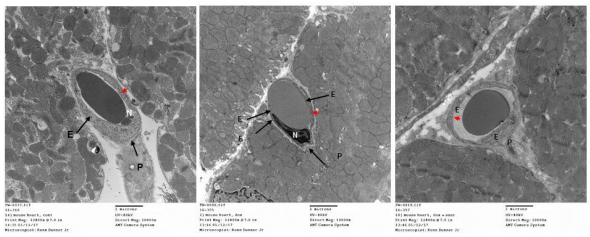


Fig 2. Exercise decreased Dox-induced autophagy. Representative transmission electron micrographs of heart sections from each group. Autophagosomes are indicated by arrows.

Fig 2. Exercise during Dox administration decreased Dox-induced autophagy in the heart. Representation transmission electron micrographs (TEMs) of heart sections from each group. Autophagosomes are indicated by arrows.

Fig 3. Effect of Dox on cardiac vascular pericytes and endothelial cells



E: Endothelial cells
P: Pericytes
Red arrows: The endothelial cells are connected by tight junctions

Fig 3. Effect of Dox therapy alone or Dox therapy + exercise on cardiac vascular pericytes and endothelial cells. Decreased pericyte coverage was observed in the cardiac vessels in hearts from mice treated with Dox alone.

Conclusion: Exercise initiated during *or* after Dox therapy decreased both acute and late cardiotoxicity without compromising Dox efficacy. Exercise interventions have the potential to decrease cardiac morbidity thereby improving cardiac health and the QOL for cancer survivors.

Paper 054 #2791329

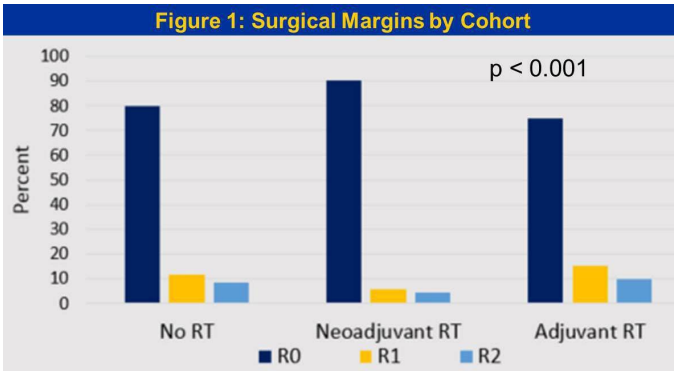
NEOADJUVANT RADIOTHERAPY IS ASSOCIATED WITH R0 RESECTION AND IMPROVED SURVIVAL IN EXTREMITY SOFT TISSUE SARCOMA PATIENTS UNDERGOING SURGERY: AN NCDB ANALYSIS

Alicia Gingrich[1]; Sarah Bateni[1]; Amanda Kirane[1]; Steven W. Thorpe[3]; Arta Monjazeb[2]; ***Robert J. Canter[1]***
[1]Surgery, UC Davis, Sacramento, CA, USA; [2]Radiation Oncology, UC Davis, Sacramento, CA, USA; [3]Orthopedics, UC Davis, Sacramento, CA, USA

Objective: Neoadjuvant radiotherapy (RT) is increasingly advocated in the management of soft tissue sarcoma (STS). Therefore, we sought to characterize the impact of neoadjuvant RT on rates of R0 resection and overall survival (OS) in extremity STS patients undergoing surgery.

Methods: From January 2003 to December 2012, we identified patients with a diagnosis of extremity STS from the National Cancer Database. After excluding patients with age < 18 years, not undergoing surgery, metastases at diagnosis, intraoperative RT, and missing/unknown data, we identified 27,968 patients. Using logistic regression and Cox-proportional hazard analysis, we compared rates of R0 resection among preoperative, postoperative and no RT cohorts and determined predictors of R0 resection and OS.

Results: The mean age was 59.5 (± 14.7) years, and 45.9% were female. Median tumor size was 10.5cm. 51% of patients did not receive RT, 11.8% received pre-operative RT and 37.2% received post-operative RT. Rates of R0 resection for preoperative RT, postoperative RT, and no RT cohorts were 90.1%, 74.9%, and 79.9%, respectively (P<0.001). Independent predictors of achieving R0 resection included academic facility type (OR 1.36, 95% CI 1.20-1.55), histologic subtype, tumor size (OR 0.99, 95% CI 0.99-0.99), Charlson score (OR 0.92, 95% CI 0.84 – 0.99), and preoperative RT (OR 1.83, 95% CI 1.61-2.07). R0 resection as well as RT (pre-operative or post-operative) was associated with increased OS.



Conclusion: Pre-operative RT independently predicts higher rates of R0 resection in patients with extremity STS undergoing surgical resection. Negative surgical margins and pre-operative or post-operative RT are associated with improved OS.

Paper 055 #2804809

QUALITY OF LIFE AND DISTRESS IN SARCOMA PATIENTS PRESENTING TO A TERTIARY REFERRAL CENTER

Elizabeth T. Loggers, MD, PhD[1]*; Seth M. Pollack[1]; Gabrielle Kane[3]; Edward Y. Kim[3]; Darin Davidson[4]; Chris Johnson[4]; Matthew Thompson[4]; Lee D. Cranmer[2]*
[1]Clinical Research, Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [2]Medical Oncology, University of Washington, Seattle, WA, USA; [3]Radiation Oncology, University of Washington, Seattle, WA, USA; [4]Orthopedic Surgery, University of Washington, Seattle, WA, USA

Objective: Distress and poor quality of life (QOL) in cancer patients (pts) is an area of increasing interest, with potential effects on survival and treatment adherence.

Methods: From 9-22-2015 to 10-30-2016 all new sarcoma pts presenting to Seattle Cancer Care Alliance, Seattle, WA, USA were screened via an email/web-survey using Functional Assessment of Cancer Treatment (FACT) – General QOL scale; Patient Health Questionnaire-2 (depression, D); General Anxiety Disorder-2 (anxiety, A); Malnutrition Screening Tool (M); 2 items, each, for functional status (FS); and existential crisis (EC); 1 item regarding concerns for dependent children (DC). Those screening positive based on predetermined cutoffs were automatically referred to social work (SW), palliative care (PC), chaplaincy (C), nutrition (N), physical therapy (PT), or child-life specialist (CL). Descriptive, t-test, Chi-square

statistics and logistic regression were used.

Results: Of 486 pts, 26.7% (n=130) did not provide an email (NE), 25.5% (n=124) were sent a survey but did not respond (NR), while 47.7% responded (n=232, SC) with 61.6% of pts (n=143 or 29.4% of total) screening positive (SP) for one or more concern vs screen negative (n=89, SN). There was no difference in age, gender or state residence, but NE/NR pts were more likely than SC/SP pts to be minority (p=.024), non-English speaking (p=.008) with non-commercial insurance (p=<.001). Mean QOL was 77.2 (median 79.8, range 26.2-108, CI 75.0-79.4), similar to all other solid tumor pts in our sample. 28.4% of pts were D, A or both. 37.5%, 22.8%, 20.7%, 19.8%, 6.5%, 6.0% of SC pts were referred to SW, PT, C, N, PC, and CL respectively. SP pts (vs SN) were more likely to find the survey burdensome (OR 2.30, 95% CI 1.14- 4.64, p=.02) and be presenting for treatment vs second opinion (OR 2.22, 95% CI 1.22- 4.06, p=.009).

Conclusion: Poor QOL and distress among sarcoma patients is relatively common, particularly among patients referring for treatment. Unfortunately, those most likely to find distress screening burdensome are also most likely to benefit. While web-based screening is feasible and efficient, targeted screening for select populations using different techniques (in-person, paper-pencil, various languages) is needed.

Paper 056 #2796148

IMPACT OF VITAMIN D SUPPLEMENTATION DURING AND AFTER CHEMOTHERAPY ON BONE MINERAL DENSITY IN YOUNG EWING'S AND OSTEOSARCOMA PATIENTS

Ulrike M. Pirker-Frühauf, Resident[2]*; Susanne Scheipl, MD, PhD*[2]*; Daniela Sperl*[3]*; Franz Quehenberger*[1]*; Barbara Obermayer-Pietsch*[4]*; Andreas Leithner*[2]

[1]Institute for Medical Informatics, Statistics and Medical Documentation, Medical University of Graz, Graz, Austria; [2]Orthopaedics and Traumatology, Medical University of Graz, Graz, Austria; [3]Paediatric Oncology and Haematooncology, Medical University of Graz, Graz, Austria; [4]Internal Medicine, Subdivision Endocrinology and Metabolism, Medical University Graz, Graz, Austria

Objective: Long-term effects of sarcoma treatment on bone mineral density in young Ewing's sarcoma and osteosarcoma survivors are repeatedly reported. Nevertheless, follow-up on bone status as well as osteoprotective medication do not seem to be part of clinical routine yet. Further, concrete recommendations are rare. Therefore, we wanted to evaluate the benefit of Vitamin D supplementation during and after chemotherapy as recommended by the United States' Children's Oncology Group.

Methods: We performed Z score based densitometry (lumbar, femoral) and laboratory measurements (vitamin D, bone turnover markers) in 60 patients (28 Ewing's sarcoma, 32 osteosarcoma), of whom 31 received standard sarcoma treatment (wide resection, chemotherapy ± radiotherapy). The remaining 29 patients additionally got vitamin D supplementation during and after chemotherapy in case of deficient vitamin D levels. Our patients' mean age was 20 years ± 6 SD. Mean follow-up was 6 years ± 4 SD.

Results: 93% of patients in the vitamin D supplementation group presented healthy bone mineral density levels in the lumbar spine according to the WHO definition, compared to 55% in the standard group. Measurement of the femoral neck of the tumor unaffected limb showed a ratio of 71% to 56%. The median vitamin D level in the supplementation group was 24,1ng/mL and 15,8ng/mL in the standard group.

Conclusion: Children undergoing sarcoma treatment experience a long time of hospitalization and inactivity in a life period of high importance for gaining their genetically programmed peak bone mass. Accumulation with seasonal/permanent vitamin D deficiency seems to potentiate the bone harming effects of chemotherapy and immobilization. Our data therefore indicates that supplementation of vitamin D during and after chemotherapy can be highly recommended. We saw the main benefit especially in the lumbar spine which is described to be very sensitive to chemotherapeutic agents.

– BASIC SCIENCE –

Poster 001 #2783577

VARIATION IN THE IMMUNE CELL INFILTRATE AND EXPRESSION OF PD-L1 IN SARCOMA SUBTYPES

N. Gokgoz, *J. Nam, D. Pinnaduwage, A. Seto, J.S. Wunder, I. Andrulis, Lunenfeld-Tanenbaum Research Institute, Sinai Health System, Toronto, Ontario, CANADA; B.Y. Lau, B.C. Dickson, Department of Pathology and Laboratory Medicine, Sinai Health System, Toronto, Ontario, CANADA*

Objective: The presence of tumor infiltrating lymphocytes (TILs) in the tumor microenvironment has been associated with clinical characteristics and prognosis in various cancers, however, their role in sarcoma remains unclear. Adult soft tissue sarcomas (STS) are a heterogeneous group of tumors that would benefit from the identification of new prognostic markers and novel therapeutic strategies.

The purpose of this study was to determine whether there are specific subgroups of soft tissue sarcomas that contain TILs and/or express immune checkpoint proteins and if so, the clinical importance.

Methods: After pathology review, slides of 25 cases of undifferentiated pleomorphic sarcoma (UPS), 25 cases of myxofibrosarcoma, 25 cases of liposarcoma and 24 cases of leiomyosarcoma were subjected to immunohistochemical (IHC) staining for the presence of TILs (CD3, CD4, CD8, CD20) and for immune checkpoint proteins PD-L1 and PD-1. RT-qPCR was utilized to quantify the relative level of PD-L1 expression in RNA extracted from primary frozen specimens including 29 UPS, 50 myxofibrosarcoma and 55 osteosarcomas (OS). Gene expression profiling from next generation RNA sequencing data was used to identify genes and networks that were differentially expressed between tumors with high versus low levels of PD-L1.

Results: We performed immunohistochemistry (IHC) on sections from 99 tumors and found that certain STS, such as leiomyosarcoma and liposarcoma, exhibit little or no immune infiltrate and immune checkpoint proteins. In contrast a subset of UPS and myxofibrosarcomas contain TILs and express PD-L1 and PD-1. Evaluation of expression of PD-L1 by IHC has been controversial; however we observed a significant positive correlation comparing the levels of PD-L1 by IHC on tumor sections and RT-qPCR of mRNA from quick frozen primary tumors. We detected PD-L1 expression in a well characterized group of osteosarcoma, in addition to UPS and myxofibrosarcoma. We are now integrating data from RT-qPCR and next generation RNA sequencing in UPS, osteosarcoma and myxofibrosarcoma cases to investigate the molecular differences in tumors with and without PD-L1 expression.

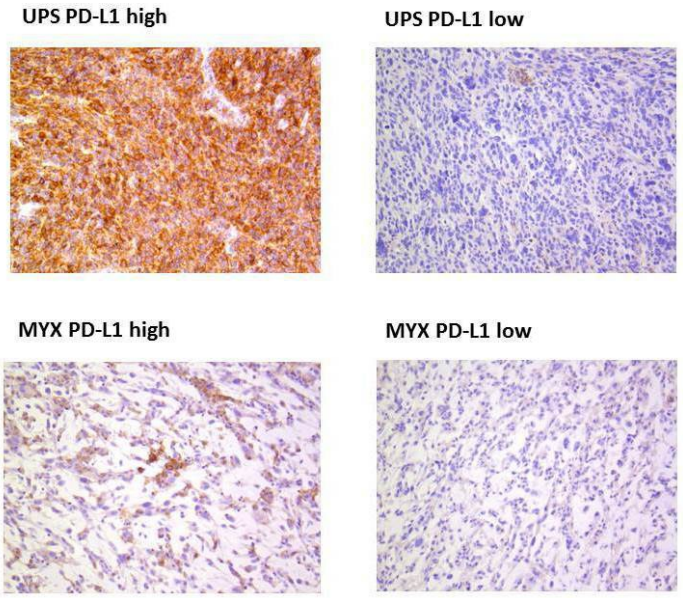


Figure 1. PD-L1 expression in UPS and myxofibrosarcoma tumor sections detected by IHC.

Conclusion: Our analyses have shown that there is a positive correlation between TILs, PD-1 positive immune cells, and PD-L1 positive tumor and immune cells. These studies suggest that there may be individuals with specific sarcomas who may be good candidates to benefit from immunotherapies targeting PD-L1/PD1 based on their tumor characteristics.

Poster 002 #2738892

IDENTIFICATION OF NOVEL SURFACE MARKERS FOR TUMOR-STROMA INTERACTION STUDIES IN DESMOID TUMORS

M. Al-Jazrawe, *Laboratory Medicine & Pathobiology, University of Toronto, Toronto, Ontario, CANADA; Q. Wei, S. Xu, J. Loree, R. Poon, Developmental & Stem Cell Biology, Hospital for Sick Children, Toronto, Ontario, CANADA; B. Alman, Duke University, Durham, North Carolina, USA*

Objective: The role of stromal fibroblasts in promoting tumor growth and invasion has been underexplored in soft tissue sarcoma partly due to lack of reliable markers that differentiate between the neoplastic and non-neoplastic mesenchymal cells. Desmoid tumors (DT), characterized by proliferating and locally invasive fibroblastic cells, are driven by mutations that increase beta-catenin (CTNNB1) levels. We aimed to identify surface markers that can distinguish between the neoplastic and non-neoplastic fibroblastic cells within DT and investigate the tumor-stroma interactions that maintain the neoplastic phenotype.

Methods: Multiple single cell expansions were established from each DT sample. CTNNB1 mutation status of each colony was identified by Sanger sequencing. Mutant and non-mutant colonies were analyzed by flow cytometry for the expression of 368 surface proteins. Candidate surface markers were validated by fluorescence-activated cell sorting (FACS) and double immunofluorescence. Differential secretome analysis was conducted by antibody arrays and by gene expression profiling. Transwell permeable supports were utilized for mutant-stromal fibroblast co-cultures in cell interaction studies.

Results: We detected both mutant and non-mutant colonies derived from primary DT cultures. The mutant colonies expressed CD142 and CD252 while the non-mutant colonies expressed podoplanin (PDPN). FACS using these surface markers identified the mutant subpopulation in heterogeneous DT samples, including specimens that previously appeared as "wildtype." In DT tissues, CD142 and CD252 expressing cells correlated with higher CTNNB1 staining and exhibited a distinct spatial distribution compared to PDPN expressing cells. Our secretome profiling revealed several candidate soluble factors for autocrine or paracrine signaling. CTHRC1 is one of the secreted proteins highly produced by the mutant population. Treatment with recombinant CTHRC1 increased cell proliferation while treatment with a CTHRC1 neutralizing antibody decreased proliferation.

Conclusion: We have identified novel surface markers that can be utilized to rapidly and sensitively detect the mutant population within DT samples. Isolation of the mutant and non-mutant subpopulations allows for the detection of secreted factors that may be involved in tumor-stroma communication, which can be targeted therapeutically. The differential expression of these surface proteins and secreted factors suggests that they may also be used as clinical biomarkers.

Poster 003 #2782147

ONCOLYTIC IMMUNOTHERAPY FOR THE TREATMENT OF BONE AND SOFT TISSUE SARCOMA - EVALUATION OF 4 ONCOLYTIC PLATFORMS

F. Tzelepis, F. Le Boeuf, A. Chen, J. Tsang, R. Arulanandam, N. Forbes, J.C. Bell, J. Diallo, Centre for Innovative Cancer Research, Ottawa Hospital Research Institute , Ottawa, Ontario, CANADA;
***J. Werier**, D. Butterwick, H. Abdelbary, Orthopedic Surgery, The Ottawa Hospital, Ottawa, Ontario, CANADA; M. Selman, Department of Medecine, University of Ottawa, Ottawa, Ontario, CANADA; H. Son, A. Jirovec, A. Bergeron, Department of Science, University of Ottawa, Ottawa, Ontario, CANADA*

Objective: The poor prognosis of patients with advanced bone and soft-tissue sarcoma has not changed in the past several decades, highlighting the necessity for new therapeutic approaches. Immunotherapy strategies utilizing oncolytic viruses (OV) have shown great promise and have been recently approved for treatment of melanoma. Our objective is to develop an effective OV-based strategy for the treatment of sarcoma.

Methods: Four clinically relevant OV platforms (Reovirus, Vaccinia virus, Herpes-simplex virus and Rhabdoviruses) were screened for their ability to infect and kill sarcoma cell lines *in vitro*, and human sarcoma specimens *ex vivo*. *In vivo* treatment efficacy was tested in murine (BALB/c) model. Given the documented potential to boost OV activity by leveraging immune response to tumor-associated antigens using an oncolytic prime-boost vaccination strategy, we also probed sarcoma tissues by IHC for expression of known cancer antigens NY-ESO-1, MAGE-A3, SSX, and Survivin to identify plausible candidates for cloning into OVs.

Results: Of the OVs tested, the oncolytic rhabdovirus MG1 demonstrated the highest potency, leading to a significant increase in long-lasting cures in sarcoma-bearing mice (40% more than untreated mice). Importantly, MG1 treatment induced the generation of memory immune response that provided protection against a subsequent tumor challenge. Probing of sarcoma specimens by IHC revealed that SSX, Survivin, and MAGE-A3 are highly expressed in sarcoma, with MAGE-A3 being expressed in 100% of samples tested.

Conclusion: Of the four oncolytic platforms, MG-1 displayed the greatest efficacy in vitro with significantly increased survival in a murine mouse model. Furthermore, our data imply that oncolytic prime-boost strategies focused on MAGE-A3, SSX, and/or Survivin may be effective in sarcoma. Importantly, one such strategy employing oncolytic MG-1-MAGE-A3 in a prime-boost strategy is currently undergoing phase I/II evaluation for MAGE-A3-positive carcinomas and suggests this approach would be rapidly translatable.

Poster 004 #2782704

IDENTIFICATION OF A BONE-SPECIFIC P53 TARGET, CD137L, THAT MEDIATES GROWTH SUPPRESSION AND IMMUNE RESPONSE OF OSTEOSARCOMA CELLS

***Y. Tsuda**, S. Tanaka, Orhopaedic Surgery, Tokyo University, Tokyo, JAPAN; M. Hirata, Laboratory of Molecular Medicine, Human Genome Center, Institute of Medical Science, Tokyo University, Tokyo, JAPAN; H. Kawano, Orthopaedic Surgery, Teikyo University, Tokyo, JAPAN; K. Matsuda, Laboratory of Clinical Genome Sequencing, Computational Biology and Medical Sciences, Tokyo University, Tokyo, JAPAN*

Objective: *p53* encodes a transcription factor that transactivates downstream target genes involved in tumour suppression. Although osteosarcoma frequently has *p53*

mutations, the role of *p53* in osteosarcomagenesis is not fully understood. We aimed to explore *p53*-target genes comprehensively in calvarial bone and find out novel druggable *p53* target genes for osteosarcoma.

Methods: We performed RNA sequencing using the calvarial bone and 23 other tissues from *p53+/+* and *p53-/-* mice after radiation exposure.

Results: Of 23,813 genes, 69 genes were induced more than two-fold in irradiated p53+/+ calvarial bone, and 127 genes were repressed. Pathway analysis of the *p53*-induced genes showed that genes associated with cytokine-cytokine receptor interactions were enriched. Three genes, *CD137L, CDC42 binding protein kinase gamma* and *Follistatin*, were identified as novel direct *p53* target genes that exhibited growth-suppressive effects on osteosarcoma cell lines. Of the three genes, costimulatory molecule CD137L was induced only in calvarial bone among the 24 tissues tested. *CD137L*-expressing cells exhibited growth-suppressive effects in vivo. In addition, recombinant Fc-fusion Cd137l protein activated the immune response in vitro and suppressed osteosarcoma cell growth in vivo.

Conclusion: We clarified the role of CD137L in osteosarcomagenesis and its potential therapeutic application. Our transcriptome analysis also indicated the regulation of the immune response through p53.

Poster 005 #2787268

METABOLIC REPROGRAMMING AS A NOVEL THERAPEUTIC STRATEGY IN UNDIFFERENTIATED PLEOMORPHIC SARCOMA

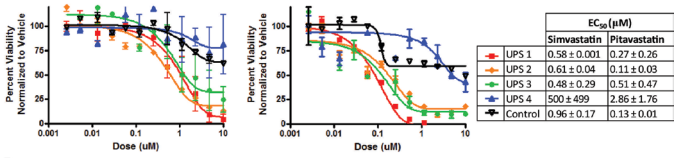
***R.E. Venier**, Y. Babichev, I. Andrulis, R.A. Gladdy, Lunenfeld Tanenbaum Research Institute, Toronto, Ontario, CANADA; R. Marcellus, R. Al-awar, Drug Discovery, Ontario Institute for Cancer Research, Toronto, Ontario, CANADA; R. Yu, L. Penn, Princess Margaret Cancer Centre, Toronto, Ontario, CANADA; A. Razak, Department of Medical Oncology, Princess Margaret Cancer Centre, Toronto, Ontario, CANADA; B.C. Dickson, Department of Pathology and Laboratory Medicine, Mount Sinai Hospital, Toronto, Ontario, CANADA; J.S. Wunder, Department of Surgery, Mount Sinai Hospital, Toronto, Ontario, CANADA*

Objective: Undifferentiated pleomorphic sarcoma (UPS) is a common sarcoma with a propensity to metastasize. Standard chemotherapy has modest utility and the prognosis for advanced disease is poor. To define more effective agents for UPS, we performed comprehensive drug screens of patient-derived cell lines. Surprisingly, UPS cell lines were highly sensitive to statins. Statins inhibit the rate-limiting step of the mevalonate (MVA) pathway – an essential component of metabolism responsible for the production of cholesterol, and metabolites required for post-translational modifications. Cancer cells exploit this pathway via PI3K, MAPK and AMPK signaling to enhance proliferation and survival. Although statins are being tested as anticancer agents in other solid tumors, the use of this well tolerated class of drugs has not been investigated in sarcoma. Thus, the ***goal of this study is to define the mechanisms responsible for reduced UPS viability following statin treatment***.

Methods: Previously, four primary UPS and one control fibroblast cell line were screened with 3,346 compounds and 25 hits were defined. Hit validation with EC50 assays identified six selective leads, two of which were simvastatin and pitavastatin, commonly used cholesterol-lowering agents (Fig A). Here, we investigate the mechanisms whereby simvastatin inhibits UPS viability with immunoblotting and qPCR.

Results: To ensure on-target specificity, we measured gene expression of many key components of the MVA pathway (HMGCR, MVD, and SREBP) and found UPS cells responded in a dose dependent manner. Next, to investigate crosstalk between the MVA and PI3K pathways, we confirmed endogenous PI3K pathway activation in UPS cell lines. Further, we assayed phosphorylation of downstream effectors such as AKT and 4EBP1 indicating that simvastatin inhibits PI3K signaling in UPS cells. To consider pre-clinical trial design and statin repurposing, we combined simvastatin with the standard of care, doxorubicin. We then performed EC50 assays analyzed by the Bliss method and found simvastatin was synergistic with doxorubicin at therapeutic concentrations (Fig B).

A



B

Simvastatin (μM)	0.003	0.005	0.011	0.024	0.050	0.104	0.218	0.457	0.956	2.000	Doxorubicin (μM)
0.013	-6.97	9.17	1.54	3.92	6.30	7.07	-1.21	-4.14	5.48	1.61	
0.027	-5.99	7.93	2.76	4.40	7.19	7.26	-0.19	-4.57	5.02	1.54	
0.057	-4.81	5.95	4.24	4.98	8.12	7.20	0.72	-5.25	4.20	1.36	
0.119	-3.68	3.12	5.61	5.50	8.68	6.57	1.09	-6.22	2.83	1.02	
0.249	-3.05	-0.22	6.22	5.63	8.26	4.97	0.40	-7.30	0.72	0.47	
0.522	-3.26	-2.93	5.46	4.98	6.44	2.36	-1.51	-7.96	-2.11	-0.28	
1.091	-4.02	-3.71	3.47	3.59	3.61	-0.54	-4.01	-7.51	-5.28	-1.04	
2.284	-4.57	-2.61	1.25	2.02	0.92	-2.68	-5.96	-5.88	1.56	-1.58	
4.779	-4.40	-1.03	-0.29	0.82	-0.78	-3.50	-6.63	-3.83	3.46	-1.77	
10.000	-3.66	-0.01	-0.96	0.15	-1.43	-3.30	-6.16	-2.15	1.98	-1.65	

Legend: Synergistic, Independent, Antagonistic

Figure 1. A) Dose response curves of simvastatin and pitavastatin in UPS cell lines. B) Assessment of simvastatin and doxorubicin synergy in UPS 3.

Conclusion: We find simvastatin reduces viability of UPS cell lines, and confirm on-target specificity of the MVA pathway. Further, simvastatin modulates the PI3K signaling pathway in UPS cells – a commonly dysregulated pathway in other high-grade sarcomas. Future studies will investigate the impact of statins on cell cycle arrest and apoptosis along with in vivo validation for pre-clinical development.

Poster 006 #2804177

SYNTHETIC LETHALITY BETWEEN PARP INHIBITOR SENSITIVITY AND SYNOVIAL SARCOMA

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Objective: Synovial sarcoma (SS) is an aggressive soft-tissue malignancy characterised by expression of SS18-SSX fusions. Treatment options are limited. Although the main pathological driver in SS is known, therapeutic targeting of SS18-SSX oncoproteins has not yet been achieved. Here, we aimed to identify therapeutically actionable dependencies in SS with translational potential.

Methods: We performed high-throughput drug sensitivity screens with 79 clinically relevant compounds (0.5–1000nM) in a SS cell line panel (SYO-1, HS-SY-II, Aska-SS, Yamato-SS and CME-1). SS drug sensitivity data was compared to sensitivity profiles of 115 non-SS tumour cell lines in 5-day assays (Mann-Whitney test). Validation inhibitory and mechanistic assays were performed with selected drugs and siRNA in SS cells, non-SS cells ectopically expressing SS18-SSX fusion proteins, and relevant other controls. Presence of replication fork stress biomarkers was assessed by (fluorescent) immunohistochemistry and DNA fibre analysis.

Results: Of all 79 compounds tested, 8 (4 cytotoxic and 4 targeted drugs) showed significantly stronger inhibitory effects in SS cells compared to non-SS cells, including two clinically used PARP-inhibitors (PARPi) talazoparib and rucaparib. Validation assays suggested selective sensitivity of SS to talazoparib and a third clinical PARPi olaparib, with equal or higher sensitivity than PARPi-sensitive *BRCA1*-mutant breast cancer and Ewing sarcoma cells. Expression of SS18-SSX1/SSX2 proteins in PARPi-resistant non-SS tumour cells significantly increased sensitivity to talazoparib (IC50 8nM vs. 1000nM) or olaparib (IC_{50} 3000nM vs. >10.000nM), establishing a causative link between SS18-SSX fusions and PARPi sensitivity. PARP1/2 siRNA knockdown did not affect SS cell viability, suggesting that these effects might be specific to small molecule PARPi. Knockdown of other DNA damage response (DDR) mediators, including *BRCA1/2*, significantly affected SS cell viability, suggesting a reliance on processes associated with stability/repair of replication forks. SS18-SSX protein expression in non-SS cells caused a mild, significantly increased replication fork stress phenotype (increased gH2AX, decreased replication fork speed and increased R-loops).

Conclusion: Our integrated assay provides the rationale for a synthetic lethal interaction between PARPi and SS, which could be exploited clinically.

Poster 007 #2804780

EPIGENOMIC REMODELING IN EWSR1 TRANSLOCATION ASSOCIATED SARCOMAS

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Objective: Epigenetic reprogramming, including promoter CpG island DNA hypermethylation and global hypomethylation, is thought to contribute to tumor initiation and progression, and is prevalent in all types of cancer, including soft tissue sarcomas. Epigenetically modified genes include important categories of tumor suppressor genes including cell cycle regulators, pro-differentiation factors, and anti-apoptotic genes, and many of these genes are known to play a role in normal development and are associated with stemness. Our objective is to understand the epigenomic landscape of EWSR1 translocation associated soft tissue sarcomas and investigate the hypothesis that these translocations drive epigenetic reprogramming back to a more stem-like state, contributing to tumor progression, metastasis, and ultimately escape from conventional therapies.

Methods: We have utilized multiple –omics platforms to help determine the epigenetic and transcriptomic landscape of EWSR1 translocation associated sarcoma cell lines, primary tumors, and controls including RNA-sequencing, global DNA methylation analysis, and miRNA-seq. RT-qPCR was used to determine the expression of specific mature miRNAs and their precursors.

Results: We have identified unique mRNA and miRNA expression and DNA methylation signatures for multiple subtypes of EWSR1 associated cancers including Clear Cell Sarcoma of the Soft Tissues (CCSST), Ewings Sarcoma (ES), Extracellular Myxoid Chondrosaroma (EMC), Myxoid liposarcoma (MLS), and Myxoid Round Cell Liposarcoma (MRCL). These patterns are distinct from non-cancerous primary cells (MSCs and melanocytes) as well as other translocation associated sarcoma subtypes including Endometrial Stromal Sarcoma and Synovial Sarcoma.

Conclusion: Our data suggest a wide-spread disruption of epigentic regulation of gene expression in EWSR1 translocation associated sarcomas. We hypothesize that the EWSR1 translocations drive a unique global epigenomic reprogramming event and disrupt endogenous EWSR1 RNA binding and chaperone activity, specifically altering miRNA processing. As many of these genes are known to be key regulators of both oncogenic proteins and tumor suppressors, manipulation of the abnormal epigenome in these cancers may restore and/or enhance their sensititivity to chemotherapy and immunotherapy, representing a unique potential therapeutic opportunity for these soft tissue sarcoma patients.

Poster 008 #2804844

THE ROLE OF BCL2 FAMILY MEMBERS IN SYNOVIAL SARCOMAGENESIS

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Objective: Synovial sarcomas are deadly soft-tissue malignancies associated with t(X;18) balanced chromosomal translocations. Expression of BCL2 is prominent in synovial sarcomas and has prompted the hypothesis that synovial sarcomagenesis may depend on it. Using mouse models of synovial sarcoma we dissected the dependency of synovial sarcomagenesis by genetic deletion or conditional overexpression of Bcl2 in combination with SS18-SSX2 expression. In addition to the genetic evaluation of Bcl2 necessity in synovial sarcomagenesis, we sought to understand whether inhibition of BCL2 and its gene family members pharmacologically affected tumor growth.

Methods: Mice conditionally expressing SS18-SSX2 were combined with either an overexpression Bcl2 allele or a floxed Bcl2 allele, resulting in deletion. These mice were assessed for survival. Additionally, their tumors were analyzed histologically and compared to synovial sarcomas with sole expression of the fusion SS18-SSX2. Human synovial sarcoma cell lines were evaluated for sensitivity to ABT-199 (BCL2i) in combination with doxorubicin or to BXI-72 (BCL-XLi). Mice bearing synovial sarcomas were treated with a BCL2-specific inhibitor ABT-199 (100 mg/kg) or doxorubicin (30 mg/kg) for 3 weeks or a BCL-XL-specific inhibitor BXI-72 (20 mg/kg) for 1 week. Tumors were physically measured with calipers to determine volumetric changes or imaged using FDG-PET/CT to quantify total lesion glycolysis (TLG). Murine synovial sarcomas treated with the control vehicle or BXI-72 were further analyzed for necrosis histologically and levels of apoptosis by immunoblotting.

Additionally, to test the association of synovial sarcoma with a predisposition toward increased BCL2 expression in a human population, we turned to the Utah Population Database (UPDB). We tested 1st-, 2nd-, and 3rd-degree relatives of synovial sarcomas for an excess of BCL2-linked cancers such as follicular lymphoma and chronic lymphocytic leukemia.

Results: In the mouse genetic experiments, we observed subtle changes in the onset of sarcomagenesis when we deleted or overexpressed Bcl2. Overexpression resulted in a 3 week earlier onset, whereas the floxed deletion of Bcl2 delayed tumor morbidity significantly especially in tumors that underwent a more complete recombination and deletion of Bcl2. ABT-199 and doxorubicin were not synergistic in in vitro cell-based experiments and similar results were seen when mice were treated with ABT-199. Despite non-significant changes in tumor volume with doxorubicin, synovial sarcomas demonstrated consistent and significant changes in tumor glycolysis when imaged with FDG-PET. Synovial sarcoma cell lines showed exquisite sensitivity to BXI-72 and 50% reduction in tumor volume was seen in mice treated with BXI-72 accompanied with increased necrosis and apoptosis.

A significant excess of BCL2-related malignancies was observed among second-degree relatives of synovial sarcoma cases (p=0.007), and borderline significant excesses were observed in first-degree (p=0.087) and third-degree (p=0.051) suggesting inherited risk for synovial sarcoma is associated with Bcl2 overexpression.

Conclusion: The association of BCL2 expression with synovial sarcoma is found to fit with a subtle, but significant impact of its enhanced presence or absence during early tumorigenesis. However, specific pharmacological inhibition of BCL2 does not demonstrate a persistent dependence in fully developed tumors. Conversely, inhibition of the BCL2 family member, BCLxL, resulted in nanomolar potency against human synovial sarcoma cell lines and 50% tumor reduction in a genetically engineered mouse model. Thus, the contributory role of BCL2 in synovial sarcomagenesis does not appear to render it as a therapeutic target, but mitrochondrial anti-apoptotic BCL2 family members may be.

Poster 009 #2804876

SYNOVIAL SARCOMAGENESIS AND THE SKELETON

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Objective: Synovial sarcoma is an aggressive soft tissue sarcoma with a penchant to occur in adolescents and young adults. Despite its misnomer, synovial sarcoma does not arise from synoviocytes. The conditional expression of the characteristic *SS18-SSX* fusion in the *Myf5* cell lineage in mice, suggested that progenitor skeletal muscle cells could be the cell of origin. However, *Myf5* expression is not restricted to committed myoblasts, but exhibits expression in earlier, undifferentiated mesenchymal progenitors, which can give rise to a wider array of differentiated cells opening the possibility that the cell of origin can be more precisely defined. One commonality that the *Myf5Cre*;*SS18-SSX*-expressing mice share with human synovial sarcoma is the consistent anatomical location adjacent to bone. We thus sought to identify what factors contribute to the unique relationship between bone and synovial sarcoma.

Methods: A series of 48 human synovial sarcoma patients was analyzed for their proximity to bone. Mouse synovial sarcomas initiated with *Myf5Cre* were likewise assessed for their juxtaposition to bone. Osteoprotegerin (OPG)/*Tnfrsf11b* was conditionally deleted from synovial sarcomas and recombinant OPG protein was injected to

developing synovial sarcomas and tumor formation was assessed in both scenarios. *Myf5Cre* mice in combination with reverse tet transactivator were used to turn on *SS18-SSX2* postnatally. Mice were subsequently crossed to initiate the fusion *SS18-SSX2* expression from different cell lineages along the path of osteoblast differentiation, including OcCre, Col1Cre, Prx1CreERT, OsxCreERT. Additionally, we added the activated allele of beta-catenin to each developmental step to characterize tumor formation.

Results: Proximity to bone was a consistent observation seen in both human and mouse synovial sarcoma. Recombinant mouse OPG injected in the tibialis anterior muscle following TATCre injection significantly enhanced GFP+ cells. While conditional deletion of *Tnfrsf11b* impacted tumor progression, synovial sarcomas still formed with a modest delay.

Initiation of the fusion *SS18-SSX2* in the embryonic osteochondroprogenitors was almost always lethal. Surviving pups demonstrated skeletal defects suggesting a loss of mesenchymal progenitor cells. Postnatal initiation of *SS18-SSX2* in pre-osteoblasts resulted in synovial sarcomas that appeared next to bone and especially bone with a propensity to secrete high levels of OPG. Combined expression of *SS18-SSX2* and stabilized beta-catenin gave rise to synovial sarcomas in postnatal pre-osteoblasts that extended along the entire periosteal surface of the forelimbs. Beta-catenin activation alone led to the inhibition of terminal differentiation of osteoblasts.

Conclusion: These data challenged our prior interpretation of the SS originating potential of the *Myf5Cre* lineage as indicating a myoblast. We must now conclude that post-natal myoblasts and even satellite cells (post-natal myogenic progenitor cells that differentiate into myoblasts) are unlikely candidates for the cell of origin. Further, exogenous OPG had a paracrine impact in enabling early growth of *SS18-SSX2*-transforming cells, and genetic silencing of Tnfrsf11b slowed synovial sarcomagenesis subtly, but significantly. Finally, early mesenchymal progenitor cells with strong osteoblast differentiation potential proved capable of tolerating *SS18-SSX2* expression and even transformation from expression of *SS18-SSX2*, especially with the added boost of β-catenin stabilization. Thus, the observation that human SS often arises in close proximity to bones and often exhibits areas of osteoid matrix production within the tumor can be explained by the transforming potential in osteochondroprogenitors and by the additional protection to early stages of synovial sarcomagenesis from the paracrine secretion of OPG, which is highly expressed in bones.

Poster 010 #2804552

COMBINATION CHEMOTHERAPY FOR AGGRESSIVE FIBROMATOSIS: PRELIMINARY RESULTS FROM BETA-CATENIN INHIBITOR, DEXAMETHASONE, AND FOCAL ADHESION KINASE INHIBITOR

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Objective: Aggressive fibromatosis (AF), commonly referred to as Desmoid tumor, is a locally aggressive lesion often treated with surgical resection, however, high local recurrence rates generate continued interest in chemotherapeutic options. Prior authors have investigated different therapies through both in vivo and in vitro studies with variable results; however, there is a paucity of literature available on multi-drug regimens. Given the infrequent occurrence of these aggressive lesions and lack of funding to generate novel chemotherapeutics, the majority of research focuses on using current FDA approved medications in hopes for a therapeutic response in AF. At the investigating institution, a prior drug screen has returned numerous medications that show promising activity in AF. Therefore, we sought to investigate various regimens from the drug screen to determine the utility of combination therapy in AF.

Methods: *Apc+/Apc^{1638N}* mice, which develop AF lesions, were treated with either monotherapy or dual therapy with BC2059 (a beta catenin inhibitor), Focal Adhesion Kinase (FAK) inhibitor, and Dexamethasone. The mice were sacrificed at 6 months following treatment and tumor number and volume analyzed. AF tumors were then analyzed through immunohistochemistry (IHC), western blot, and real time PCR for markers of proliferation and apoptosis (KI67 and caspase), as well as beta catenin and downstream protein activity. Human cell cultures undergoing the same treatment combinations were then performed. Funding for this study was provided by the Desmoid Tumor Research Foundation.

Results: Preliminary results from gross tumor analysis from *Apc+/Apc^{1638N}* mice has shown significant decrease in tumor number with BC2059 mono-therapy compared to control ($p=0.0004$). Mon-therapy with FAK inhibitor and Dexamethasone trended toward diminished tumor burden, however, these results were not significant. Combination therapy with BC2059 and dexamethasone, as well as FAK inhibitor and dexamethasone showed significant decreased tumor number compared to control ($p<0.0001$) [figure 1]. Average tumor volume showed a similar response to treatment with combination therapy, with dual treatment outperforming control and monotherapy. These differences, however, were not significant [figure 2]. Protein, RNA, and human cell culture treatment analysis are currently being performed.

Conclusion: Desmoid tumors are locally aggressive lesions, and due to high local recurrence rates, there is a

need for effective chemotherapeutic options. Based on the preliminary results of this study, combination therapy with FAK inhibitors, Dexamethasone, and BC2059 (a beta catenin inhibitor) appear to be effective treatment options, which may warrant further evaluation with phase II clinical trials. Further analysis on these tumors will provide more insight into the therapeutic effects of these medications.

Poster 011 #2804724

ADI-PEG20 PRIMES MALIGNANT PERIPHERAL NERVE SHEATH TUMORS FOR CONDITIONAL LETHALITY BY AUL12 THROUGH ALTERATION OF MTORC1

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Objective: Many cancers use a unique feature of converting glucose to lactate acid to produce cellular energy, interestingly in multiple Malignant peripheral nerve sheath tumors (MPNST) cell lines, oxidative phosphorylation (OXPHOS) is the primary process used to utilize the energy of a carbon source for ATP generation driving proliferation. Based on our previous findings we found that targeting the OXPHOS process at complex I, via the novel drug AUL12, changed the mitochondrial dynamics and lead to an induction of apoptosis. In this study, we investigate the underlining biology that drives the OXPHOS phenotype in MPNST and sought to maximize the effects of the novel AUL12.

Methods: Four malignant peripheral nerve sheath cell lines, three plexiform nuerofibroma and a human schwann cell lines were used for mitochondrial isolation experiments, dual-link proximity assays and ADI-PEG20:AUL12 drug combination studies.

Results: Mitochondrial isolation experiments showed that the active pool of mTORC1 is at the mitochondria within MPNSTs. Depleting the arginine source in ASS1 negative MPNSTs with ADI-PEG20 prevents this translocation of active mTORC1 to the mitochondria. Further, dual-link experiments show active mTORC1 in complex with HKII at the mitochondria membrane. This complex was prevented when MPNST cell lines are depleted of arginine with ADI-PEG, changing MPNST reliance on OXPHOS. We hypothesized that the active pool of mTORC1 forms a complex with hexokinase II and is located at the mitochondria, fueling the OXPHOS phenotype and that inhibition of mTORC1:HKII translocation by ADI-PEG20 augments the potency of AUL12 in MPNST.

Conclusion: This study reveals one possible mechanism by which MPNST prefer an OXPHOS phenotype over a glycolytic phenotype. This phenotype is preferred by translocating mTORC1 to the mitochondria allowing for a complex to form with HKII at the membrane. As a result, cells will consume glucose more efficiently leading to an increase in ATP production. Alteration of arginine homeostasis using ADI-PEG20 potentiates the effects of AUL12 on mitochondrial biology as well as on the activated pool of mTORC1 at the mitochondria.

Poster 012 #2740549

EGFR INHIBITORS IDENTIFIED AS A POTENTIAL TREATMENT FOR CHORDOMA IN A FOCUSED COMPOUND SCREEN

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Objective: In view of the unmet need for effective treatment of patients with chordoma, we undertook a large scale compound screen with the aim of identifying therapeutic targets, and understanding the mechanism by which this disease develops.

Methods: In a focused compound screen we tested 1097 compounds, comprising 2 libraries (PKIS and PKIS2) with a total of 886 small molecule kinase inhibitors provided by GlaxoSmithKline (GSK), 160 Calbiochem (Merck KGaA) kinase inhibitors, an Anticancer Library (n=43) (Selleckchem), and 8 compounds reported to be inhibitors of Aldo-Keto Reductase Family 1 Member B10 (AKR1B10) (Selleckchem). We screened 3 well-characterised chordoma cell lines at a single concentration (1 μM).EC50s of the inhibitory hits were determined in chordoma cells and normal fibroblasts in order to select compounds which selectively killed chordoma cells but not fibroblasts. Cell death analysis was conducted. We then included 6 compounds to validate the key target class in an extended panel of 7 chordoma cell lines. Validation experiments included Western Blots, ELISA, FISH, and cancer gene hotspot mutation analysis. The most promising compound was tested at South Texas Accelerated Research Therapeutics (START) in 2 xenograft mouse models.

Results: 154 compounds were selected from the single concentration screen. Twenty-seven compounds selectively killed chordoma cells but not dermal fibroblasts. Twenty-one of 27 (78%) chordoma selective hits were EGFR/ERBB inhibitors. When EGFR inhibitors were studied on an extended panel of 7 chordoma cell lines, 4/7 cell lines were sensitive to EGFR inhibition. The compounds induced apoptosis and suppressed phospho-EGFR and

its downstream-pathways in a dose-dependent manner. Sapitinib significantly reduced chordoma growth in vivo. Chemical substituent trend analysis suggested that EGFR-inhibitors with small aniline substituents in the 4- position of the quinazoline ring were more effective than inhibitors with large substituents. One of the resistant cell lines (U-CH2) expressed high levels of phospho-MET. Neither amplification in EGFR, ERBB2, and MET, nor mutations in cancer gene hotspots were detected in any of the cell lines.

Conclusion: Our findings are in line with reported (p-) EGFR expression in the vast majority of clinical chordoma samples. They provide an evidence base for pursuing a randomised clinical trial using EGFR inhibitors, and for further exploration of possible mechanisms of primary and acquired resistance to these compounds.

Poster 013 #2783057

IMMUNE GENE SIGNATURES PRIOR TO NEOADJUVANT RADIOTHERAPY ARE ASSOCIATED WITH CLINICAL OUTCOMES IN SOFT TISSUE SARCOMA

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Objective: Immune therapies may synergize with radiotherapy (RT), but little is known about how the soft tissue sarcoma (STS) immune microenvironment changes during neoadjuvant RT and how these correlate with clinical outcome. We tested whether expression of established gene sets sampled before and after RT are related to recurrence free survival (RFS) and overall survival (OS).

Methods: Fifty-six STS patients (over the age of 18 years) treated with neoadjuvant RT +/- chemotherapy were retrospectively identified. Clinical characteristics and outcomes were abstracted from the institutional medical record. Formalin fixed, paraffin embedded tissue samples from diagnosis (PRE) and at surgical resection (POST) were obtained.

Gene expression was quantified using the Nanostring platform. Set-based kernel association test (implemented in the MiRKAT software) was conducted on PRE, POST and PRE-POST gene-expression to analyze the relationship between 9 established immune-related gene sets, RFS at 3 years, and OS at 5 years. Initial tumor size and FNCLCC grade were analyzed as adjusting covariates. Lasso penalized Cox regression identified the genes in each set most closely associated with of RFS/OS.

Results: Gene expression data were available for 45 PRE and 47 POST samples; PRE-POST were available for 36 patients. Most tumors were greater than 5 cm (79%), and most received chemotherapy (64%). Spindle cell sarcoma was the most common histology (N=13).

Four PRE gene sets (T-cell receptor (TCR) signaling, CD8, Treg, myeloid derived suppressor cell (MDSC)) predicted RFS and 2 PRE gene sets (TCR, CD8 T-cell) predicted OS (Table 1). One POST gene set (MDSC) was related to RFS. Models from these gene sets included 13 unique genes.

The Cox model identified 2 and 4 genes from the CD8 activation PRE gene set that were associated with RFS ($p<0.001$) and OS ($p<0.0005$), respectively. Two genes from the Treg activation PRE set ($p=0.01$) and two genes from the MDSC activation test ($p<0.001$) were associated with OS. No significant POST genes from the MDSC activation set were identified.

Conclusion: Genes signatures related to TCR signaling and CD8, Treg, and myeloid suppressor cell activation

Set-based Kernal Association Test Results for Pre-determined Gene Sets

		Recurrence free survival (3y)			Overall Survival (5y)	
Gene Set	PRE (p-value)	POST (p-value)	PRE-POST (p-value)	PRE (p-value)	POST (p-value)	PRE-POST (p-value)
Merck 18-gene	0.229	0.202	0.688	0.054	0.577	0.115
IFNγ 6-gene	0.756	0.693	0.911	0.721	0.415	0.683
IFNγ 10-gene	0.822	0.685	0.799	0.654	0.513	0.684
T-cell receptor signaling	0.047	0.083	0.842	0.025	0.654	0.683
M1 macrophage	0.427	0.675	0.821	0.392	0.538	0.227
M2 macrophage	0.211	0.063	0.498	0.097	0.301	0.055
CD8 T-cell	0.047	0.054	0.401	0.026	0.237	0.416
Regulatory T-cell (Treg)	0.087	0.2	0.076	0.01	0.58	0.245
Myeloid derived suppressor cell	0.196	0.112	0.75	0.007	0.266	0.041

Results depict p-values from the set-based kernal association test implemented in MiRKAT software for each pre-determined gene set. PRE = pre-treatment sample, POST = post-treatment sample, PRE-POST = pre-treatment minus post-treatment.

are associated with RFS and OS. These genes represent exciting biomarkers that potentially improve risk stratification and delineate future targets for immunotherapy. Ongoing work is using multiplex IHC to analyze the microenvironment and validate the signatures in an external cohort.

Poster 014 #2789008

VALIDATION OF A CROSS-SPECIES DRUG DISCOVERY PIPELINE

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Objective: Preclinical modeling of cancer drugs is essential to bring new therapeutics into the clinic. Yet, nine out of ten attempts to bring novel anti-cancer drugs into the clinic fail. Therefore, there is an unmet clinical need to develop new preclinical practices to more rapidly and accurately identify new cancer therapies.

The overall objective of our project is to develop a novel, cross-species preclinical platform than can rapidly and accurately screen and validate drugs for translation into the clinic.

Methods: A protocol was established to utilize resected sarcomas from dogs and humans. These tumors were used to 1) generate canine/patient-derived xenografts in immunodeficient mice; and 2) develop novel cell lines. Drug screens were performed in conjunction with the Duke Functional Genomics Shared Resource. Validation of the top candidates will be performed in human and dog PDXs to identify the most efficacious treatment.

Results: We generated a panel of seven canine PDXs and six human PDXs. We also developed a novel cell line from our D418 canine PDX. We performed a high throughput drug screen of over 100 FDA approved cancer drugs on a panel of 4 human and 4 canine osteosarcoma cell lines. We also performed a screen of 2,100 small molecules using the BioActives compound library in the newly-established D418 cell line. From these screens, we identified several candidate therapies: 1) inhibitors that target the CRM1 protein; 2) proteasome inhibitors; and 3) targeted agents that are known to be active against specific mutations (e.g. FGFR, mTOR/PI3Kinase and MEK pathway). We are currently validating the top candidates in vivo using both dog and human PDXs for translation to dog and human clinical trials.

Conclusion: For both dogs and humans with metastatic sarcomas, treatment options are often ineffective. Therefore, to develop more effective treatments, we have established a system to rapidly screen and validate drugs using canine- and human-derived cell lines and PDXs. We hope that our efforts help lead to a paradigm shift toward precision treatment for sarcomas.

Poster 015 #2791317

RADIOTHERAPY ENHANCES NATURAL KILLER HOMING AND CYTOTOXICITY IN PRE-CLINICAL CANINE SARCOMAS AND FIRST-IN-DOG CLINICAL TRIAL

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Objective: We have previously shown that radiotherapy (RT) augments natural killer (NK) functions in pre-clinical models of human and mouse cancers, including sarcomas. Since dogs are an excellent outbred model for evaluating novel immunotherapy protocols, we sought to assess RT plus NK immunotherapy in canine sarcomas.

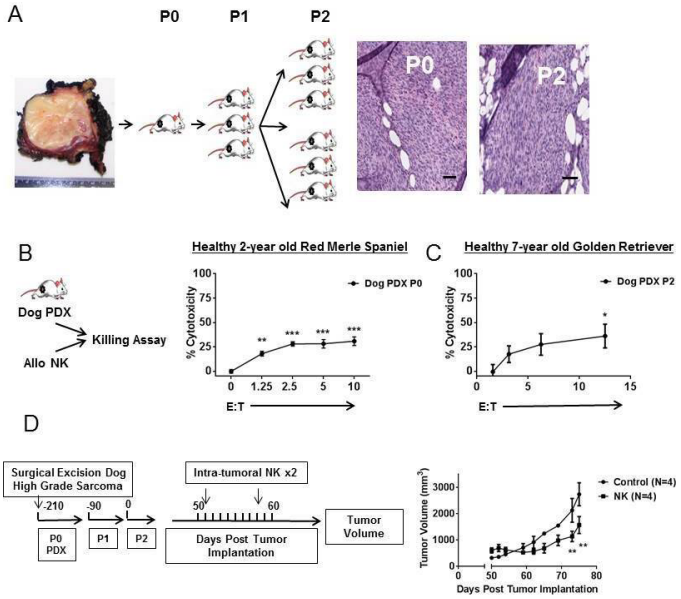
Methods: Dog NK cells (CD5dim, NKp46+) were isolated from 10-15 mL fresh PBMCs and expanded via co-culture with irradiated K562-C9-mIL21 feeder cells and 100IU/mL recombinant human IL-2. NK homing and cytotoxicity ± RT were evaluated using canine osteosarcoma tumor lines, fresh canine primary sarcomas, and patient-derived canine xenografts. In a first-in-dog clinical trial of adoptive autologous NK transfer, we evaluated RT and intra-tumoral NK in dogs with osteosarcoma.

Results: Mean NK expansion was 46.2-fold (±12.7) with

Patient and NK Injection Characteristics for Dog Clinical Trial Subjects

Breed	Age	Sex	Weight (kg)	Injection #1 (x 106)	Viability (%)	Injection #2 (x106)	Viability (%)
Black Lab	14.8	M	29.6	30	79.3	0.3	1.0
St. Bernard	9.1	M	59	114.6	94.8	139.7	99.0
Shepherd Mix	9.1	M	23.8	75.9	98.6	26.7	97.2
Shepherd Mix	5.8	M	46	129.5	99.2	86.9	99.2
St. Bernard	1.2	F	57.6	139.5	95	94.5	96.0
St. Bernard	6.3	M	94	25	70	280	76.0
Pyrenees	7.5	F	57.1	180	95.0	175	94.0
Doberman	5.0	M	66	115	95.0	17	95.0
Retriever Mix	8.9	F	32	221.8	83	142	90.0
Rhodesian Ridgeback	10.2	F	35.1	114.6	94.8	139.7	99.0
Mean	7.8		50.0	114.6	90.5	110.2	84.6

an average of 258.9(±76.1) x106 cells. Post-RT, NK cytotoxicity in vitro increased in a dose-dependent fashion reaching 74 – 88% cytotoxicity at effector:target ratios of ≥ 10:1 (P<0.001). NK cytotoxicity was also observed after RT of ex vivo primary canine sarcoma specimens. In dog sarcoma patient-derived xenograft (PDX) models using focal RT and intravenous NK transfer, we observed significantly increased NK homing to tumors, and intra-tumoral allogeneic NK transfer produced significant PDX tumor growth delay (P<0.001). Of 10 dogs with spontaneous osteosarcoma treated with focal RT and autologous NK transfer in a clinical trial, 5 remain metastasis-free at the 6-month primary endpoint with resolution of suspicious pulmonary nodules in one patient.



Expanded Dog NK Cells are Cytotoxic against Canine Patient-Derived Specimens. A. The schema depicts generation of canine patient-derived xenografts from a freshly excised high grade (grade III) soft tissue sarcoma from a dog at the UCD Center for Companion Animal Health. Three mm³ fragments were implanted into the flanks of 7 – 8 week old female NSG mice. Tumors were allowed to grow to approximately 15 – 20 mm in maximal dimension for ex vivo killing assays or passaging into additional mice. For in vivo therapy experiments, mice were randomized to treatment groups when tumors were 5 – 7 mm in maximal dimension. Representative photomicrographs from passages 0 and 2 demonstrate characteristic tumor morphology consistent with canine soft tissue sarcoma. Scale bar = 50 µM. **B – C.** When dog PDX tumors reached approximately 20 mm in size from indicated passages, they were excised, and mechanical and enzymatic digestion was used to create single cell suspensions. Tumor cells were then incubated with 51Cr for 1 hour. We then co-cultured labelled cells with activated NK cells at the indicated E:T ratios in 96-well plates for 4 hours. Tumor cell lysis was assessed with a scintillation counter, and percent cytotoxicity was calculated using standard formulas. Representative data from 2 – 3 experiments are shown. **D.** Graphic depicts schema for in vivo experiment assessing therapeutic efficacy of intra-tumoral NK cells with rhIL-2 similar to our clinical trial protocol. When passage two dog PDX tumors reached approximately 5 – 7 mm in size, we randomized mice in groups of four to intra-tumoral NK plus 100,000 IU rhIL-2 versus control injections. Mice received two NK/IL-2 injections one week apart and were followed until euthanasia protocols were indicated. Tumor volume was measured twice weekly by external caliper. We observed significant tumor growth delay in the NK/rhIL-2 treated mice, and these growth differences persisted for the remainder of the study period. ** P<0.01 via one-way ANOVA with Tukey's post-test.

Conclusion: NK cell homing and effector functions are increased following RT in canine models of sarcoma. Results from a first-in-dog clinical trial are promising, including possible abscopal effects. Canine clinical trials are a tremendous resource, particularly for novel NK immunotherapy protocols and can support clinical extrapolation of this innovative bench-to-bedside approach.

Poster 016 #2804329

DIFFERENT STRUCTURAL FEATURES OF EWS ARE REQUIRED FOR DISTINCT MODES OF EWS/FLI-MEDIATED ONCOGENIC GENE REGULATION

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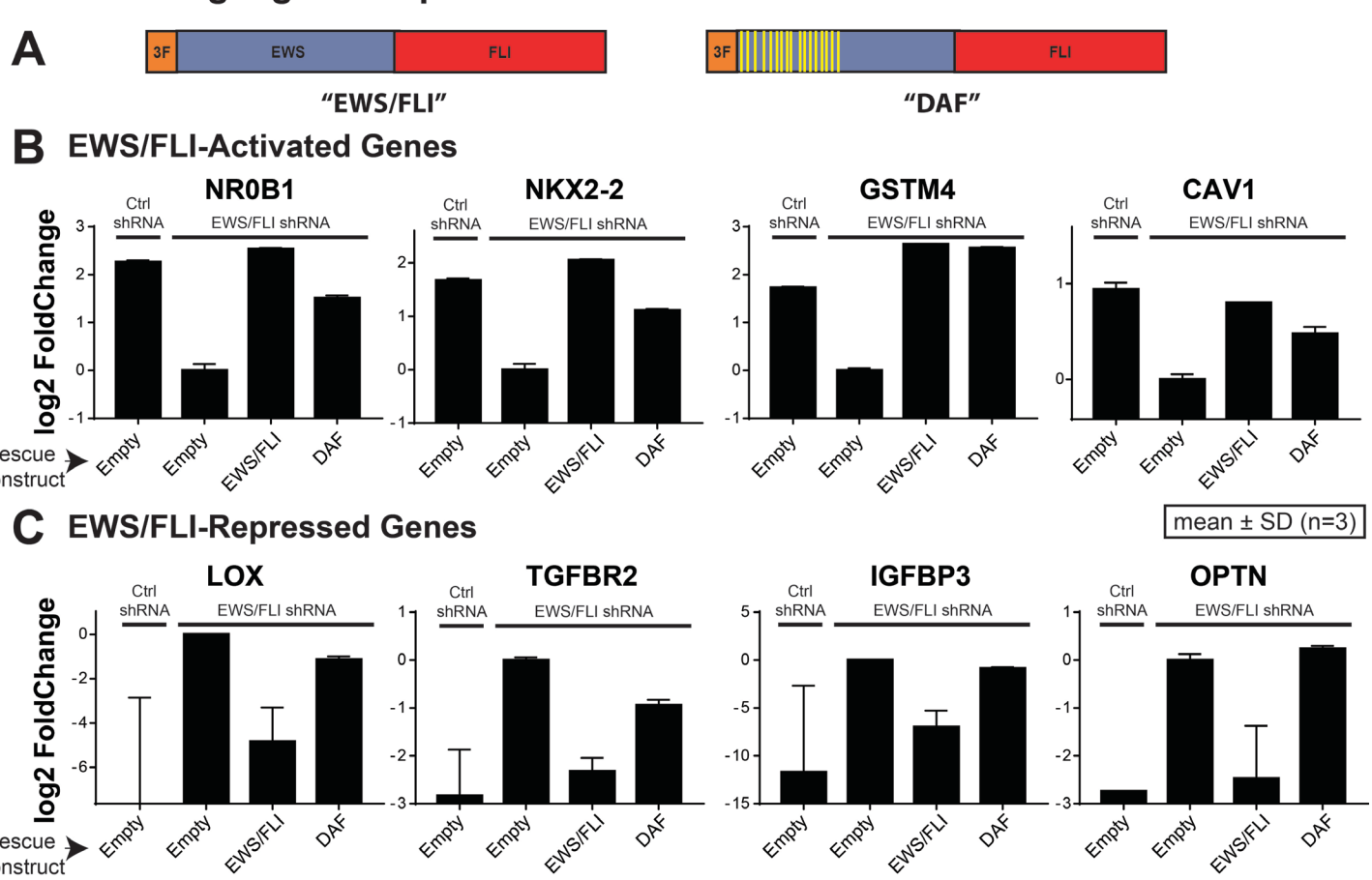
Objective: EWS/FLI is the fusion oncogenic transcription factor that drives Ewing sarcoma. While EWS/FLI is well-characterized as a transcriptional activator, both gene activation and repression are necessary for EWS/FLI-mediated oncogenesis. Whether EWS/FLI-mediated repression is active or passive is unknown. We previously demonstrated recruitment of the nucleosome modeling and deacetylase (NuRD) and lysine specific demethylase 1 (LSD1) complex is important for repression, supporting an active model. Targeted inhibition of either the histone deacetylase (HDAC) activity of NuRD or LSD1 impairs repression. Interestingly, LSD1, but not HDAC, inhbition disrupts gene activation, suggesting different protein complexes dictate different modes of transcriptional regulation. We hypothesize that EWS/FLI-mediated activation and repression result from separate active molecular mechanisms driven by distinct elements within the EWS domain. Prior studies using a deletion mutant strategy failed to identify a mutant which activated target genes, but didn't repress, or vice versa.

Methods: Exploring EWS structure/function relationships is limited by its disordered and repetitive nature. We used a strategy in which conserved tyrosine residues in repetitive regions are mutated to alanine. This mutant, DAF, was assayed for regulation of EWS/FLI targets and transformation using a knockdown-rescue approach with subsequent qRT-PCR, RNA-seq, ChIP-seq, and agar assays. We also evaluated the function of DAF at microsatellite elements in reporter assays.

Results: DAF is the first mutant profiled which partially rescues EWS/FLI function. We observe DAF activates microsatellite-driven target genes, including NR0B1, CAV1, and GSTM4, while failing to repress IGFBP3, LOX, and TGFBR2. RNA-seq studies largely confirm this. Rescue of EWS/FLI knockdown with DAF expression fails to rescue the growth of A673 cells in soft agar, demonstrating DAF is incapable of transformation. In luciferacse assays, DAF activates gene expression from the NR0B1 microsatellite.

Conclusion: We conclude DAF separates microsatellite-driven gene activation from other modes of EWS/FLI-mediated gene regulation. Whether this difference is due to altered DNA-binding or protein recruitment is unknown and studies are underway to investigate these questions. The DAF mutant is an important new tool to dissect the molecular requirements for distinct mechanisms of EWS/FLI function and will enable identification of novel therapeutic liabilities in Ewing sarcoma.



A) Schematic of DAF mutant characteristics. B) DAF activates gene expression at EWS/FLI-activated microsatellite genes. C) DAF fails to repress critical EWS/FLI target genes.

Poster 017 #2804629

A NEW COMBINATION OF PRO-APOPTOTIC AGENTS AND RADIOTHERAPY FOR TREATMENT OF SOFT TISSUE SARCOMAS

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Objective: Pre-operative radiotherapy improves local control but often fail to importantly reduce the tumor size. The aim of this project was to synergistically improve radiation treatment and cancer cell death in soft tissue sarcomas (STS) via addition of pro-apoptotic drugs.

Methods: STS cell lines established from primary human sarcomas were treated with various combinations of irradiation and pro-apoptotic drugs (Venetoclax and Navitoclax) targeting anti-apoptotic BCL-2 family members. The characterization of STS cell responses after irradiation (2 to 10 Gy) was performed by flow cytometry (cell cycle and apoptosis), V-PLEX immunoassays (secretome), and long-term survival (proliferation and colony formation). Cell responses were also evaluated in a 3D culture model.

Results: We confirmed that irradiation alone was sufficient to reduce the ability of primary STS cells to form colonies. Irradiated cells demonstrated very low level of cell death but displayed a proliferation arrest that explains reduced colony formation. Alternatively, the addition of pro-apoptotic drugs after radiation induced rapid apoptosis in all irradiated cell lines, with little effect on non-irradiated controls, leading to significant reductions in colony formation via increased cell death. Importantly, combo treatments of irradiation and pro-apoptotic drugs in 3D culture models yielded a diminution in spheroids size as opposed to spheroids treated with irradiation alone (Fig. 1).

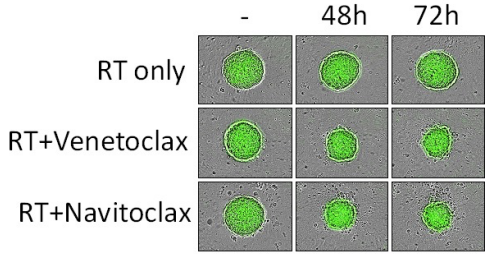

Figure 1 After spheroids formation, STS93 cell line was treated with 8Gy alone (RT) or the combination of 8Gy and Venetoclax (5uM) or Navitoclax (0,5uM).

Conclusion: The cytostatic phenotype observed after the irradiation of STS cell lines could reflect the lack of important tumor size reduction following pre-operative radiotherapy. Radiotherapy-induced cytostasis in STS can be overcome through the administration of a pro-apoptotic BCL2/BCLxL inhibitor during the time window between RT and surgery. Important reduction in tumor size will diminish the volume of STS surgery and its associated morbidities.

Poster 018 #2804748

INTRATUMORAL INJECTION OF TLR4 AGONIST G100 INDUCES A T CELL RESPONSE IN THE SOFT TISSUE SARCOMA MICROENVIRONMENT

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Objective: Soft tissue sarcomas (STS) are a heterogeneous group of mesenchymal neoplasms which, despite advancements in multimodal therapy, still represents a morbid and lethal disease. G100 is a stable oil-in-water emulsion of glucopyranosyl lipid A, a highly potent toll-like receptor 4 agonist, which has already been utilized as an adjuvant for vaccines without significant toxicity. We hypothesized that intratumoral (IT) injections of G100 into the STS microenvironment would induce a robust anti-tumor immune response, leading to improved outcomes for patients.

Methods: 15 patients with metastatic STS, including at least one superficial injectable lesion, were treated with weekly injections of IT G100 for 8-12 weeks; 12 patients received concurrent radiation for 2 weeks at the beginning of therapy, while 3 underwent IT G100 alone for 6 weeks prior to radiation. Biopsies and peripheral blood were collected pre and post treatment, and flow cytometry was performed on fresh tumor samples. TCR deep sequencing was performed on select samples. RECIST v1.1 criteria and the Common Terminology Criteria for Adverse Events (CTCAE) were used to monitor clinical outcomes.

Results: Median prior lines of treatment was 3 (range 0-5), and average size of tumor was 5.6cm (1-20cm). No grade 3 or higher treatment-related toxicity was observed, and local tumor control of injected site was achieved in 93% (14/15). 40% (6/15) had stable disease at the end of treatment, and one patient (P06) had complete regression of injected tumor. This tumor was notable for a high percentage of infiltrating pre-treatment immune cells, as 11.9% of live cells were CD45+ on flow cytometry compared with 2.7% for all other tumors. TCR sequencing revealed that the change in clonality of PBMC after treatment was higher in P06 (389% increase) compared to 6 other patients (mean change 34%).

In patients considered evaluable for tumor-associated macrophage phenotypes (tumors containing more than 1000 CD45+CD11b+ cells), 71% had a shift from an M2 to M1 phenotype. In all patients who received G100 alone first, there was an increase in T cell infiltration into tumor following IT G100. In P14, the proportion of CD3+ live cells in tumor went from less than 1% to over 60%; of these, 51% were CD4+ while 44% were CD8+. Furthermore, TIL from this patient had a 251% increase in T cell clonality after treatment, driven by expansion of pre-existing clones as well as development of new clones. The most frequent TCR clone expanded from 4% pre-G100 to over 45% after G100 injections alone. At the same time, percentage of live tumor cells that were PD-L1+ increased from 0.02% to 1.3%.

Conclusion: Our pilot study of IT G100 demonstrates that it is well tolerated (with no CTCAE grade 3 AEs) and effective, with impressive local control of metastatic STS (93% control of disease at injected site and 1 patient with complete resolution of tumor). With or without radiation, G100 appears to shift the tumor microenvironment into a more inflammatory one, with significant infiltration of T cells. The increase in T cells after G100 alone is driven in large part by clonal expansion of pre-existing clones, as well as development of new clones, suggesting a tumor-specific response. By combining G100 with other modulators such as PD-1 blockade, there may be future opportunities to further enhance the adaptive anti-tumor response.

Poster 019 #2755143

FIRST-IN-CLASS SMALL MOLECULE INHIBITORS OF CD99 AS NOVEL THERAPEUTICS FOR EWING SARCOMA

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Objective: CD99 is a transmembrane cell surface protein that is highly expressed on Ewing Sarcoma (ES) cells, and used as a diagnostic marker. Earlier work demonstrated that CD99 blockage with antibodies inhibit ES growth and can also be used as a therapeutic target. We aimed to discover small molecules that can inhibit CD99 activity in ES cells.

Methods: We used surface plasmon resonance technology in a Biacore instrument to screen small molecules that can directly bind to purified extracellular domain of CD99 protein. Initial hits were then evaluated in secondary assays that involved cell viability (14 ES cells and 28

non-ES cells), CD99 dimerization, CD99 protein partner binding (IP-WB) and ES xenografts (3 ES lines).

Results: We identified two structurally similar FDA-approved nucleoside analogues, clofarabine and cladribine that selectively inhibited the growth of ES cells in a panel of 14 ES vs. 28 non-ES cell lines. Both drugs inhibited CD99 dimerization and its interaction with downstream signaling components cyclophilin A and PKA-RIIα as well as led to reduced ROCK2 expression and migration in ES cells. A membrane-impermeable analog of clofarabine showed similar cytotoxicity in culture, suggesting that it can function through inhibiting CD99 without any effect on DNA metabolism. Both drugs drastically inhibited anchorage-independent of growth of ES cells, but clofarabine was more effective in inhibiting ES xenografts.

Conclusion: Our findings suggest that clofarabine is a selective CD99 inhibitor and based on this novel molecular mechanism it is a good candidate for early phase clinical trials in children with ES.

Poster 020 #2763329

IMMUNE MONITORING IN PATIENTS WITH BONE AND SOFT TISSUE SARCOMA

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Objective: Sarcomas are very rare and biologically heterogeneous malignancies. As conventional chemotherapy has shown limited benefit in patients with bone and soft-tissue sarcoma (STS), a new therapy is needed. Recently, immunotherapy has received focus as a fourth treatment in some cancers. Therefore, in the present study, we investigated the effects of standard therapy (chemotherapy and surgical treatment) on immune cells in sarcoma patients to detect a new immune-related biomarker and to obtain a rationale supporting combination therapy including immunotherapy.

Methods: We conducted immune monitoring using the peripheral blood sample of advanced sarcoma patients who underwent surgery, preoperative chemotherapy or chemotherapy. After obtaining permission from our center's Institutional Review Board (IRB), eligible patients (at least 10 years of age with histologically proven sarcoma) were prospectively enrolled. We prospectively sampled blood at pre-treatment and after treatment in the course of clinical practice. We then analyzed 43 immune cell subsets (including T cell subset, B cell subsets, NK cell subsets and immune suppressor subsets) by multicolor-flow cytometry.

Results: Samples of 105 patients were analyzed. We divided the sarcoma patients into group 1 (intermediated and grade 1) and group 2 (grade 2 and 3) based on the FNCLCC grading system and compared the proportion of immune cell subsets between the two groups. In group 2 patients, the proportion of monocytic-myeloid-derived suppressor cells (MDSCs), myeloid dendritic cells (DCs) and plasmacytoid DCs was significantly higher at pre-treatment than after treatment (P=0.03, <0.01 and 0.04, respectively). On an examination of only the surgery cases (n=51), the proportion of CD8+ effector memory T cells (TEM) was significantly higher 1 month after therapeutic intervention than pre-surgery (P=0.01). In addition, among the chemotherapy cases, the numbers of monocytic-MDSCs were significantly lower after therapeutic intervention than pre-treatment (P=0.03).

Conclusion: These results suggested that the peripheral immune status might be correlated with the malignancy grade in sarcoma patients, and surgery and chemotherapy for these patients will strongly influence the tumor immunity. We are currently conducting an analysis using frozen samples and will investigate the relationship with the prognosis based on the clinical data.

Poster 021 #2803399

PHARMACOLOGICAL MODULATION OF DOG1 ACTIVITY AFFECTS CELL MIGRATION, INVASION AND METABOLISM IN GASTROINTESTINAL STROMAL TUMORS (GIST) IN VITRO

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Objective: The protein DOG1 (Discovered On GIST 1, gene code ANO1) is a Ca2+-activated Cl- channel (synonym TMEM16A, and Anoctamin 1). DOG1's high specificity for GIST has made the protein an important diagnostic marker for GIST. In other cancers, DOG1 has been implicated to affect migration and invasion, but also clinical outcome. The functional role of DOG1 in GIST is not completely understood.

Methods: Well-established cell lines with different mutational status (G48 and G882) shown to express DOG1 were used. To modulate channel activity two pharmacological drugs were used; T16-inh (DOG1 inhibitor, with previous data existing showing reduction of chloride currents), CaCC-inh A01 (DOG1 inhibitor) and E-act (DOG1 activator). Electrophysiological patch-clamp methods were used to verify the drugs effects on DOG1 currents. Scratch assay was used to assess cell's migratory capacity. An invasion assay consisting of a two-chamber

system were used to study invasion rate. To assess metabolic changes, a bioenergy system was used (Seahorse XF24). For all experiments, regular cell medium was used as a control.

Results: Patch-clamp experiments show a 78±5% reduction in DOG1-current in the presence of 30 mM CaCC-inh A01, and 167±24% activation following E-act (30 mM). E-act treated GIST cells showed an increased invasion and migration rate. Metabolic measurements revealed a decreased basal metabolism in T16-inh treated cells, while E-act treated cells showed a similar metabolic profile as the controls.

Conclusion: We show for the first time that DOG1-modulation affects migration and invasion rates in GIST cells in vitro. The effect is likely not dependent on cellular metabolic changes. Since DOG1 is highly expressed in more than 95% of all GISTs, modulation DOG1 could potentially serve as novel pharmaceutical target pathway in GIST.

Poster 022 #2769439

GENOMIC ANALYSIS OF A LONGITUDINAL SERIES OF SURGICAL PROSTATE CANCER BONE METASTASES AND XENOGRAFTS FROM THE SAME PATIENT REVEALED SELECTION OF A PROGRESSIVELY THERAPY RESISTANT METASTATIC CLONE

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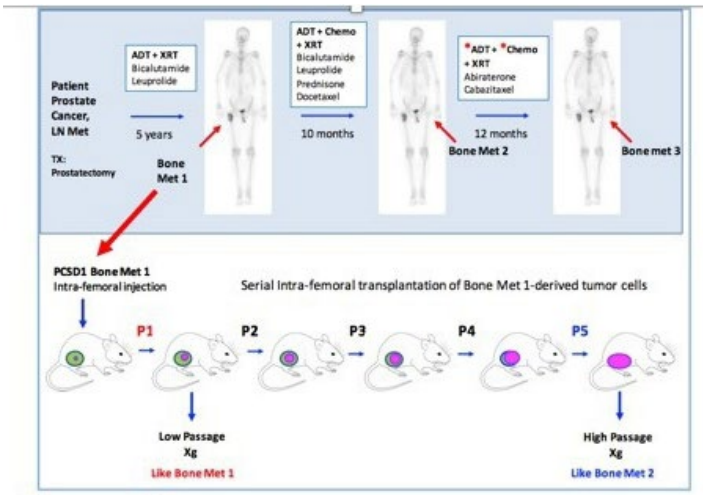
Objective: Prostate cancer metastasizes to bone in 50-90% of patients with advanced disease yet relatively little is known about genome-wide alterations in the prostate cancer bone metastases themselves. To understand the changes that occur that lead to therapy resistance in prostate cancer bone metastases we investigated the genomic variation in a longitudinal series of surgical bone metastasis samples and xenografts derived from the same patient.

Methods: We performed genomic analyses on a unique set of longitudinal samples from one patient including: blood (germ line), primary prostate tumor, surgical bone metastasis sample 1 (after ADT and radiation, right femur), bone metastasis 2 (after ADT, radiation and docetaxel, left femur), bone metastasis 3 (after abiraterone, radiation, plus cabazitaxel, left femur). We also performed these analyses on intra-femoral PCSD1 (Prostate Cancer San Diego 1) xenograft tumors generated from the same patient. DNA sequencing was performed using Roche Nimblegen V3, Affymetrix Oncoscan analysis was used to determine genome-wide CNV, transcriptome analysis was performed using Affymetrix GeneChip Human Transcriptome Array 2.0.

Results: Whole genome CNV analyses of patient bone metastasis sample 1 and low passage PCSD1 intra-femoral xenograft showed they were almost identical while patient bone metastasis samples 1 and 2 were significantly different. Surprisingly, patient bone metastasis sample 2 and high passage PCSD1 xenograft (derived from patient bone met sample 1) were very similar. WES analysis revealed germline alterations in DNA repair genes (BRCA2, ATM and CHEK2) in PCSD1 as well as tumor suppressor genes (TP53, PTEN) in all four PDXs. Phylogenetic tree analysis of WES supported the hypothesis that there was clonal selection in later bone metastases.



Xenografts PCSD1 mouse model

In one person, what genome changes led to progressive therapy resistance of prostate cancer bone metastases?

Serial surgical bone metastasis specimens

met1 > met2 > met3

Conclusion:

1. Aggressive sub-population of tumor cells pre-existed and was selected in bone over time in the treated patient and in serially passaged xenografts.
2. Clinical implication: early detection and targeted treatment of these lethal metastatic clones.

Conclusion: Comparison of genome-wide copy number variation (CNV), and whole exome sequencing (WES) revealed selection of a therapy-resistant sub-population - a metastatic clone - in both the patient bone metastases and in the xenograft, PCSD1, derived from the same patient (PDX). This is the first direct evidence that the therapy resistant sub-clone was already present in the heterogeneous early patient bone metastasis. We have used our new PDXs for the genomic characterization of the lethal metastatic clones in order to generate a multi-marker sig-

nature which may be used to detect and therapeutically target lethal metastases early in the disease.

Poster 023 #2772815

TELOMERASE-SPECIFIC ONCOLYTIC ADENOVIRUS ENHANCES RADIATION-INDUCED APOPTOSIS IN SOFT TISSUE SARCOMA CELLS BY ABLATING ANTI-APOPTIC MCL1 EXPRESSION

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Objective: Soft tissue sarcomas(STS) are mainly treated with surgical resection, radiotherapy and chemotherapy. In spite of the development of combined modality treatments in recent years, a significant proportion of patients with sarcomas respond poorly to adjuvant therapy, leading to local recurrence or distant metastasis. Therefore, novel therapeutic strategies for improvement of patient prognoses are urgently needed. We previously showed the therapeutic potential of OBP-301, a telomerase-specific oncolytic adenovirus, and OBP-702, a tumor suppressor p53-armed OBP-301 against human osteosarcoma(OS) and STS cells. Although OBP-301 enhanced irradiation-induced anti-tumor effect against human OS and STS cells in the preclinical settings, the radiosensitizing effect of OBP-702 remains obscure. In this study, we aimed to investigate the radiosensitizing effect of OBP-702 against human STS cells.

Methods: We used three human STS cell lines, HT1080 (fibrosarcoma), NMS-2 (malignant peripheral nerve sheath tumor), and SYO-1 (synovial sarcoma). Cells were irradiated 24 hours after infection with OBP-702, and cell viability was assessed by XTT assay 4 days after irradiation. Combined effect of radiation with OBP-702 was analyzed with the CalcuSyn software (BioSoft). These cells were also analyzed for apoptosis and DNA damage using Western blot analysis.

Results: While OBP-702 showed anti-tumor effect for STS cell lines, HT1080 and NMS-2 cells were highly resistant to radiation. When combined with radiation, OBP-702 enhanced the anti-tumor effect of radiation in all STS cell lines. The calculation of combination index demonstrated additive or synergistic anti-tumor effect in combination therapy. Further analysis revealed that OBP-702 enhanced radiation-induced apoptosis in STS cells. Notably, the radio-sensitizing effect of OBP-702 was associated with increase of p53 expression and interruption of anti-apoptotic myeloid cell leukemia 1 (MCL1) expression.

Conclusion: Our study suggested that OBP-702 had anti-tumor effect for STS cells, and increased the sensitivity of various types of STS cells to the cytotoxic effects of ionizing radiation. Currently, a clinical trial of OBP-301 in combination with radiotherapy is underway, and preclinically OBP-702 accumulates good therapeutic results in various tumor cells. Thus, OBP-702 would be a promising approach for enhancing STS treatment and provide a wide application of radiotherapy for localized as well as advanced STSs.

Poster 024 #2775866

ANTI-TUMOR EFFECTS OF ERIBULIN MESYLATE ON HUMAN CLEAR CELL SARCOMA CELL LINES

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Objective: Clear cell sarcoma (CCS) is an aggressive soft-tissue sarcoma and highly resistant to conventional chemotherapy and radiation therapy. CCS is defined by EWSR1-ATF1 fusion gene resulting from chromosomal translocation t(12;22) (q13;q12) and characterized by melanocytic differentiation. Eribulin mesylate (Eribulin) is a novel, non-taxane, synthetic microtubule inhibitor exhibiting antitumor activity in various tumors including soft-tissue sarcomas. The previous studies suggested that Eribulin induced cellular differentiation toward the adipocytes or smooth muscles in liposarcoma or leiomyosarcoma cell lines, respectively. In the present study, we investigated growth inhibition, melanocytic differentiation effects, and mechanism of action of Eribulin on four CCS cell lines.

Methods: We utilized four human CCS cell lines, Hewga-CCS, MP-CCS-SY, KAS and SU-CCS1. Hewga-CCS was established in our laboratory. We first examined effects of Eribulin on cell proliferation, cell cycle, apoptosis induction, and xenograft tumor growth in CCS cell lines. Next, we evaluated melanin synthesis, melanocytic differentiation markers including MITF, TYR, TRP1 and TRP2, and ERK1/2 phosphorylation status by immunoblot analysis in vitro and in vivo.

Results: Eribulin suppressed cell proliferation of all CCS cell lines in a dose-dependent manner (IC50: Hewga-CCS: 1.09nM, KAS: 1.21nM, MP-CCS-SY: 1.93nM, SU-CCS1: 2.05nM). By cell cycle analysis, 1nM of Eribulin exposure increased G2/M phase population and 10nM of Eribulin exposure increased sub-G1 phase population in all CCS cell lines. Cleavage of caspase-3 was dose-dependently expressed after Eribulin treatment by immunoblot analysis. Intriguingly, treatment with Eribulin upregulated melanin synthesis and melanocytic differentiation markers such as MITF, TYR, TRP1, and TRP2 in Hewga-CCS and MP-CCS-SY. Furthermore, Eribulin was shown to inhibit

phosphorylation of ERK1/2, while it was known that the activation of ERK1/2 phosphorylated MITF and caused ubiquitination and degradation of MITF. Consistently, in xenograft models Eribulin notably repressed CCS tumor growth and increased Fontana-Masson positive pigments indicating melanin synthesis.

Conclusion: Taken together, we first demonstrate that Eribulin has potent antitumor activity and promotes melanocytic differentiation via inhibition of ERK1/2 in CCS cell lines. Eribulin is a candidate to play therapeutic roles in targeting conditions affecting the melanocyte lineage in CCS.

Poster 025 #2787534

COMPUTATIONAL ANALYSIS OF THE IMMUNE LANDSCAPE OF GENETICALLY COMPLEX SARCOMA REVEALS NOVEL TUMOR-SPECIFIC DETERMINANTS OF IMMUNE INFILTRATION AND ACTIVITY

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Objective: Checkpoint blockade-based immunotherapy has shown early signals of activity in certain types of sarcoma, yet the determinants of activity in each sarcoma type and in individual patients are currently unknown. In other cancers, response to checkpoint blockade has correlated with several factors, including baseline leukocyte infiltration, mutational load, aneuploidy and expression of PD-L1. The objective of this study is to quantify the type and variation of immune infiltrates in genetically complex sarcoma and to identify mechanisms that lead to immune infiltration in sarcoma.

Methods: We analyzed the RNAseq data from 191 primary sarcoma samples (44 UPS, 17 MFS, 80 LMS, and 50 DDLS) in The Cancer Genome Atlas for the presence and constitution of immune infiltrate using the following bioinformatics tools: Estimate, Cytolytic index, Cibersort, MIXCR, vdjtools, and PVACSeq. Tumor samples were then clustered and differential gene expression and gene set enrichment analysis were used to identify genes and pathways that discriminated the immunologically distinct groups. Candidate genes were tested in an independent cohort of 17 UPS samples that were characterized immunologically by flow cytometry. The potential of these candidate pathways to determine the extent and activity of the tumor immune infiltrate is currently being tested in immune competent autochthonous murine models of UPS and LMS.

Results: Evidence of immune infiltrates were detected in each type of genetically complex sarcoma. The degree and cytolytic activity in each sarcoma correlated to the published response rates observed with immune checkpoint therapy. There was a predominance of M2-like macrophage activity across all sarcoma types. A subset of UPS had substantial clonal T-cell infiltrates. CD39, a metabolic regulator of cytotoxic T-cell activity, was found to be specifically expressed in non-infiltrated LMS samples. A second metabolic immune checkpoint, CD73, was expressed in a subset of UPS samples with low levels of immune infiltration. WNT/beta-catenin signaling was negatively correlated with general immune infiltration in all sarcoma types. We have validated the correlation between the presence of beta-catenin with immune phenotype by immunohistochemistry in our independent UPS cohort.

Conclusion: This study demonstrates the utility of bulk tumor RNAseq as an effective immunophenotyping assay. We have computationally identified both common and type-specific determinants of immune infiltration in a range of genetically complex sarcomas. We are currently testing the immunotherapeutic efficacy of modulating these pathways in mouse models. The analysis framework developed in this study will form the scientific rationale for future combination immunotherapy trials in sarcoma and enable the development of response biomarkers to immune checkpoint blockade.

Poster 026 #2791915

ANOIKIS RESISTANCE IN SARCOMA IS SUPPRESSED BY AN E-CADHERIN/TBX2/CREB GENE REGULATORY NETWORK

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Objective: Sarcomas are highly aggressive cancers that arise from tissues of a mesenchymal lineage, such as the bone and muscle. Interestingly, despite their mesenchymal lineage, a subset of sarcomas expresses biomarkers consistent with a more epithelial phenotype. One of these epithelial biomarkers in human sarcomas is the cell-cell adhesion molecule, E-cadherin. Interestingly, E-cadherin expression is prognostic for better overall survival in sarcoma patients. However, the mechanism by which E-cadherin acts as a tumor suppressor in sarcomas is unknown. This study strives to understand the mechanistic underpinnings through which E-cadherin inhibits sarcoma

aggressiveness.

Methods: We created sarcoma cell lines that ectopically over-expressed E-cadherin. Migration and invasion were assayed in cells expressing an empty vector or E-cadherin using scratch wound assays and Boyden chamber assays, respectively. Soft agar assays were used to determine changes in anchorage-independent growth. Si-RNA mediated knockdown, RT-qPCR and western blotting were performed to examine how E-cadherin modulated down-stream effectors to determine aggressiveness.

Results: E-cadherin is an epithelial driver in carcinomas. Therefore, we hypothesized that E-cadherin would convert sarcomas to a more epithelial-like state, thereby making them less invasive and metastatic. However, contrary to our hypothesis, E-cadherin had no effect on the expression of mesenchymal biomarkers, migration, or invasion. Instead, E-cadherin significantly reduced anoikis resistance. Furthermore, transcription factors TBX2 and CREB were down-regulated upon E-cadherin expression. TBX2 or CREB knockdown phenocopied the effect of E-cadherin expression on anoikis resistance. Furthermore, knockdown of TBX2 phenocopied the downregulation of CREB by E-cadherin, suggesting that E-cadherin acts, at least in part, through TBX2 and CREB to suppress anoikis resistance in sarcomas.

Conclusion: We identified an E-cadherin/TBX2/CREB axis that controls sarcoma anoikis resistance and aggressiveness. This axis acts independently of canonical epithelial-mesenchymal transition pathways. Our work highlights potential key-effectors in this pathway that can be targeted to reduce sarcoma aggressiveness and improve clinical outcomes.

Poster 027 #2804619

ARGININE DEPRIVATION ALTERS GLOBAL LIPID METABOLISM IN ASS1 DEFICIENT SARCOMAS

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Objective: Argininosuccinate Synthetase 1 (ASS1) is silenced in ~90% of sarcomas. This deficiency in the urea cycle causes sarcomas to become dependent on extracellular arginine for continued cell growth and survival, a condition named arginine auxotrophy. Arginine starvation induced by pegylated arginine deiminase (ADI-PEG20) induces dramatic alterations in global metabolism as well as an induction of autophagy. We investigated the specific changes in the lipidome of leiomyosarcoma cell lines induced by ADI-PEG20. By examining the alterations in esterified and non-esterified fatty acid metabolism, we sought to understand the changes in the lipidome that are capable of being therapeutically exploited.

Methods: The cell lines SKLMS1 and SKUT1 were treated with ADI-PEG20. Cell pellets were collected, and 33 esterified and non-esterified fatty acids were measured using GC/MS. Pathway analysis was then performed. Cell lines were then treated with a combination of ADI-PEG20 and perhexiline (beta-oxidation inhibitor) to determine synthetic lethality.

Results: There were clear alterations in lipid metabolism induced by arginine deprivation. The fluctuations in lipid metabolism indicated pathways susceptible to inhibition by a variety of small molecule inhibitors, namely that arginine deprivation sensitizes to inhibition of beta-oxidation. Cell culture experiments with ADI-PEG20 and a number of different small molecule inhibitors demonstrated synthetic lethality upon co-treatment with ADI-PEG20 and a beta-oxidation inhibitor.

Conclusion: Arginine deprivation causes global changes in lipid metabolism. The changes in metabolism are capable of being targeted by small molecule inhibitors with the result being an induction of a synthetic lethality. By understanding the changes in the lipidome induced by arginine deprivation, we are building a multi-agent synthetic lethal therapy for sarcoma based on metabolism that avoids chemotherapy.

Poster 028 #2804808

INHIBITION OF OSTEOBLAST DIFFERENTIATION BY BIGH3/TGFBI PROMOTES OSTEOLOYSIS IN RENAL CELL CARCINOMA BONE METASTASIS

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Objective: Bone metastasis from renal cell carcinoma (RCC) has a unique osteolytic phenotype that is resistant to pharmaceutical treatment. After forming, there is a high incidence of pathologic fractures. Current therapies that target osteoclast activity in attempting to limit osteolysis have been inadequate. Understanding the molecular mechanisms will identify strategies that are more effective. An alternative and unexplored possibility for producing osteolysis in bone metastasis is osteoblast inhibition. Our central hypothesis is that factors secreted in the bone microenvironment by metastatic renal cell carcinoma cells inhibit bone formation, tilting homeostasis towards osteolysis (Figure 1). In this mechanism the osteoblast plays a central role. The objective of our study is to characterize the effect of BIGH3, secreted by metastatic RCC cells, on the osteolytic phenotype of bone metastasis.

Methods: We used a SCID mouse RCC xenograft model and in vitro co-culture studies with osteoblast cell lines. We tested multiple RCC cell lines, but focussed on those that produce osteolytic bone metastases. The clear cell RCC cell line, 786-O Bo consistently creates osteolytic metastasis. BIGH3 was then knocked down in 786-O Bo

cell lines using shRNA, which were then evaluated for osteoblast inhibitory effects in 3D co-culture; and for osteolytic metastasis formation via injection in SCID mice femora.

Results: The bone homing cell line (786-O Bo) was used to create a xenograft mouse model for osteolytic metastasis. In vitro, conditioned medium from these cells inhibited primary mouse osteoblast (PMO) differentiation and mineralization, as demonstrated by decreased alkaline phosphatase activity and staining; decreased osteocalcin expression; and decreased mineralization. Proteomic analysis of secreted factors from concentrated conditioned medium of 786-O Bo cells showed that BIGH3/TGFBI, a 68 kDa protein involved in tumorigenesis, was secreted at high levels. Purified BIGH3/TGFBI also was shown to inhibit PMO differentiation and mineralization. Next, BIGH3 knockdown 786-O Bo cell lines were created and tested. Conditioned medium from knockdown cell lines did not inhibit alaline phosphatase activity or osteocalcin expression. In our mouse xenograft model osteolytic bone metastasis formation was decreased with knockdown cell lines in comparison with controls (Figure 2).

Conclusion: BIGH3 is highly secreted by the bone metastastic kidney cancer cell line, 786-O Bo. BIGH3 appears to act on osteoblasts in the bone microenvironment, and specifically inhibits bone formation. Moreover, BIGH3 secretion promotes the formation of osteolytic bone metastasis. This mechanism has not been previously explored, but may play a significant role in metastatic disease by tilting bone homeostasis towards bone lysis, and may be a good target for improving the treatment of osteolytic bone metastasis.

Poster 029 #2740356

EXPRESSION AND THERAPEUTIC POTENTIAL OF SOX9 IN CHORDOMA

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Objective: Chordoma is a rare cancer and accounts for 1-4% of all bone malignancies. Conventional chemotherapeutic agents are ineffective in the treatment of chordoma, hence its reputation of resistance. Aberrant expression and activation of sex-determining region Y (SRY)-box 9 protein (SOX9) is associated with the growth and survival of a diverse and expansive list of cancer cell types. However, the role of SOX9 in chordoma remains unknown.

Methods: We examined the expression of SOX9 in chordoma patient tissues. We also evaluated the function of SOX9 in the proliferation and motility of chordoma cells. In addition, we determined the effect of the combination of chemotherapy agents with inhibition of SOX9 on chordoma cells.

Results: Tissue microarray and immunohistochemistry analysis showed that higher expression levels of SOX9 correlated with poor prognosis. RNA interference (RNAi)-mediated knockdown of SOX9 inhibited chordoma cell growth, decreased cell motility, and induced apoptosis as well as cell cycle arrest. Moreover, the combination of SOX9 inhibition and chemotherapeutic drugs had an anti-cancer effect on chordoma cells.

Conclusion: These findings suggest that SOX9 is a critical component of chordoma cell growth and could be a promising therapeutic target for treatment.

Poster 030 #2784716

INDOLE-3-CARBINOL (I3C) ENHANCES EFFICACY OF GEMCITABINE IN LEIOMYOSARCOMA

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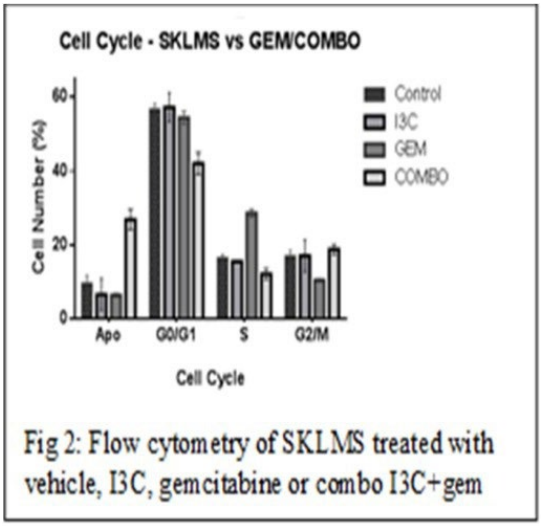
Objective: Adjuvant Gemcitabine have recently been shown to improve progression free survival in some types of leiomyosarcoma. Adequate cellular uptake of the drug remains a challenge. We aimed to evaluate the role of nucleoside transporter activator (I3C) in increasing the in vitro efficacy of gemcitabine in the treatment of leimyosarcoma.

Methods: Leiomyosarcoma cells (SKLMS) were incubated with DMEM+10% FBS + 1% Antibiotics. Dose response curves were generated for gemcitabine and I3C to identify the IC-50 values. Triplicates of cells were then plated in 96 well plates (3000 cells/well) and allowed to adhere. The adherent cells were further treated with gemcitabine in the presence or absence of I3C and compared with controls (DMSO treatment). MTS cell viability assays were done and absorbance was monitored in a micro-plate reader. Flow cytometry was performed with Propidium Iodide (PI) staining. Scratch assays were done to assess cell migration.

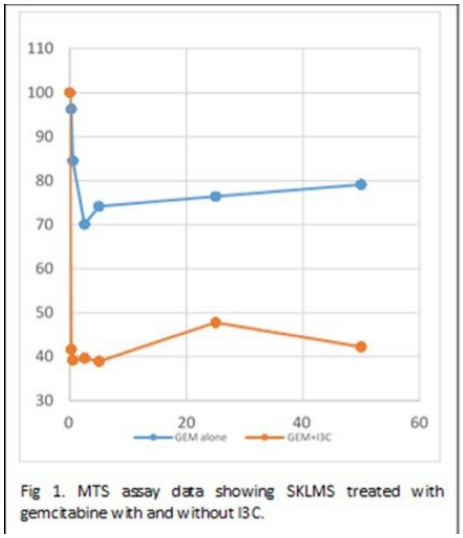
Results: Viability assay showed significant increase in the cytotoxicity of gemcitabine in presence of I3C compared to controls. Flow cytometry data showed gemcitabine alone treatment has arrested the cell cycle at G0/G1 phase without increase of cell death. On the contrary, use of gemcitabine in combination with I3C increased the cell death by at least three folds compared to control as well as gemcitabine alone treated cell population. Scratch assay over a 16 hour period showed that the rate of cellular migration significantly dropped by 1.5 folds upon treatment with gemcitabine combined with I3C compared to gemcitabine alone.

Conclusion: The use of I3C enhanced cellular uptake and cytotoxicity of gemcitabine in SKLMS cells. Further

studies are warranted and underway to elaborate on intracellular mechanisms of action to optimize the use of I3C as a potential adjunct in preclinical and clinical leiomyosarcoma treatment.



Flow cytometry of SKLMS treated with vehicle, I3C, Gemcitabine and combo I3C+Gemcitabine.



MTS Assay data showing SKLMS treated with gemcitabine with and without I3C

Poster 031 #2791630

CHANGES IN SERUM TH1 CYTOKINE EXPRESSION, NOT BASELINE EXPRESSION, PREDICT METASTASIS IN SOFT TISSUE SARCOMA PATIENTS WITH LOCALIZED DISEASE

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Objective: With the expanding use of immunotherapy for cancer therapy, there is a growing need for biomarkers of response and prognosis. The objective of the current study was to determine the prognostic and predictive value of serum cytokine expression during neoadjuvant treatment for localized soft tissue sarcoma (STS).

Methods: From 7/2009 to 11/2011, eight patients (Cohort 1) were enrolled in a phase I clinical trial (NCT00864032) of neoadjuvant radiotherapy plus sorafenib. Th1 cytokines were measured before and after therapy. From 3/2013 to 2/2015, 33 patients (Cohort 2) with suspicious soft tissue tumors undergoing upfront surgery underwent cytokine measurements. Cytokine levels were analyzed to predict risk of STS, grade, and oncologic outcome.

Results: Among cohort 1, we enrolled 8 patients (5 female, median age 44, 3 liposarcoma, 3 high grade pleomorphic, 2 other). Median tumor size was 16 cm, and all tumors were lower extremity. Median follow-up was 56 months with 5 metastases. Comparing patients who remained metastasis-free to those who did not, IFN-γ increased during neoadjuvant therapy (25.9±12.7 to 44.3±13.4 pg/mL versus 9.4±9.2 to 5.1±4.8 pg/mL, P=0.05), TNF-α increased (4.8±2.2 to 10.2±4.9 pg/mL versus 6.8±4.0 to 5.5±3.2, P=0.002), and IL-6 was unchanged (undetectable before/after versus 9.5±8.2 to 75.7±122.8, P<0.001). There were no significant differences in IL-2 levels between metastatic and non-metastatic patients (Figure 1). Among cohort 2, there were 17 females with a mean age of 57. There were five benign tumors, 16 low grade STS (13 liposarcoma, 2 leiomyosarcoma, 1 chondrosarcoma), and 12 high grade STS (5 liposarcoma, 4 leiomyosarcoma, 1 angiosarcoma, 1 undifferentiated pleomorphic, 1 synovial). In cohort 2, there were no significant differences in baseline cytokine levels between benign and malignant or between low grade and high grade STS. Among STS patients in cohort 2, there were no significant differences in baseline cytokine levels between patients who developed metastases and those who did not with

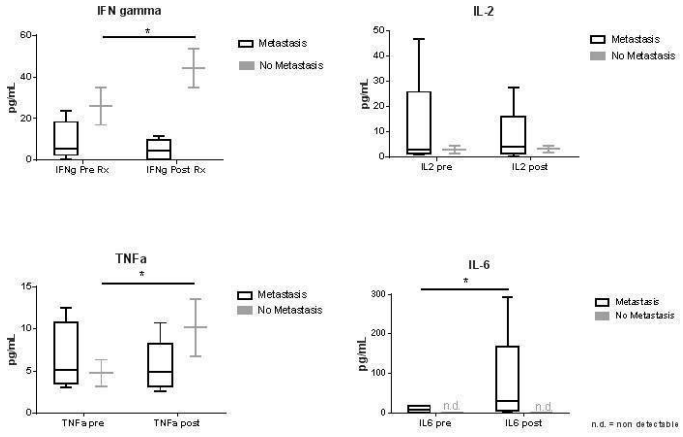

Figure: Serum Th1 cytokines pre- and post-neoadjuvant radiotherapy and sorafenib in STS patients with locally advanced disease. Comparing patients who remained metastasis-free (gray) to those who developed metastasis (black), IFN-gamma increased significantly, TNF-alpha increased significantly, and IL-6 was unchanged. There were no significant differences in IL-2 levels before/after treatment between metastatic and non-metastatic patients.

the exception of IFN-g which was significantly higher in non metastatic STS (mean ± SD: 125 ± 216 vs 14 ± 16 pg/mL; P= 0.05).

Conclusion: In these select STS patients, changes in serum Th1 cytokine levels during neoadjuvant therapy were predictive of subsequent oncologic outcome, while baseline levels were not. If validated, serial measurement of Th1 cytokines may identify important immune biomarkers for predicting response to combined modality therapy in STS patients.

Poster 032 #2740908

CLUSTERING OF 22Q12 DELETIONS IN A SUBSET OF OSTEOBLASTOMA

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Objective: Osteoblastoma is a rare benign bone-forming tumor that most commonly affects children and young adults in the age range 10-30 years. When resected with free margins recurrences are uncommon and the prognosis is excellent. Genetic studies of osteoblastoma have revealed few acquired chromosomal aberrations. In a subset of osteoblastomas, we have previously found recurrent deletions affecting parts of chromosome 22. In the present study, we aimed to determine the prevalence of chromosome 22 alterations in osteoblastoma and identify the target gene/s of these mutations.

Methods: Fresh frozen tumor biopsies were available for 18 osteoblastomas, which had not previously been analyzed using high-coverage genome analyses. Whole-genome DNA copy number alterations were investigated in all of them (Cytoscan HD arrays, Thermo Fischer Scientific). For nine of the tumors, high-quality RNA was obtained and global gene expression analysis was performed using RNA sequencing (TruSeq, Illumina).

Results: Acquired DNA copy number alterations were detected in 5 of 18 osteoblastomas. Three of them displayed losses of large parts of chromosome arm 6q, with two of them also harboring homozygous deletions affecting parts of chromosome 22, including the genes ZNRF3 and NF2. RNA data was available for one of the tumors with homozygous deletions. In this case, the deletions were associated with a low gene expression level of NF2.

Conclusion: Less than one-third of the analyzed osteoblastomas showed acquired chromosomal imbalances. The detected alterations were most commonly losses affecting parts of chromosomes 6 and 22. Combined with previously published cases, we have found complete or partial deletions of chromosome arm 6q in five osteoblastomas. Four of these showed additional homo- or hemizygous deletions in chromosome band 22q12. Further analyses are currently ongoing to identify the target gene in 22q12.

Poster 033 #2776792

ELEPHANT P53 (EP53) ENHANCES AND RESTORES P53-MEDIATED APOPTOSIS IN SARCOMA

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Objective: Amplification of elephant p53 (EP53) was recently described as a potential mechanism for cancer resistance in elephants, with increased apoptosis in elephant versus human cells. Osteosarcoma and Ewing sarcoma (ES) are the most common pediatric bone tumors. Osteosarcoma contains a very high rate of TP53 alterations leading to genomic instability, while TP53 alterations in ES are infrequent but associated with poor prognosis. We sought to determine if EP53 protein expression could enhance and/or restore p53 function to trigger p53-mediated sarcoma cell death as a potential future therapeutic.

Methods: We expressed various EP53 proteins in canine and human osteosarcoma cell lines (OSCA-40, U-2 OS, Saos-2) and ES cell lines (A673, CHLA-9, CHLA-10) by transfection or viral transduction. Expression of EP53 was confirmed by western blot. Apoptosis of cells transfected/transduced with EP53 was compared to cells transfected/transduced with negative control vectors. Apoptosis was measured by fluorescence microscopy and caspase activity. As an additional measure of enhanced p53 function in ES cells post-EP53 transfection, DNA damage was induced with ionizing radiation (5 Gy) as an additional measure of EP53 function and response in ES cells. DNA damage and repair was measured by counting gamma-H2AX foci over time.

Results: We observed a significant increase ($p<0.001$) in caspase activity (normalized to cell viability) of U-2 OS (TP53-wild type) and Saos-2 (TP53-null) human osteosarcoma cells expressing EP53 protein compared to

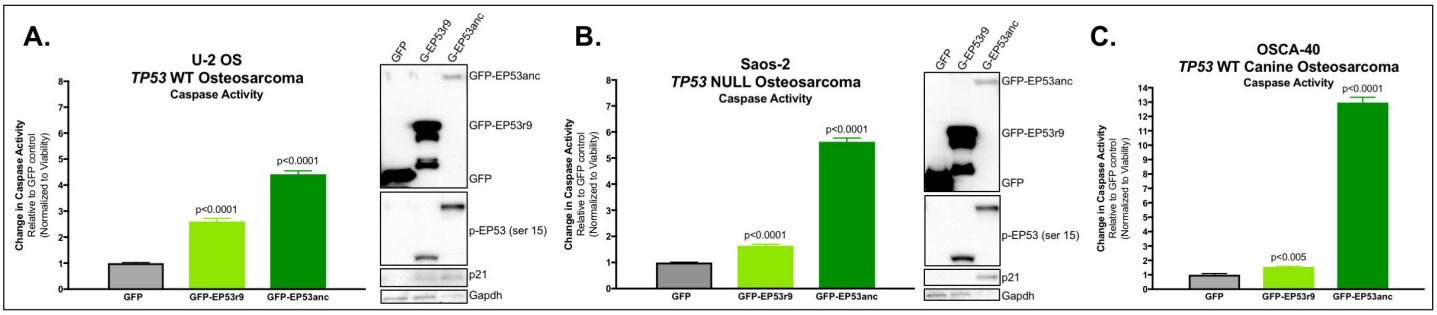

Figure 1: EP53 increases apoptosis in human and canine OS cells in the presence and absence of endogenous wild type p53 expression. A, Caspase activity and EP53 protein expression in human TP53 wild type (WT) OS cell line, U-2 OS. B, Caspase activity and EP53 protein expression in human TP53 null OS cell line, Saos-2. C, Caspase activity in canine TP53 WT OS cell line, OSCA-40. G = GFP; G-EP53r9 = GFP-EP53-retro9; G-EP53-anc = GFP-EP53-anc.

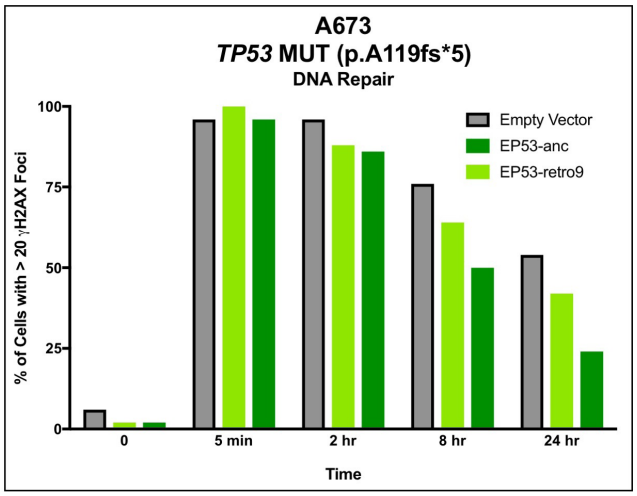

Figure 2: EP53 increases the rate of DNA damage repair in TP53 mutant (MUT) ES cells. Following transduction to induce expression of EP53, A673 cells were treated with 5 Gy ionizing radiation, and DNA damage was measured over time. Empty vector transduced cells were included as a negative control.

negative control cells (Fig 1A-B). Canine osteosarcoma cell line, OSCA-40 (TP53-wild type), also underwent significantly more apoptosis ($p<0.005$) with EP53 expression (Fig 1C). ES cells (TP53-wild type: CHLA-9, TP53-mutant: CHLA-10, and TP53-mutant: A673) underwent apoptosis as visualized by microscopy. Experiments to confirm these results with caspase activity assays are underway. EP53 expression in A673 cells increased the rate of DNA damage repair (Fig 2).

Conclusion: These data suggest that EP53 can function in both osteosarcoma and ES cells to promote cell death. Results with ES cell line A673 suggest that EP53 can rescue deficient DNA damage repair in TP53-mutant cells (in addition to inducing apoptosis). Efforts to define the mechanism of action of EP53 in osteosarcoma and ES cells are ongoing. We are expanding in vitro experiments to include rhabdomyosarcoma, PMNSTs, and rhabdoid tumors. Our results support further exploration of EP53-based sarcoma clinical therapeutics for both humans and dogs.

– CHONDROSARCOMA –

Poster 034 #2804197

METABOLOMIC PROFILING REVEALS ELEVATED LEVELS OF FATTY ACIDS IN ISOCITRATE DEHYDROGENASE (IDH) MUTANT CHONDROSARCOMAS

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Objective: A majority of chondrosarcomas harbor somatic mutations in the isocitrate dehydrogenase genes (IDH1 and IDH2). These mutation result in the loss of the IDH enzyme to catalyze conversion of isocitrate to alpha-ketoglutarate (alpha-KG) in the citric acid cycle (TCA) and instead there is excess accumulation of oncometabolite, D-2-hydroxyglutarate (D-2HG). It has been shown in vivo that mutant IDH1 or D-2HG inhibits growth-plate chondrocyte differentiation, driving enchondromatosis, the benign precursor to malignant chondrosarcomas (Makoto et al., PNAS, 2015). Due to these findings, it has been predicted that chondrosarcomas harboring IDH1/2 mutations may display various other alterations in cellular metabolomics compared to tumors without these mutations. Here we performed metabolomic profiling of wildtype and mutant IDH1 chondrosarcomas to uncover large scale metabolic differences.

Methods: With institutional review board (IRB) approval, human chondrosarcoma tumor samples were obtained fresh from surgery. Tumors were implanted in interleukin-2 receptor gamma chain (gamma)-null NOD/SCID (NSG) mice and excised once tumor capacity size was reached. Xenograft tissues were pulverized, weighed, and homog-

enized to prepare for metabolomic analysis. Gas chromatography/mass spectrometry-based metabolic profiling was performed to identify levels of fatty acid species (acylcarnitines) in each sample group. Wildtype and IDH1 mutant tumor groups contained 4 samples each. Metabolite data was normalized to DNA content from each tumor sample and data analysis was performed using Student's t-test ($p<0.05$).

Results: Data analysis of the acylcarnitine panel revealed several long chain fatty acids to be significantly elevated ($p<0.05$) in IDH1 mutant tumors compared to wildtype tumors. Palmitate (16:0) was found in a 3.2-fold increase in IDH1 mutant tissue, hydroxypalmitate (C16:1-OH/C14:1-DC) had a 2.3-fold increase, oleate (C18:1) experienced a 5-fold increase, and stearate (C18:0) and linoleate (C18:2) ($p=0.08$) both experienced a 4-fold increase.

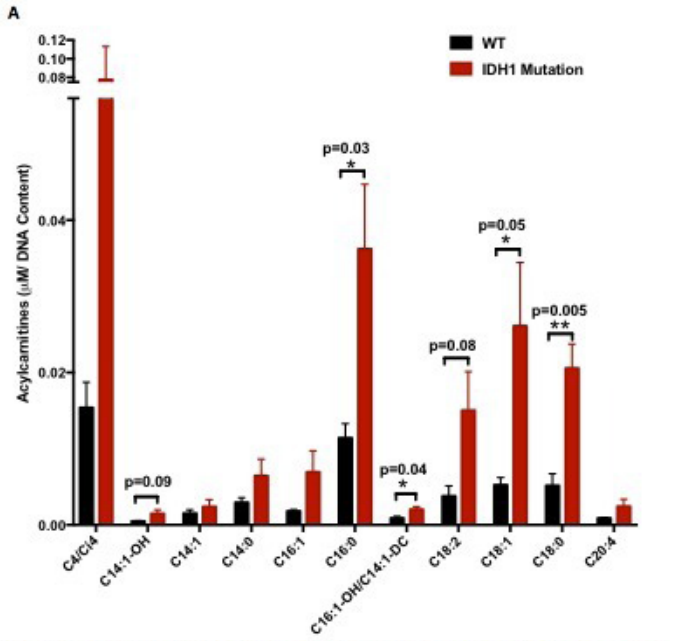

Figure A: IDH1 Mutant Xenograft Chondrosarcoma Tissues Display Elevated Acylcarnitines. Acylcarnitine levels in homogenized tumor samples. Data represents means ± SEM from 4 tumors in WT and IDH1 Mutation groups.

Conclusion: This data suggests that palmitate, hydroxypalmitate, linoleate, oleate, and stearate were the most elevated fatty acids in IDH1 mutant xenograft chondrosarcomas compared to wildtype tumors. These exact fatty acid species have been previously attributed to incomplete fatty acid oxidation, causing lipid-induced mitochondrial stress (Koves et al., Cell Metabolism, 2008). The possibility that IDH1 mutant tumors could exhibit a similar metabolic perturbation warrants further investigation as this may help elucidate key biochemical pathways and oncometabolites involved in chondrosarcoma formation and progression.

Poster 035 #2804860

LARYNGEAL CHONDROSARCOMA: A RETROSPECTIVE ANALYSIS OF A LARGE SERIES TREATED AT A SINGLE INSTITUTION

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Objective: Laryngeal chondrosarcoma is very rare bone sarcoma that accounts for only 1% of all laryngeal neoplasms and has only been previously reported as case reports or in small series. We present our results of 18 patients treated at a single institution to gain insights on treatment outcomes after definitive therapy.

Methods: Electronic and paper medical records were reviewed retrospectively for patients with laryngeal chondrosarcoma that was diagnosed by pathology, and treated at our institution between 1960 and 2016. Under IRB approval, information was collected on patient history, clinical and pathologic features, treatment details, oncologic outcome, and toxicity. Overall survival (OS) and local control (LC) were estimated using the Kaplan-Meier method.

Results: Eighteen cases were identified from a total of 1255 chondrosarcomas. All had non-metastatic disease. There were 9 male and 9 female with median age of 63 y (range: 40-78). Two patients had prior heavy consumption of alcohol, 7 ever smoked, and no patients had a prior history of radiation exposure. Patients presented with dyspnea (9), hoarseness (8), cough (4), dysphonia (2), dysphagia (2), hemoptysis (1), or throat pain (1). All cases originated from the cricoid cartilage, with the involvement tracheal cartilage in 2 cases. Two cases showed myxoid differentiation, while the remaining 16 were all conventional hyaline type chondrosarcomas. Low-grade tumors (13) were most common, while moderate- and high-grade ones (4 and 1 respectively) were less commonly seen. Median tumor size was 3.25 cm (range: 2-6.3). Treatment consisted of surgery alone (17) and post-operative RT with 3D photons of 72 Gy (1). Surgical types included partial laryngectomy (8), laryngofissure (6), near-total laryngectomy (1), and transoral laser resection (1), with 2 cases of unknown type. No patient received chemotherapy.

After a median follow-up of 105 months (range: 1-584), the 10-year OS is 78% and median OS is 261.7 months (95% CI: 123.0-400.4). The 10-year LC is 63%, median is 146.2 months (95% CI: 9.4-283.0). No patient ever had regional lymph node involvement or distant metastasis, or died from chondrosarcoma. Compared with laryngofissure (5 local recurrences), laryngectomy (2 local recurrences) achieved better LC (Log rank $p=0.049$). The most common toxicity was laryngeal/tracheal stenosis/obstruction (5), all seen in cases that received laryngectomy with negative gross margin ($p=0.031$).

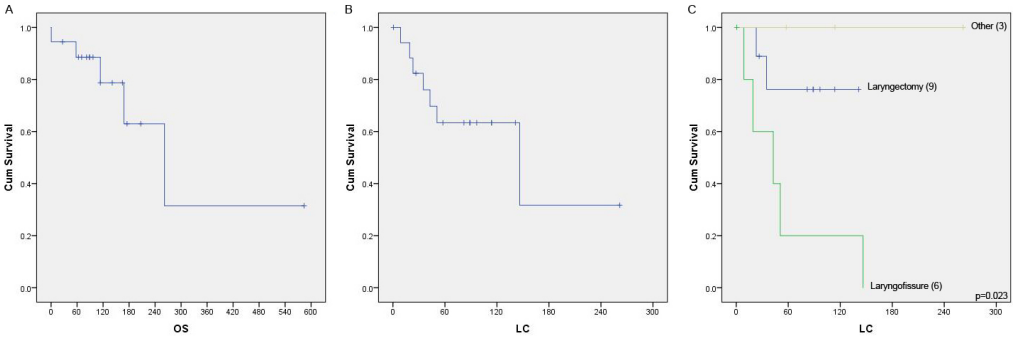

Fig 1. Kaplan-Meier curves of overall survival (A), local control (B), and local control by surgical type (C).

Conclusion: In this single institution series, laryngeal chondrosarcoma is a very rare tumor with favorable prognosis. Attempt to achieve wide resection should be cautious with the preservation of function and possibility of future recurrence and laryngeal/tracheal stenosis.

Poster 036 #2804450

ASSESSMENT OF NEXT GENERATION SEQUENCING (NGS) FOR PATIENTS WITH CHONDROSARCOMA

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Objective: The application of next generation sequencing (NGS) based molecular testing in chondrosarcoma is undefined. We report the results of NGS in a large cohort of chondrosarcoma patients (pts).

Methods: This is a retrospective study of chondrosarcoma pts at UT MD Anderson Cancer Center that underwent NGS using several CLIA-certified platforms (multigene PCR, targeted gene panels ranging from 46 to 405-genes). Our aim was to identify genomic alterations and to evaluate the utility of matching pts with actionable gene alterations onto targeted therapies through clinical trials or commercially available therapeutics. A companion non-CLIA 200-gene panel (T200) was performed for exploratory purposes. Analytical plan included descriptive statistics and survival analysis (Kaplan-Meier method). Bioinformatics analysis was performed with R-based software.

Results: Of 82 pts tested, 69 yielded results (Table 1). Alterations were noted in 61 pts and 60 had mutations on CLIA testing panels. A median of 2 mutations/patient (m/p) was detected (0 – 36). The T200 was performed on 10 pts with a median of 6.5 m/p (1 – 54). Sources of testing included primary tumor (n=44), metastasis (n=29), locally recurrent tumor (n=10), and plasma (n=6). A total of 528 somatic mutations and 356 copy number alterations (CNA) were detected (Figure 1). Missense mutations (n=465) were the common form of mutation. The most common mutations involved TP53 in 23/54 (43%) and IDH1 in 18/54 (33%); both were specific to conventional & dedifferentiated subtypes. The only recurrent mutations for clear cell chondrosarcomas were GNAS and LRP1B, and TSC1 for mesenchymal chondrosarcoma. The most common CNA included CDKN2A/B loss in 10 pts,

Clinical Characteristics

N (with test pass)	69 (100%)
Age, median (range)	48 years (7 - 78)
Gender	
Male : Female	39 (57) : 30 (43)
Vital Status	
Alive : Dead	36 (52) : 33 (48)
Overall Survival (months)	
Entire Cohort, median (range)	92.5 (2.5 - 286.2)
Conventional (n = 37)	92.5 (2.5 - 286.2)
Dedifferentiated (n = 22)	18.8 (5.4 - 48)
Mesenchymal (n = 6)	Undefined (14.6 - 111.1)
Clear Cell (n = 4)	173.9 (72.4 - 175.5)
Primary Site	
Extremities	26 (37.7)
Ribs/Chest Wall	19 (27.5)
Pelvis	16 (23.2)
Other (Spine & Craniofacial)	8 (11.6)
Primary Tumor Size (cm)	
Median (range)	8.4 (1.7 - 34)
Current Stage of Disease	
I & II	1 (1.4)
IV	55 (80)
Locally recurrent disease	6 (8.6)
No evidence of disease	7 (10)

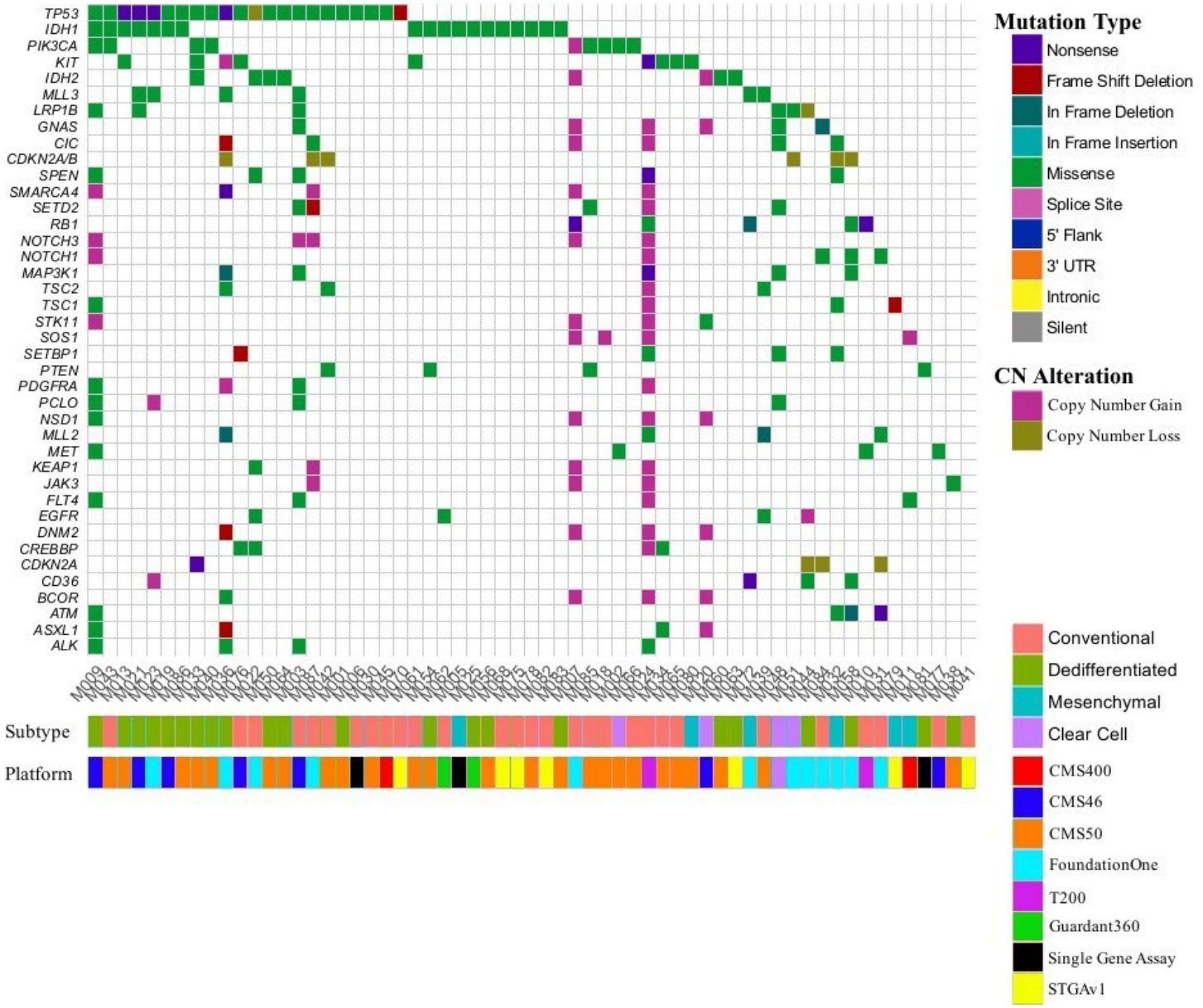

Figure 1: Genomic Landscape Plot (alterations with frequency of 2 or more were included)

NOTCH3 amplifications (amp) in 5 pts, SMARCA4 amp in 4 pts, and SOS1 amp in 4 pts. 22% (15/69) pts received genomically-matched (ATM, CDKN2A, IDH1, IDH2, PIK-3CA, PTCH1, PTEN, SMO, TP53) therapies with only 2 off protocol. No responses were noted but 33% (5/15) pts had SD and 4 had a PFS ratio >1.3 (range, 2.1 – 9). From a prognostic standpoint, only IDH2 mutations (median OS: 11.9 months for m-IDH2 vs 52.7 months for wt-IDH2; P<0.0001) and IDH1 mutations + TP53 mutations (median OS: 12 months for m-IDH1 + m-TP53 vs 145.7 months for m-IDH1 + wt-TP53; P=0.04) were associated with inferior OS.

Conclusion: Clinical genomic testing is a useful tool for genomic discovery, & recruitment onto targeted therapeutic trials. Correlations with specific mutational events and survival warrant further study.

Poster 037 #2774628

RESULTS OF SURGICAL TREATMENT OF LOW-GRADE CHONDROSARCOMA INVOLVING THE APPENDICULAR SKELETON: A SINGLE INSTITUTION EXPERIENCE WITH MINIMUM 10-YEAR FOLLOW UP

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Objective: The aim of this study was to assess the long-term results of Intralesional procedures versus wide local surgical resection for low-grade chondrosarcoma of long bones, in terms of oncologic (local recurrence, metastases) and functional (MSTS scores) outcomes.

Methods: Using an institutional musculoskeletal oncologic database we retrospectively reviewed medical records

of 45 patients with low grade chondrosarcoma of the appendicular skeleton, that underwent surgical treatment between 1985 to 2007. The final cohort was further narrowed down to 17 patients (18 tumors), 11 females and 6 males, that had at least ten years of clinical and radiologic follow-up.

Results: Of the 18 tumors, 9 were treated with intralesional procedures (4 with no adjuvant, 3 with additional phenol, 1 with liquid nitrogen and one with H202) with either bone graft or cement augmentation, while 9 others were treated with wide local excision and reconstruction with intercalary/osteoarticular allograft or megaprosthesis. There was a mean follow-up of 13.5 years in the intralesional cohort (range, 10-19 years) and 15.9 years in the wide local excision cohort (range, 10-28 years, p=0.36). Tumor size varied significantly between groups and was larger in patients treated with wide local excision (8.2±3.1cm versus 5.4±1.2cm, at the greatest dimension, p=0.021). There were two local recurrences, one in the intralesional group and one in the wide local excision group, occurring at 3.5 months and 2.9 years, respectively, and both required revision. No further local recurrences could be detected with long term follow up. The MSTS score at final follow-up was significantly higher for patients managed with intralesional procedures (28.7 ± 1.7 versus 25.7 ±3.4, p=0.033). There were less complications requiring reoperation in the intralesional group compared with the wide local excision group, although this difference was not found to be statistically significant (one versus four patients, respectively; p=0.3).

Conclusion: Low-grade chondrosarcoma can be safely treated, when appropriate, with intralesional procedures with good oncological outcomes, excellent functional outcomes and a relatively low rate of postsurgical complications. In our series, the local recurrences detected were diagnosed relatively early following the index procedure, and none were detected in the late post-operative period.

Poster 038 #2771476

RISK FACTORS FOR LOCAL RECURRENCE FROM ATYPICAL CARTILAGINOUS TUMOUR AND ENCHONFROMA OF THE LONG BONES

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Objective: The purpose of our study is to verify possible clinical and radiological findings with regard to distinguishing enchondroma from atypical cartilaginous tumour (ACT). In addition, this study determined risk factors that are associated with local recurrence of enchondroma or ACT treated with curettage.

Methods: We retrospectively reviewed the records of 54 patients with enchondroma and 35 patients with ACT of the long bones treated by curettage between 1986 and 2015. The minimum follow-up was 18 months. The relationship between clinical and radiological factors and the tumour type or local recurrence was assessed using Chi-square test or Fisher's exact test.

Results: Endosteal scalloping (p = 0.004) and soft tissue extension (p = 0.017) were shown to statistically favour ACT over enchondroma; by contrast, pain (p = 0.034) was more frequent in enchondroma compared to ACT. All patients with enchondroma had no local recurrence; in contrast, local recurrence occurred in four patients with ACT (11%). Soft tissue extension (p = 0.049) and the diagnosis of ACT (p = 0.021) were associated with an increased risk of local recurrence. We had a disease progression in three of four patients with local recurrence, and these had higher histological grade than the original tumour.

Conclusion: Our data show that endosteal scalloping and soft tissue extension could be helpful in the differential diagnosis between enchondroma and ACT. We suggest following only those patients with ACT after surgery to identify any possible recurrence and, in case of recurrence, treat these patients with resection for the risk of disease progression.

TABLES:

Table 1 Summary of data in 89 patients with either enchondroma or atypical cartilaginous tumour

Factor (n=89)	No. of patients	Enchondroma (n=54)	Atypical cartilaginous tumor (n=35)	p value
Site				0.387#,a
Proximal femur	8 (9.0%)	4 (7.4%)	4 (11.4%)	
Distal femur	29 (32.6%)	17 (31.5%)	12 (34.3%)	
Proximal tibia	15 (16.9%)	9 (16.7%)	6 (17.1%)	
Distal tibia	2 (2.2%)	2 (3.7%)	0 (0%)	
Proximal humerus	31 (34.8%)	21 (38.9%)	10 (28.6%)	
Calcaneus	2 (2.2%)	0 (0%)	2 (5.7%)	
Distal radius	2 (2.2%)	1 (1.9%)	1 (2.9%)	
Lesion size (cm)				0.709
<6	53 (59.6%)	33 (61.1%)	20 (57.1%)	
6≤	36 (40.4%)	21 (38.9%)	15 (42.9%)	
Calcifications (Radiography)				0.152#
Yes	81 (91.0%)	51 (94.4%)	30 (85.7%)	
No	8 (9.0%)	3 (5.6%)	5 (14.3%)	
Endosteal scalooping (CT or MRI)				0.004*
Yes	30 (33.7%)	12 (22.2%)	18 (51.4%)	
No	59 (66.3%)	42 (77.8%)	17 (48.6%)	
Soft tissue extension (CT or MRI)				0.017*,#
Yes	9 (10.1%)	2 (3.7%)	7 (20.0%)	
No	80 (89.9%)	52 (96.3%)	28 (80.0%)	
Pain				0.034*,b
At a rest	41 (46.1%)	23 (42.6%)	18 (51.4%)	
Only at working	10 (11.2%)	7 (13.0%)	3 (8.6%)	
Only a tenderness	20 (22.5%)	17 (31.5%)	3 (8.6%)	
No pain	18 (20.2%)	7 (13.0%)	11 (31.4%)	

#:Fisher exact test was used. a:Comparison of proximal femur and the others. b:Comparison of no pain and the others. *Statistically significant.

Table 2 Univariate analysis of association of factors with occurrence of local recurrence

Factor (n=89)	Without recurrence (n=85)	With recurrence (n=4)	P value (Fisher exact test)
Age (years)			0.566
<50	55 (64.7%)	3 (75.0%)	
50≤	30 (35.3%)	1 (25.0%)	
Gender			0.200
Male	29 (34.1%)	0 (0%)	
Female	56 (65.9%)	4 (100%)	
Site			0.319
Proximal femur	7 (8.2%)	1 (25.0%)	
The others	78 (91.8%)	3 (75.0%)	
Lesion size (cm)			0.535
<6	51 (60.0%)	2 (50.0%)	
6≤	34 (40.0%)	2 (50.0%)	
Calcifications (Radiography)			0.319
Yes	78 (91.8%)	3 (75.0%)	
No	7 (8.2%)	1 (25.0%)	
Endosteal scalloping (CT or MRI)			0.109
Yes	27 (31.8%)	3 (75.0%)	
No	58 (68.2%)	1 (25.0%)	
Soft tissue extension (CT or MRI)			0.049*
Yes	7 (8.2%)	2 (50.0%)	
No	78 (91.8%)	2 (50.0%)	
Pain			0.398
Yes	67 (78.8%)	4 (100%)	
No	18 (21.2%)	0 (0%)	
Tumor type			0.021*
Enchondroma	54 (63.5%)	0 (0%)	
Atypical cartilaginous tumor	21 (36.5%)	4 (100%)	

*Statistically significant.

– EPITHELIOID SARCOMA – (SARCOMA OF THE YEAR)

Poster 039 #2775549

IN VITRO AND *IN VIVO* MODELS FOR PRE-CLINICAL EVALUATION OF NOVEL THERAPEUTIC APPROACHES FOR THE TREATMENT OF PAEDIATRIC INFLAMMATORY MYOFIBROBLASTIC TUMOUR

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Objective: This project is driven by the unmet clinical need for effective, durable treatment regimens for ALK-rearranged IMT. We aim to establish patient derived in vitro and in vivo models of paediatric Inflammaroy Myofibroblastic Tumour (IMT) and utilise these models for pre-clinical evaluation of novel therapeutic strategies for the treatment of IMT.

Methods: Five children have presented to the Sydney Children's Hospital Randwick, with multi-focal or metastatic ALK-rearranged IMT.Three of these patients were diagnosed with an agressive epitheliod subtype (eIMS). Though all initially responded to crizotinib, two patients experienced relapse and one died of progressive disease (IMT-1). Viable cell samples were collected from three of these patients, including series of samples from various stages of disease progression.

We have utilised malignant ascites from IMT-1 at diagnosis (IMT-1A) and third relapse (IMT-1D) to establish in vitro cell cultures. PDX models were established by intraperitoneal and subcutaneous injection of IMT-1D or IMT-1A cells into non-obese diabetic severe combined immune deficient mice with IL-2 receptor gamma chain deficiency.

Results: Mice develop multi-focal intraperitoneal tumours closely associated with abdominal organs, that recapitulated pathological and immunohistochemical features of the patient's tumour, including expression of perinuclear ALK and CD30. In vitro cell cultures and cell cultures established from mouse peritoneal fluid were also positive for ALK by immunohistochemistry and CD30 by flow cytometry.

Having confirmed CD30 positivity in patient tumours, we are utilising our models to investigate the CD30 targeted antibody-drug conjugate brentuximab vedotin as a treatment for IMT. We have shown that brentuximab vedotin reduces IMT cell viability in vitro.

Conclusion: Our in vitro cultures and in vivo PDX models of ALK-driven IMT are the first of their kind, and provide a unique opportunity for molecular and functional characterization of ALK-rearranged IMT at various stages of disease and for pre-clinical evaluation of novel therapeutic approaches. We have utilised this model to test Brentuximab Vedotin as a potential therapy for IMT. Brentuximab vedotin is currently used in treatment of Hodgkin and anaplastic large cell lymphoma, thus it may be possible to rapidly translate our findings to the clinic.

Poster 040 #2799277

LYMPH NODE EVALUATION AND SURVIVAL IN EPITHELIOID SARCOMA – 22 YEARS EXPERIENCE FROM A SINGLE INSTITUTION

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Objective: Epithelioid sarcoma (ES) is reported to metastasize to lymph nodes (LN) more often than most soft tissue sarcomas (STS), however, reported rates of LN involvement in ES vary greatly, and the benefit of LN evaluation and management is unknown. We report the incidence and long-term prognosis of ES patients (pts) with LN involvement.

Methods: We retrospectively reviewed consecutive cases of ES diagnosed by experienced STS pathologists between 1995 and 2017 from the pathology consult database. Kaplan-Meier curves were used to show overall survival (OS) and recurrence-free survival (RFS). The log-rank test was used to compare time-to event-distributions.

Results: We identified 283 pts with ES, with follow-up information available for 81 cases, including pathologic LN status at staging. The median age at diagnosis was 40 years (yrs) (range 15-84), and 52% of pts were male. Extent of disease at diagnosis included localized disease (N0 and NX), 49/81 (60%), localized multifocal disease (N0 and NX), 5/81, (6%), node-positive localized disease (N1), 15/81, (19%), and metastatic disease (M1), 12/81,

(15%). The median follow-up for pts still alive (59%) was 4.9 yrs (95% CI: 2.4-6.7) and the 5-yr OS was 62% (47-73%). Among pts with localized disease, median OS (mOS) was not reached and mOS for M1 pts was 1.5 yrs (95% CI: 0.1-2.2) (p<0.001). Amongst the subset of pts with non-multifocal localized disease, 35/64 (55%) had LN status evaluated at diagnosis. In pts with LN evaluation, 20/35 (57%) were N0 and 15/35 (43%) were N1. There was no LN evaluation (NX) in 29/64 (45%). mOS among N0 and NX pts was not reached and was 3.6 yrs (95% CI: 0.6-∞) among pts with N1 status (p=0.009). Median RFS was 8.8 yrs (95% CI: 0.8-∞) among N0 pts, 1.3 yrs (95% CI: 0.4-1.5) among N1 pts and 3.4 yrs among NX pts (95% CI: 1.4-∞) (p=0.001).

TABLE:
Table 1. Clinical and Pathologic Characteristics (n=81)

Gender, n (%)	
Male	42 (52%)
Female	39 (48%)
Age at Diagnosis, years	
Median (Range)	40 (15-84)
Clinical Stage at Diagnosis, n (%)	
Distant Metastatic	12 (15%)
Localized (N0)	20 (25%)
Node-Positive Localized (N1)	15 (18%)
Localized (NX)	29 (36%)
Localized Multifocal (N0 and NX)	5 (6%)
Primary Location, n (%)	
Extremity	36 (45%)
Trunk	44 (54%)
Unknown	1 (1%)
Tumor Size, cm	
Median (Range)	4 (0.3-22)
Mitotic Count, per 10 HPF (n=45)	
Median (Range)	6 (0-39)
Tumor Depth, n (%)	
Deep	63 (78%)
Superficial	15 (19%)
Unknown	3 (3%)
Histologic Subtype, n (%)	
Proximal	43 (53%)
Classic	38 (47%)
Margins, n (%)	
Negative	50 (62%)
Positive	17 (22%)
Unknown	14 (17%)

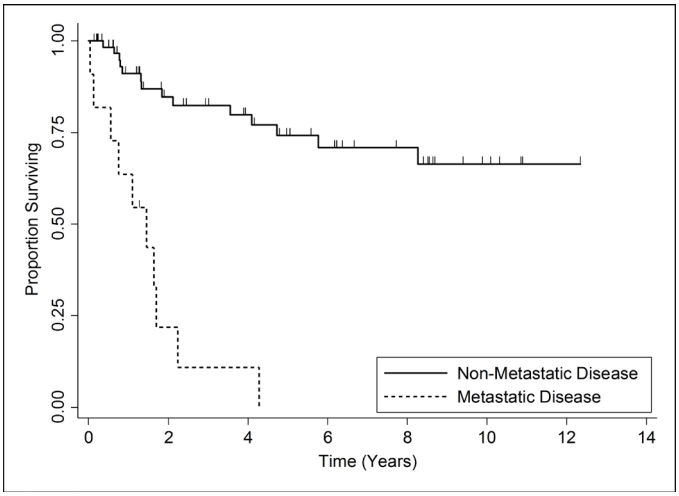

Figure 1. Overall Survival of Metastatic vs Localized Patients by Clinical Stage at Diagnosis (p<0.001).

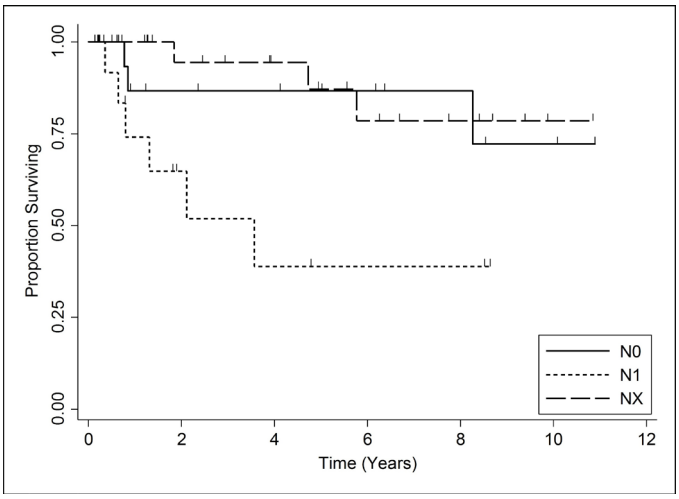

Figure 2. Overall Survival by Lymph Node Involvement at Presentation in Non-Multifocal Localized Disease (p=0.007).

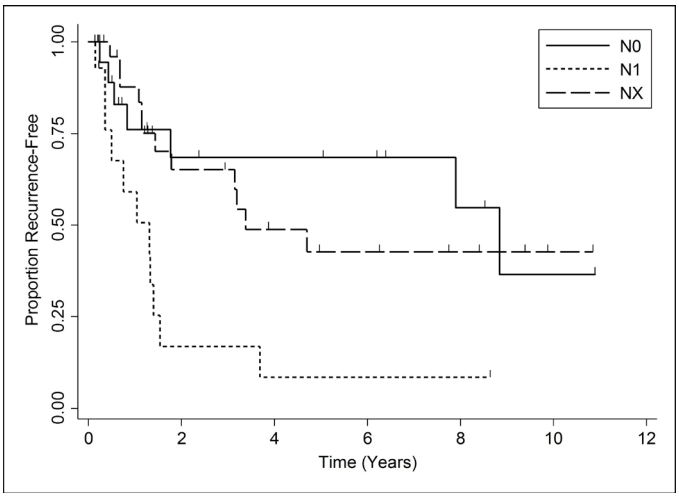

Figure 3. Recurrence-Free Survival by Lymph Node Involvement in Non-Multifocal Localized Disease (p=0.001).

Table 2. Clinical Management and Outcomes (n=81)

Surgical Management at Diagnosis, n (%)	
Wide Excision	36 (44%)
Wide Excision with Sentinel LN Biopsy	24 (30%)
Wide Excision with Complete LN Dissection	8 (10%)
None	9 (11%)
Unknown	4 (5%)
Neoadjuvant/Adjuvant Radiation, n (%)	
Primary and LN	3 (4%)
Primary	29 (36%)
None	37 (46%)
Unknown	12 (15%)
Neoadjuvant/Adjuvant Chemotherapy, n (%)	
Neoadjuvant Chemotherapy	7 (9%)
Adjuvant Chemotherapy	4 (5%)
None	58 (71%)
Unknown	12 (15%)
Recurrence in M0, n (%) (n=64)	
Distant	15 (23%)
Local	5 (8%)
Regional	8 (13%)
None	25 (39%)
Unknown	11 (17%)
Alive, n (%)	
Alive	56 (69%)
Dead	24 (30%)
Unknown	1 (2%)

Conclusion: This is the largest reported cohort of pts with ES reviewed at a single center with high rates of pathologic LN evaluation as compared to previously reported rates. Within our cohort, N1 status is associated with inferior RFS and OS, though factors such as tumor size or imaging concerning for nodal involvement may have contributed to a selection bias. Pts without pathologic LN evaluation are at uncertain clinical risk of recurrence and may have shorter RFS compared to pts with proven N0 LN status. Given worse clinical outcomes among N1 LN disease, routine LN staging may play a role in informing prognosis. Further study is needed to determine the optimal approach to lymph node evaluation and management of N1 disease which may be answered best through a multi-institutional approach.

Poster 041 #2804686

EPITHELIOID SARCOMA (ES): AN INSIGHT INTO EPIDEMIOLOGY AND NATURAL HISTORY

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Objective: ES is a rare sarcoma with distinctive features and the potential to respond to new targeted agents. The epidemiological hallmarks and the natural history of this disease are unknown.

Methods: We used the RARECAREnet, the SEER18 cancer registry (CR) and the Japanese National CR to highlight ES epidemiological hallmarks in the EU, US and Japan (ICD-O3 code 8804). World-age adjusted IR and relative survival (RS) were calculated for patients diagnosed between 2000-07 and followed-up at least up to 31st Dec 2008. 497 new cases of ES were identified through 94 CR from 27 EU countries, 301 in the US, 62 in Japan. Between 1995 and 2015, 71 consecutive patients with primary localised disease underwent surgery at 3 major Italian referral centers. Diagnosis was reviewed by expert sarcoma pathologists. At the time of submission, full data were available for 54 patients. Patient characteristics, treatment and outcome were analysed.

Results: Age-adjusted IR were 0.02/100,000 in EU and Japan, 0.05/100,000 in US. IR in the childhood population (<14 yrs) was 0.01, i.e. 5% of all new ES cases. 5-yr RS was 50%, 52% and 62% in the EU, US and Japan respectively. Demographics and treatment from the referral centres series are summarised in Table 1. At a median follow-up of 58 months (IQR 34-112) 32 patients (59%) recurred (Table 2). Eight patients developed a second recurrence, 9 recurred 3 or more times. Among patients who recurred, 12 are alive, 6 disease free. The LR-free and DM-free survival at 5-yr were 63% and 52% respectively. DFS and OS at 5-yr were 40% and 63% (Figure 1). Size>5 cm was shown to be a predictor of DFS (P=0.049) and associated with an unfavourable trend in OS. Clas-

sic-type morphology was associated with a favourable 5-yr OS (69% vs 48%) and 5-yr DM-free survival (56% vs 44%) compared to proximal-type (both not statistically significant). Primary site, chemotherapy and radiotherapy were not associated with any study end-point.

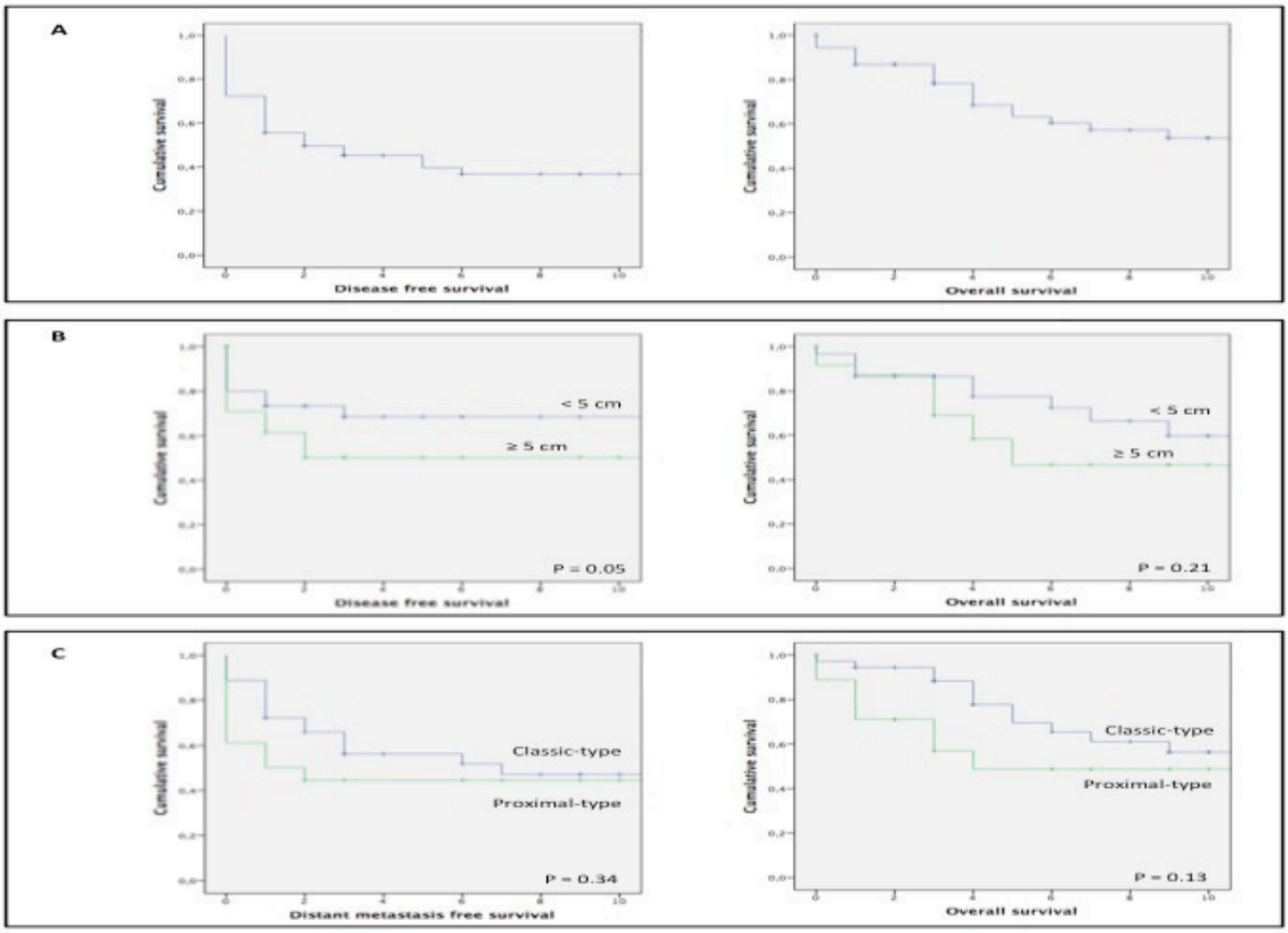

Figure 1. Kaplan Meier curves. Panel A: DFS and OS in the whole population (n=54). Panel B: DFS and OS in patients with primary tumor size < 5 cm (n=30) or ≥ 5 cm (n=24). Panel C: DM-free survival and OS in patients with morphological classic-type (n=36) and proximal-type (n=18).

Table 1. Patients characteristics and treatment.

Characteristic	Patients (%)
Median age (IQR)	36 years (26-48)
Gender	-
Male	30 (56)
Female	24 (44)
Primary sites	-
Distal	37 (69%)
Hand	10
Forearm/arm	17
Foot	3
Leg/thigh	7
Proximal	17 (31%)
Axilla	1
Groin	6
Buttock	5
Urogenital	3
Vulvar	3
Median size (IQR)	4 cm (2-6)
Morphological subtype (WHO 2013)	-
Classic-type	36 (67)
Proximal-type	18 (33)
Type of surgery	-
Marginal	14 (26)
Wide	37 (69)
Radical	3 (5)
Perioperative treatment	-
Radiotherapy	24 (44)
Chemotherapy	16 (30)

Table 2. Pattern of recurrence

Type of recurrence	Patients (N=32)
LR only	5 (16%)
DM only	14 (44%)
LR + LNM	4 (13%)
LR + DM	8 (25%)
LR + LNM + DM	1 (2%)

LR: local recurrence; LNM: lymph nodal metastases; DM: distant metastases

Conclusion: ES is an exceedingly rare cancer, particularly in childhood. The clinical behavior can be indolent, with multiple relapses over time, but overall outcome is dismal, with a metastasis and death risk as high as 50%. Proximal-type morphology is associated with a more aggressive course. The value of a multimodal approach in a subgroup of high-risk patients (large lesion, proximal-subtype) should be explored.

Poster 042 #2804704

CLINICAL OUTCOMES FOR PATIENTS WITH ALK-POSITIVE EPITHELIOD INFLAMMATORY MYOFIBROBLASTIC SARCOMA (EIMS) AND INFLAMMATORY MYOFIBROBLASTIC TUMOURS (IMT) TREATED WITH CRIZOTINIB IN AUSTRALIA AND NEW ZEALAND

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Objective: Epithelioid inflammatory myofibroblastic sarcoma (eIMS) and inflammatory myofibroblastic tumours (IMT) are rare tumours occurring across the age spectrum. Tumours commonly arise in the abdomen or chest but multifocal and metastatic disease is common. IMT natural history ranges from indolent, smouldering disease to rapidly progressive, life-threatening presentations. The identification of recurrent ALK translocations (≈50%), and other cryptic rearrangements, including ROS, PDGFR-β and ETV6, has transformed eIMS/IMT biology and treatment. Although ALK inhibitors (ALKi) are effective in ALK-positive tumours, knowledge gaps in eIMS/IMT biology, the optimal duration of ALKi therapy and treatment options for ALKi relapsed/refractory disease remain. To address these gaps we developed a collaborative Australian and New Zealand (ANZ) ALK-positive eIMS/IMT translational research program with the objective of reporting the clinical outcome of a homogenously treated cohort of ALK-positive eIMS/IMT patients and developing relevant pre-clinical laboratory models.

Methods: We reviewed the clinical presentation, pathology, treatment and clinical outcome of 8 paediatric patients diagnosed with ALK-positive eIMS/IMT in 4 centres across ANZ. All patients were treated with the ALKi, crizotinib, provided by a Pfizer sponsored, non-commercial, named patient, access scheme.

Results: Since 2009, 8 patients (4♂ and 4♀) were diagnosed with ALK-positive IMT (n=4) or eIMS (n=4). The median age at presentation was 7.1y (range 0.7-14.7) and patients have been followed for a median duration of 2.7y (range 0.5-8.2) following diagnosis. All but one patient presented with large multifocal, metastatic tumours and the majority (7/8) had abdominal or pelvic primaries. The median time from diagnosis to commencing crizotinib was 19 days (range 5-1504) with 2 patients receiving conventional therapy (naproxen and/or prednisolone), prior to crizotinib. Crizotinib was well tolerated with the median duration of treatment being 0.9y (range 0.2-3.0) and all patients responding to therapy. The best objective responses to crizotinib included 3 complete responses (CR), 4 partial responses (PR) and 1 patient with stable disease (SD). Resection of residual tumour allowed 3 patients with a PR to achieve a CR. Two patients, both with eIMS, experienced early recurrences within 12 months of diagnosis after achieving a CR and PR to crizotinib. One patient died of progressive disease whilst the other achieved a long term CR with additional surgery and alternative ALKi treatment. Two patients continue on crizotinib therapy 0.4 and 0.9y from diagnosis. Four patients have stopped crizotinib after a median treatment duration of 0.9y (range 0.2-3.0). None of these 4 patients have experienced disease recurrence or progression at a median of 1.8y (range 0.5-3.2) after stopping crizotinib. The 2-year overall (OS) and progression free survival (PFS) of the cohort is 0.83 (+/- SE 0.15) and 0.76 (+/- SE 0.12) from commencing crizotinib. Tumour samples from 5 patients have been subjected to RNA-capture sequencing and viable tumour samples from 3 patients have been used to generate ALK-positive eIMS laboratory models.

Conclusion: Crizotinib and surgery are effective for ALK-positive eIMS/IMT. Despite promising initial responses, two ALK-positive eIMS patients experienced early disease progression with only one patient being successfully salvaged with additional therapy. No recurrences or disease progression occurred in patients with ALK-positive IMT. Crizotinib therapy has been ceased in 4 patients without disease progression or recurrence suggesting that crizotinib may be safely ceased in a subset of patients. We have established patient derived laboratory models of ALK-positive eIMS which will be useful for the pre-clinical identification and validation of additional therapies for eIMS.

Poster 043 #2797315

CLINICAL OUTCOME AND MANAGEMENT OF NODAL METASTASIS IN THE PATIENTS WITH EPITHELIOID SARCOMA

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Objective: An epithelioid sarcoma (ES) is a very rare soft tissue sarcoma (STS), which shows both epithelial and mesenchymal differentiation and accounts for <1% of all STSs. ES patients often develop local recurrence and frequently show lymph node metastasis. However, because of the rarity of this tumor, the impact of nodal metastasis and its appropriate management remain unclear. In this study, we investigated the clinical outcomes of patients with epithelioid sarcomas with a focus on lymph node metastasis.

Methods: We retrospectively evaluated the clinical outcomes of 27 patients with epithelioid sarcomas treated between 1985 and 2015. The log-rank test was used to assess the prognostic variables.

Results: The overall local recurrence rate was 33%, and the estimated overall 5-year survival rate was 62%. Hand and foot locations were associated with favorable overall survival. We could not find any survival benefit of adjuvant therapy for the ES patients. During the follow-up period, new nodal metastasis was noted in 14 patients (52%). The incidence of local recurrence was higher in patients with new nodal metastasis than in patients who did not develop nodal metastasis. Large tumor size, local recurrence and nodal metastasis at presentation were significant risk factors for the development of new nodal metastasis. The development of new nodal metastasis had a tendency to worsen survival; however, this association was not statistically significant. Lymphadenectomy did not affect overall survival.

Conclusion: Peripheral tumor location is associated with a better prognosis. The prophylactic nodal resection should be consider for the patients with nodal metastasis at presentation or large primary tumor. The development of new nodal metastasis tends to be associated with poor prognosis; however, among patients with nodal metastasis, resection of the metastatic lesions has a low impact on survival.

Poster 044 #2797557

IN-DEPTH GENETIC ANALYSIS OF SCLEROSING EPITHELIOID FIBROSARCOMA REVEALS RECURRENT GENOMIC ALTERATIONS AND POTENTIAL TREATMENT TARGETS

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Objective: Sclerosing epithelioid fibrosarcoma (SEF) is a highly aggressive soft tissue sarcoma closely related to low grade fibromyxoid sarcoma (LGFMS). Despite the overlap of gene fusion variants between these two tumor types, SEF is much more aggressive. The present study aimed to further characterize SEF and hybrid SEF/LGFMS genetically and better understand the role of the characteristic fusion genes in tumorigenesis.

Methods: We performed whole exome sequencing, SNP array analysis, RNA-sequencing, global gene expression analyses and/or IHC on a series of 13 SEFs and 6 hybrid SEF/LGFMS. We also expressed the FUS-CREB3L2 and EWSR1-CREB3L1 fusion genes conditionally in a fibroblast cell line; these cells were subsequently analyzed by RNA-seq and expression of the CD24 protein was assessed by FACS analysis.

Results: The SNP array analysis detected a large number of structural aberrations in SEF and SEF/LGFMS, many of which were recurrent, notably DMD microdeletions. RNA-seq identified FUS-CREM and PAX5-CREB3L1 as alternative fusion genes in one case of SEF each. CD24 was strongly upregulated, presumably a direct target of the fusion proteins. This was further confirmed by the gene expression analysis and FACS analysis on Tet-On 3G cells expressing EWSR1-CREB3L1.

Conclusion: While gene fusions are the primary tumorigenic events in both SEF and LGFMS, additional genomic changes explain the differences in aggressiveness and clinical outcome between the two types. CD24 and DMD constitute potential therapeutic targets.

– EWING SARCOMA –

Poster 045 #2767659

THERAPEUTIC TARGETING OF KDM1A/LSD1 IN EWING SARCOMA WITH SP-2509 ENGAGES THE ENDOPLASMIC RETICULUM STRESS RESPONSE

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Objective: Multi-agent chemotherapeutic regimes remain the cornerstone treatment for Ewing sarcoma, the second most common solid bone malignancy diagnosed in pediatric and young adolescent populations. We have reached a therapeutic ceiling with conventional cytotoxic agents, highlighting the need to adopt novel approaches that specifically target the drivers of Ewing sarcoma oncogenesis. As KDM1A/LSD1 (Lysine Specific Demethylase 1) is highly expressed in Ewing sarcoma cell lines and tumors, with elevated expression levels associated with worse overall survival (P=0.033), this study has examined biomarkers of sensitivity and mechanisms of cytotoxicity to targeted KDM1A inhibition using SP-2509 (reversible KDM1A inhibitor).

Methods: The anti-proliferative effects of SP-2509 was determined through Cell Titre Glo assays following 72 hours of treatment in a comprehensive panel of 17 Ewing sarcoma cell lines with varying STAG2/TP53 mutational status and basal KDM1A expression levels. RNA-seq analysis of six Ewing sarcoma cell lines -/+ SP-2509 treatment (2μM, 48hrs) was also conducted.

Results: We report, that innate resistance to SP-2509 was not observed in our Ewing sarcoma cell line cohort (72hr IC50 range 81nM-1593nM), in contrast resistance to the next generation KDM1A irreversible inhibitor GSK-LSD1 was observed across multiple cell lines (144hr IC50>300μM). Although TP53/STAG2 mutational status and basal KDM1A mRNA and protein levels did not correlate with SP-2509 response, induction of KDM1B (mammalian homologue of KDM1A) following SP-2509 treatment was strongly associated with SP-2509 hypersensitivity (R2=0.562). Indeed shRNA mediated knockdown of KDM1B significantly reduced the cytotoxic effects of SP-2509 (4.3 fold IC50 increase) only in hypersensitive cell lines. Mechanistically, RNA-seq analysis revealed that SP-2509 imparts robust apoptosis through engagement of the endoplasmic reticulum (ER) stress pathway, and that hypersensitive cell lines (IC50<300nM) share similar transcriptomic profiles. In addition, ETS1/HIST1H2BM were specifically induced/repressed respectively following SP-2509 treatment only in hypersensitive cell lines. Finally, we demonstrate that the transcriptional profile driven by SP-2509 strongly mirrors KDM1A genetic depletion.

Conclusion: Together, our findings provide key insights into the mechanisms of SP-2509 cytotoxicity as well as biomarkers that can be used to predict KDM1A inhibitor sensitivity in Ewing sarcoma.

Poster 046 #2784408

A PHASE I STUDY OF THE POLY-ADP RIBOSE POLYMERASE (PARP) INHIBITOR, NIRAPARIB (NIR), IN COMBINATION WITH TEMOZOLOMIDE (TMZ) IN PATIENTS WITH ADVANCED EWING SARCOMA (ES): FINAL RESULTS OF SARC025 ARM 1

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Objective: In pre-clinical models, PARP inhibitors were identified both mechanistically and via a chemical screen to be of potential therapeutic value in ES. The co-administration of PARP inhibitors with an alkylating agent exhibits notable synergistic anti-cancer activity in vitro and in vivo. We initiated a phase I study of the potent and highly selective PARP-1 and -2 inhibitor niraparib (NIR) with temozolomide (TMZ) with the objective to determine the dose-limiting toxicities (DLT) and maximum tolerated dose (MTD) of the combination in pts with pre-treated incurable ES.

Methods: Using a continuous reassessment model (CRM), eligible pts with advanced ES were assigned to Cohort A with continuous NIR 300 mg daily (qd) and escalating TMZ qd on D2-6 of 28D cycle. If DLTs were observed within the first 3 dose levels, pts were assigned to cohort B using a 3+3 model with NIR dosing for escalating durations (D1-7, 1-14 or 1-21) and TMZ dosing from Cohort A. In Cohort C, TMZ was to be re-escalated in 10 mg/m2/d increments from MTD determined from cohort B.

Results: From 07/14-05/16, 17 eligible pts (14M/3F) with a confirmed EWSR1-FLI1 translocation were enrolled at 5 dose levels. Median age was 23 (range 13-44), and median prior therapies was 4 (range 1-10) with 16 pts receiving prior radiation. As DLTs were observed in dose level A1, the study progressed to cohort B using the 3+3 design thereafter. 5 pts experienced at least 1 DLT at 3 dose levels per table below. Peak myelosuppression occurred predominantly around D15-22. No DLTs occurred at final dose level C1 but there was one death due to unrelated causes. No responses were observed. Pharmacodynamic parameters in serial tumor biopsies and blood are undergoing evaluation.

Conclusion: The MTD reached in this study is NIR 200 mg qd D1-7 in combination with TMZ 30 mg/m2 qd on D2-6 with DLTs being hematologic in nature. Given toxicities observed, continued dose escalation of TMZ was not pursued. Instead, in view of compelling pre-clinical data and non-overlapping single agent toxicities, exploration of a combination of NIR and irinotecan is ongoing in Arm 2.

Dose Levels and DLTs Observed

Dose Level	No. of pts	Doses	DLTs Observed
A1	3	NIR 300 mg qd D1-28 TMZ 20 mg/m2 qd D2-6	G4 Thrombocytopenia (n=2) G4 Neutropenia (n=1)
B1	3	NIR 300 mg qd D1-7 TMZ 20 mg/m2 qd D2-6	G4 Thrombocytopenia (n=2) G4 Neutropenia (n=1)
B4	3	NIR 200 mg qd D1-7 TMZ 20 mg/m2 qd D2-6	
B5	5	NIR 200 mg qd D1-14 TMZ 20 mg/m2 qd D2-6	G4 Thrombocytopenia (n=2) G4 Neutropenia (n=1)
C1	3	NIR 200 mg qd D1-7 TMZ 30 mg/m2 qd D2-6	

Poster 047 #2780008

THE EWS-FLI1 ONCOPROTEIN LEVEL MODULATES CXCR4/CXCR7-NFKB SIGNALING IN EWING SARCOMA

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Objective: The goals of this study are 1) to determine the impact of CXCR4/CXCR7 signaling on NF-kB target genes in Ewing sarcoma and then 2) to investigate how the EWS-FLI1 fusion oncoprotein modulates this response . Recent studies demonstrate that lower levels of the EWS-FLI1 fusion oncoprotein enhances metastatic capability in Ewing sarcoma. NF-kB is a critical mediator of CXCR4 and CXCR7 signaling that drives metastasis in several cancers, and given that increased CXCR4 and increased CXCR7 expression have each been associated with increased metastasis and poor prognosis in Ewing sarcoma, we sought to investigate the impact of EWS-FLI1 on the NF-kB on the CXCR4/CXCR7-dependent NF-kB signaling in this pediatric tumor.

Methods: Ewing sarcoma cell lines including A673, CHLA9, CHLA10, TC32 and TC71 were utilized. CXCR4 and CXCR7 cell surface expression were determined via flow cytometry. EWS-FLI1 levels were modulated via siRNA and confirmed by western blot and RT-PCR analysis. Nuclear p65 DNA binding was measured via ELISA. NF-KB target gene expression was assessed via RT-PCR. The clinically available CXCR4/CXCR7 inhibitor, AMD3100, was utilized in blocking studies.

Results: Consistent with IHC analysis of primary and metastatic patient tumor samples, the paired primary and metastatic Ewing sarcoma cell lines CHLA9 and CHLA10 showed dramatic differences in CXCR4 and CXCR7 expression, with CHLA10 demonstrating much higher expression of both receptors when analyzed by both RT-PCR and flow cytometry. Other cell lines (non-paired) showed variable and heterogeneous CXCR4 and CXCR7 expression. Knock-out of the CXCR4 receptor lead to significant decrease in both MMP9 and CXCL12/SDF-1 expression while IL-6 expression remained unchanged. Knock-out of the CXCR4 receptor did not alter endogenous EWS-FLI1 mRNA levels.
Conversely, lowering the level of EWS-FLI1 via siRNA lead to enhanced NF-kB signaling, indicated by an increase in p65 DNA binding. Consistent with this observation, treating Ewing cell lines with EWS-FLI1 siRNA also resulted in increased NF-kB target gene expression at baseline compared to control siRNA treated cells and target gene expression was further enhanced upon CXCR4/CXCR7 receptor stimulation with the receptor ligand CXCL12/SDF-1.

Conclusion: Our findings indicate that EWS-FLI1 negatively modulates CXCR4/CXCR7-dependent NF-kB signaling. This suggest that EWS-FLI1 low, CXCR4/CXCR7 high cells, which are associated with enhanced metastasis and poor prognosis, would be anticipated to demonstrate significantly enhanced expression of NF-kB target genes. The NF-kB pathway is a druggable target that could potentially serve as an “Achilles heel” in this subset of high risk tumors. Current work is ongoing in this area.

Poster 048 #2790253

EXPRESSION OF THE NOVEL THERAPEUTIC TARGET PREGNANCY ASSOCIATED PLASMA PROTEIN A (PAPP-A) MEDIATES GROWTH AND INDUCTION OF IMMUNE TOLERANCE IN EWING SARCOMA

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Objective: Ewing sarcoma (EWS) patients with metastatic/relapsed disease still face a poor prognosis, indicating a clear need for novel targeted therapies. We identified Pregnancy Associated Plasma Protein A (PAPP-A) as one of the top 5 membrane-associated genes overexpressed (RNAseq) in EWS (log2FPKM=3.93, n=122) compared to normal tissue (log2FPKM= -1.56, n=96). PAPP-A is a placental antigen, highly expressed by the syncytiotrophoblast and a key regulator of fetal growth. PAPP-A is a metalloproteinase that cleaves IGFBP-2, -4 and -5, thus increasing the local bioavailability of free IGF. The impact of IGF signaling in EWS is illustrated by the antitumor activity of a-IGF-1R in clinical trials, an approach plagued by the rapid development of resistance. We reported delayed tumor growth (p=0.0302) and prolonged survival (p=0.0234) in EWS bearing NSG mice treated with a PAPP-A neutralizing mAB and enhanced efficacy in conjunction with a-IGF1R (p=0.0003). Here we investigate the molecular pathways associated with PAPP-A expression and its role in EWS progression.

Methods: We generated PAPP-A knockout (KO) clones utilizing CRISPR/Cas9 and performed RNAseq to compare gene expression profiles of PAPP-A-KO clones (n=5) with controls (n=3).

Results: PAPP-A KO abrogated metalloproteinase activity capable of cleaving IGF-1 from IGFBP-4, resulting in diminished free IGF-1 and decreased cell growth in vitro. GSEA analysis of differentially expressed genes revealed significant ($p<0.05$) downregulation of hallmark pathways associated with disrupted IGF signaling and cell cycle/proliferation, such as pi3K/mTOR, E2F targets and MYC targets. Contrary, hallmark pathways showing the strongest induction upon PAPP-A-KO were largely immune related, such as Interferon response, TNF-a signaling and inflammatory response suggesting an increased immunogenicity in EWS tumors lacking PAPP-A. Indeed, PAPP-A KO clones showed increased expression of HLA class I, augmented secretion of chemokines, such as CCL5 and CXCL10 and activated T-cells showed alloreactivity against PAPP-A-KO but not control clones in vitro.

Conclusion: PAPP-A is a novel, highly tumor-specific cell surface target in EWS. Our data demonstrates a clear role for PAPP-A in maintaining IGF-1 signaling, which is required for optimal tumor growth. We have also discovered a novel role for PAPP-A in evasion of immunosurveillance, consistent with its primary role as a placental protein. Targeting PAPP-A could provide new therapeutic options for the treatment of EWS.

Poster 049 #2792251

SYNERGISTIC EPIGENETIC AND POSTTRANSLATIONAL TARGETING OF EWING SARCOMA

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Objective: Ewing sarcoma is typified by the EWS-FLI1 fusion gene, but these tumors harbor few or no other genetic mutations, limiting use of drugs against activating gene mutations. Novel targeted therapeutic approaches can instead be designed against biological pathways that are preferentially activated in Ewing sarcoma. BRD4 recognizes acetylated lysine residues on histones and promotes gene transcription. BRD4 expression is associated with cancer progression, and BRD4 inhibition has been shown to inhibit Ewing sarcoma growth, but with delayed activity and at doses that will be difficult to achieve clinically. Aurora Kinase A (AURKA) promotes mitotic spindle formation, chromosome segregation, and cytokinesis, and BRD4 inhibition has also been shown to have some activity against Ewing sarcoma. The objective of this study is to inhibit proliferative and antiapoptotic pathways by targeting both epigenetic upregulation of gene expression via BRD4 inhibition and by targeting postranslation protein functions with AURKA inhibition.

Methods: Ewing sarcoma cell lines ES2 TC32, TC71 and SK-ES, BRD4 inhibitor IBET-151, and Aurora Kinase A (AURKA) inhibitor Alisertib were used. For in vitro assays, both drugs were diluted in DMSO, at doses from 10-4000 nM. Synergistic drug effects on inhibiting monolayer cell growth were measured with the Incucyte Zoom and calculated with Compusyn software. For western blot and RT-qPCR assays, cells were treated with drugs at 1000 nM dose. For in vivo studies, IBET-151 was dissolved in 10% cyclodextrin/5% DMSO solution, and alisertib was dissolved in 10% cyclodextrin/1% sodium bicarbonate solution. For in vivo assays, 5x106 cells were suspended in 50 mcL of PBS and 50 mcL of Matrigel and implanted SC into the flanks of SCID mice (Envigo). When tumors grew to ~200 mm3, mice were treated with vehicle, Alisertib (15 mg/kg orally daily), IBET-151 (15 mg/kg intraperitoneally daily), or both drugs for up to 5 weeks or until endpoint achieved.

Results: Both drugs had efficacy in inhibiting cell growth in vitro across the three cell lines at 96 hrs (IBET-151 IC50 500-5000 nM; Alisertib IC50 200-800 nM) . In combination, the two drugs were significantly synergistic in inhibiting cell growth, with combination index (CI) <0.5 for most dose combinations tested in all cell lines (CI<1 is synergistic) and IC50 achievable with doses of IBET-151 <400 nM and alisertib <200 nM. The combination of both drugs together was more effective at inhibiting transcriptional expression of common drug targets, including AURKA, BCL2, and MYC, than use of alisertib alone, by RT-qPCR, and the combination was more effective at repressing protein expression of the same targets than either drug alone. In vivo, the drug combination significantly slowed tumor growth and extended survival as compared to vehicle control or either drug alone (p>0.01 for all tumor xenografts).

Conclusion: BRD4 and AURKA inhibition are synergistic in inhibiting oncogenic biological pathways, cell proliferation, and tumor xenograft growth in Ewing sarcoma. AURKA inhibition alone stimulates reflexive transcriptional upregulation of proliferative pathways, which is specifically repressed with BRD4 inhibition. Use of both drugs together is more effective at repressing protein expression of these pathways than either drug alone. IBET-151 and Alisertib co-treatment is tolerated in mice, and the drug combination is effective in inhibiting tumor growth at doses significantly lower than either drug alone. Synergistic BRD4 and AURKA inhibition offers a novel therapeutic combination for increased efficacy against Ewing sarcoma, for development and/or combination with chemotherapy.

Poster 050 #2804565

PRECLINICAL EFFICACY OF THE ENDOGLIN-BASED ANTIBODY-DRUG CONJUGATES OMTX703 FOR THE TREATMENT OF EWING SARCOMA

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Objective: Endoglin (ENG) is a TGF-b accessory receptor that modulates angiogenesis, vascular development and cell signaling. ENG is overexpressed in the tumor-associated vascular endothelium and in variety of solid tumors, including Ewing sarcoma (ES) that is the second most common bone cancer in adolescents and young adults. In this study, we present evidence of the preclinical efficacy of OMTX703, a novel antibody-drug conjugate (ADC) that consists of a fully human ENG monoclonal antibody conjugated through an optimized vc-PABA linker to the microtubule-disrupting cytotoxic drug TAM470 cytolysin (OMTX703-ADC).

Methods: The expression of the ENG protein target was characterized by flow cytometry and immunofluorescence analyses in a panel of five ES cell lines (ES8, TC32, TC71, A4573 and A673). The ES8 cell line exhibited the highest ENG expression and was therefore selected to evaluate the efficacy of OMTX703 in vitro and within in vivo xenograft animal models. To evaluate the pharmacodynamic effects of drug exposure upon the TGF-B and its downstream signaling network, reverse phase protein lysate arrays (RPPA) was used to assess proteomic changes

in xenograft tumors linked to OMTX703 ADC treatment in comparison to control groups (Naked ENG antibody and saline treatments) and selected proteins were validated by western blotting.

Results: High expression levels of ENG in ES8 correlated with efficient internalization, efficacy, and cytotoxic effects in vitro through intracellular tracking of OMTX703 and cell proliferation assays. OMTX703-ADC demonstrated potency in the low nanomolar range in vitro, and subsequent xenograft experiments demonstrated significant tumor growth delay when provided at 60mg/kg weekly for consecutive three weeks (Figure 1, $p<0.0001$). Preliminarily toxicity studies in mice treated with an identical dosing regimen showed no adverse effect on body weight. As measured by RPPA, novel ADC effects occurred in xenografts treated at the highest dose level (60mg/kg) as compared to other groups treated with a placebo, 10 mg/kg of unconjugated ENG antibody (OMTX003) or 30mg/kg of the OMTX703.

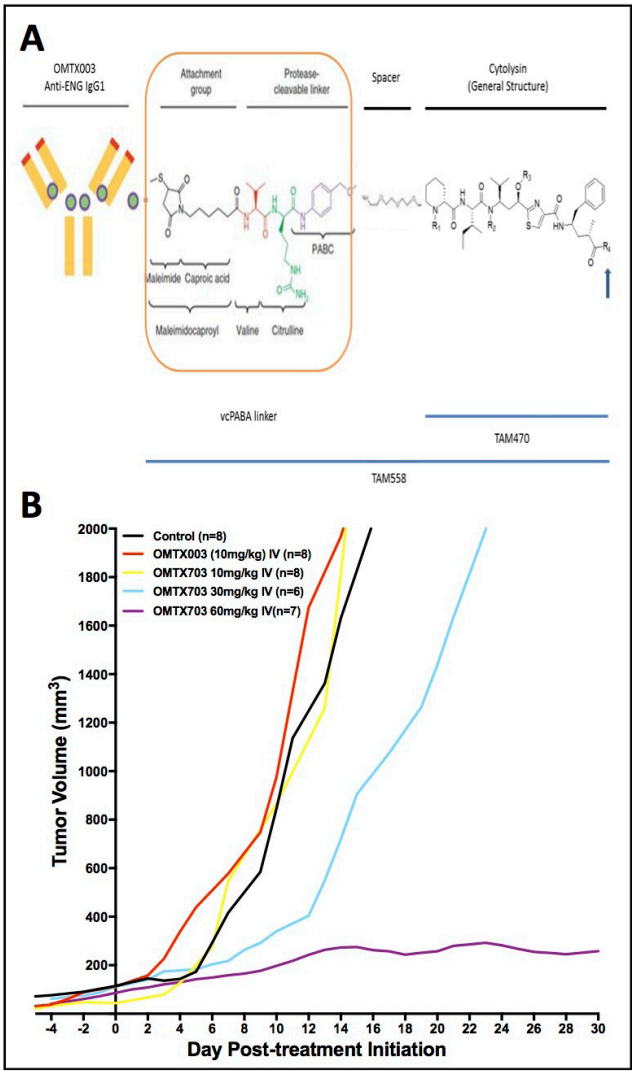

Figure 1: Antitumor efficacy of OMTX703 in ES8 xenograft animal model of Ewing sarcoma. **A)** Architecture of OMTX703. **B)** Tumor growth. Statistical analysis was performed using unpaired t test with Gaussian distribution and followed with welch correction.

Conclusion: Taken together, our study suggests that OMTX703-ADC has strong anti-cancer activity in selected ENG-overexpressing ES preclinical models and warrants a more comprehensive approach to gauge its therapeutic value across a broader panel of ES xenografts and/or patient-derived xenografts.

Poster 051 #2761063

BROMODOMAIN BET INHIBITORS CAN BE PROPOSED FOR THE TREATMENT OF EWING SARCOMA PATIENTS WITH HIGH EXPRESSION OF THE INSULIN-LIKE GROWTH FACTOR 2 MRNA BINDING PROTEIN 3 (IGF2BP3)

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Objective: Clinical heterogeneity of Ewing sarcoma (EWS) mainly relies on epigenetic mechanisms, including DNA methylation, transcriptional and post-transcriptional control of gene expression. In this context, the role of RNA binding proteins has never been explored. Here we investigated the significance of the RNA binding protein IGF2BP3 in the regulation of EWS aggressiveness.

Methods: In total, 128 patients with localized EWS were studied in two cohorts. In the training set, 29 tumor samples were analyzed using Affymetrix GeneChip array. In the validation phase, 99 EWS were examined using qRT-PCR. Patient-derived cell lines and experimental models were used for functional studies.

Results: Univariate and multivariate analyses indicated IGF2BP3 as a potent indicator of poor prognosis. ABCF1 mRNA has been identified as a novel partner of IGF2BP3. Functional studies indicated that IGF2BP3 is the oncogenic driver and ABCF1 mRNA acts as a sponge that by binding IGF2BP3 partly represses its functions. The combined evaluation of IGF2BP3 and ABCF1 allows prediction of patients' outcome: high IGF2BP3 and low ABCF1 identified patients who, despite localized tumor, have poor chance of survival (25% probability), whereas low IGF2BP3 and high ABCF1 indicated a very good probability to survive (85.5%). The bromodomain and extra-terminal domain inhibitor (BETi) JQ1 effectively decreased IGF2BP3 expression and the capability of EWS cells to grow in anchorage-independent conditions and to migrate. In vivo experiments will be performed to assess therapeutic value in patient-derived xenograts (PDX) from high IGF2BP3 expressors.

Conclusion: The combined assessment of IGF2BP3 and ABCF1 predicts recurrence in patients with EWS. For patients with high expression of IGF2BP3 and inferior probability of survival, the use of BETi, such as JQ1, may be proposed for a clinical evaluation.

Poster 052 #2775945

DNA BINDING PROPERTIES AND GENE REGULATORY ACTIVITIES OF EWS-FLI1 IN MURINE EWING SARCOMA

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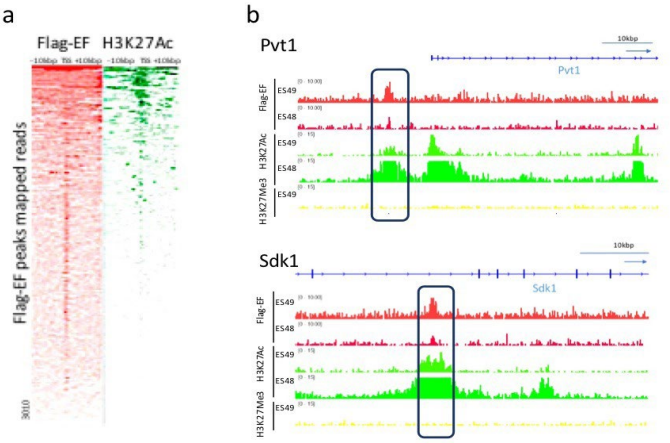
Objective: EWS-FLI1 (EF) plays an essential role in tumorigenesis and malignant progression of Ewing sarcoma (ES) where EF binds Ets binding sites (EBS) as well as GGAA microsatellites and regulate transcription of target genes. We have developed an ES mouse model by introducing EF into embryonic chondrogenic progenitors. Our model shared common biological characteristics with human ES, though genomic distributions of GGAA microsatellites are not well conserved between human and mouse. In this study, we tried to reveal common and distinct DNA binding properties of EF between human and mouse ES, and to get insights into the functional role of EF in tumorigenesis.

Methods: ChIP-seq were performed using mouse ES cell lines to identify EF binding sites and to evaluate histone modification. The results of ChIP-seq were compared with gene profiling data of mES obtained by DNA microarray analysis to identify EF target gene candidates. These candidates were further assessed by luciferase reporter assay and knockdown of EF. The functions of new candidates of EF target genes were analyzed by gene silencing and cell growth assay.

Results: The ChIP-seq analysis identified 3,013 peaks of EF binding with 1,433 neighbor genes in the mouse ES cell. Ets binding motifs and GGAA microsatellites were significantly selected in EF binding peaks. Association of EF and histone H3K27Ac peaks were noted (Fig. 1), and strong association with EF bindings at GGAA microsatellites was observed. Eighty-two genes were found upregulated in the vicinity of EF binding at GGAA microsatellites (Table1). Trib1 is one of such candidate target genes of EF. Knockdown of Trib1 in mouse and human ES suppressed cell proliferation significantly. In addition, FOX family binding motifs were frequently detected within ES binding peaks, suggesting that FOX family transcription factors might cooperatively bind DNA with EF. Gene expression profiles in mouse ES and reporter assays identified Foxq1 as a novel EF collaborator.

Conclusion: In mouse ES, EF recognizes GGAA microsatellites and EBS as in human ES, though most of GGAA microsatellites were not associated with reported target genes, many of which were upregulated also in mouse ES. The results suggest that there might be unidentified EF's regulatory mechanisms. The present study also identified Foxq1 as a novel EF collaborator in DNA binding and gene regulation.

Fig. 1 EWS-FLI1 binding in mouse Ewing sarcoma



a. Heatmap of EWS-FLI1 / H3K27Ac peaks
b. Examples of EWS-FLI1 binding loci

Table 1. Upregulated genes in mES with EF binding peaks. GGAA microsatellites were involved within the peaks.

Candidate target genes of EWS-FLI1

Gene ID	FC (mES vs NC)	Gene ID	FC (mES vs NC)
Zfp804a	19.221073	Bnip2	3.6737566
Gk5	18.816088	Dync2h1	3.595428
Cacna2d1	18.23245	Trib1	3.5089362
Nrg1	17.906794	Prdx6	3.4701226
Mmel1	17.165981	Lgals7	3.467468
Runx1t1	16.064648	Mrc1	3.3653455
Zfp462	13.486474	Ctnna1	3.3271399
Rtn4rl1	12.675605	Alg14	3.3012626
Tmem30a	12.449227	Gnai1	3.2405715
Tmtc2	10.291719	Ppp1r12a	3.2306406
Fam198b	8.824051	Rsrc1	3.1680355
Pdk1	8.551397	Plekhf2	3.0987062
Zswim6	8.471297	Rpe	3.0138807
Pvt1	8.080182	Crct1	3.013433
A330008L17Rik	7.96985	Nsmce2	2.9473429
Cdh8	7.9308286	Pbx3	2.579756
Zwilch	7.445383	Slc44a1	2.4115438
BC030870	7.443368	Adck5	2.340664
Fam163b	7.34422	Hnrnpd	2.2598321
Gramd4	7.0775676	Tspan13	2.2394335
Dner	6.8534117	Usp48	2.2056463
Foxb1	6.6307135	Papd7	2.155838
Galnt13	6.3955026	Adamtsl2	2.0822933
Larp7	6.137986	Vsnl1	2.0196126
Npl	6.113625	Cerk	1.9524685
Kirrel	5.625364	Tpcn1	1.9471177
Fnip2	5.625112	Plbd2	1.9462708
Ccl20	5.389443	Agpat9	1.9164855
Herc3	5.2840495	Fgf12	1.894477
Dhx9	5.271922	Abcc1	1.8421985
Rbbp8	5.0233135	Ddx51	1.8294599
Rgs8	4.631972	Filip1	1.8065757
Rap2b	4.5172486	Supv3l1	1.7267275
Shox2	4.451562	Fbxl6	1.7225976
Ezh2	4.360556	Mapkap1	1.6754221
Ddx21	4.250491	Ank2	1.6417086
Bzw2	4.1731167	Ptprd	1.6253871
Phf14	4.047317	Cpsf1	1.6123836
Cnn3	3.9319432	Rapgef4	1.599395
Smad3	3.9285662	Syt2	1.5291388
Myc	3.7663488	Dhx35	1.50267

(mES: mouse ES, NC: normal tissue, FC>1.5, p<0.05)

Poster 053 #2790139

CLINICAL BENEFIT OF GANITUMAB USING PATIENT-DERIVED ORTHOTOPIC XENOGRAFT (PDOX)-DIRECTED THERAPY IN A PATIENT WITH A RARE EWING'S SARCOMA

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Objective: Demonstrate that individual PDOX models can direct personalized therapy in sarcoma patients with clinical benefit.

Methods: A 46-year old female patient with a FUS-ERG fusion Ewing's sarcoma family tumor of the chest wall underwent 14 cycles of doxorubicin-based chemotherapy [neoadjuvant (2 cycles) and adjuvant (12 cycles)]. At the time of surgical resection, a PDOX model of the patient's tumor was established in the chest wall of nude mice by surgical orthotopic implantation. Traditional chemotherapy and targeted inhibitors were tested against the patient's PDOX model and the results were used to direct her oncologic management (see Figures 1 and 2).

Results: Foundation Medicine testing of the patient's tumor demonstrated the FUS-ERG fusion, and the loss of CDKN2A/B. The patient's PDOX model was established by 59 days after surgery, and was found to be resistant to doxorubicin, and sensitive to palbociclib (CDK4/6 inhibitor) and linsitinib (IGF-1R inhibitor) within 3 months of surgical resection [Figure 1]. One year after completing the 14 cycles of doxorubicin-based therapy, the patient developed diffuse bone metastases and pancytopenia necessitating transfusions and filgrastim. Due to cytopenias, she was unable to receive traditional second-line chemotherapy. The PDOX response data was used to obtain a compassionate-use investigational new drug (IND) approval for the patient to be treated with ganitumab, a monoclonal antibody against IGF-1R (NCT 03029481). After the first dose of ganitumab, the patient did not require any additional blood or platelet transfusions. She went on to receive 8 doses of ganitumab at 18mg/kg IV over the course of 4 months before progressing. The patient's PDOX model was subsequently tested against multiple additional therapies, and irinotecan/temozolomide resulted in tumor regression [Figure 2]. Based on this data, the patient began irinotecan/temozolomide, and again demonstrated a rapid clinical response and reported a reduction in narcotic analgesia while on the PDOX-identified therapy; treatment is ongoing.

Conclusion: Individual PDOX mouse models can precisely identify both effective and ineffective therapies in sarcoma patients and can be used to inform oncologic decision-making to beneficially impact patient outcomes.

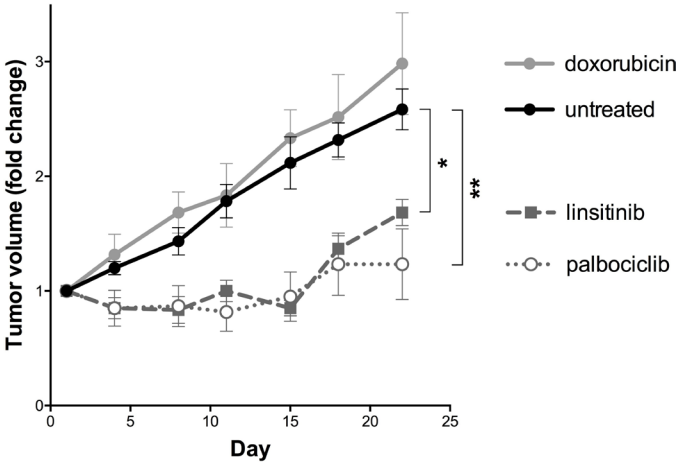

Figure 1: First round of drug testing in a PDOX model of Ewing's family sarcoma reveals doxorubicin resistance. Doxorubicin: i.p., 3 mg/kg, weekly, 2 weeks. Linsitinib: p.o., 25 mg/kg, daily, 14 days. Palbociclib: p.o., 100 mg/kg, daily, 14 days. * p<0.05, ** p<0.01.

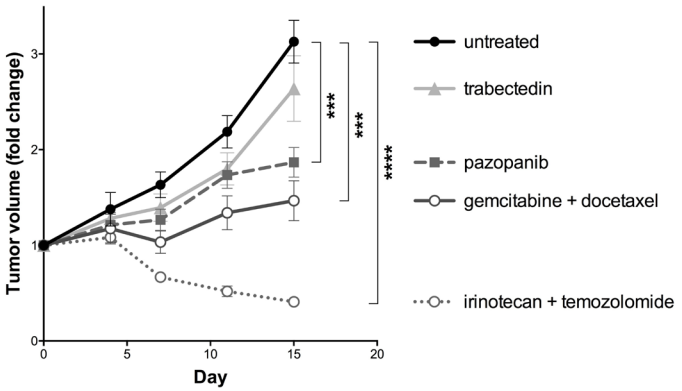

Figure 2: Second round of drug testing in a PDOX model of Ewing's family sarcoma demonstrates tumor regression after irinotecan/temozolomide. Trabectedin: i.v., 0.15mg/kg, weekly, 2 weeks. Pazopanib: p.o., 100mg/kg, daily, 14 days. Gemcitabine: i.p., 100mg/kg, weekly, 2 weeks. Docetaxel: i.p., 20mg/kg, weekly, 2 weeks. Irinotecan: i.p., 4mg/kg, weekly, 2 weeks. Temozolomide: p.o., 25mg/kg, daily, 14 days. *** p<0.001, **** p<0.0001.

Poster 054 #2769945

TARGETING INTEGRIN-MEDIATED SIGNALING IN METASTATIC EWING SARCOMA

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Objective: Background: Metastatic Ewing sarcoma (ES) has an extremely poor overall survival, necessitating examinations into molecular mechanisms to identify novel targets and develop new therapies. We performed a nov-

el in vivo study designed to provide insights into metastatic transcriptomic and proteomic signatures for ES to identify potential therapeutic targets. Comparing profiles of primary tumors to corresponding metastatic lesions, we identified aberrant expression of integrin ß3 (ITGB3) and downstream activation of integrin-linked kinase (ILK) in metastatic lesions compared to primary tumors, implicating this pathway as a key regulator of ES metastasis.

Hypothesis: Upregulation of ITGB3 and its downstream signaling events play a key role in ES metastasis and are viable therapeutic targets.

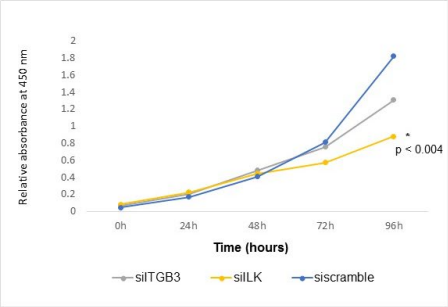
Objective: To investigate the role of ITGB3 and its downstream signaling pathways in driving establishment of metastasis in ES and to investigate this pathway as a potential therapeutic target.

Methods: To investigate the role of ITGB3 and ILK in ES metastasis, we used siRNA to knock down ITGB3 and ILK expression in established ES cell lines and then assessed the effects of this change on tumor cell properties by performing functional assays in vitro, including cell proliferation and invasion/migration assays. We also tested inhibition of this ITGB3 signaling pathway using available small molecule inhibitors targeting ITGB3, ILK and the downstream target AP-1, using Cilengitide, Compound 22 and SR11302, respectively, and again performed functional assays in vitro to assess effects on tumor cell properties.

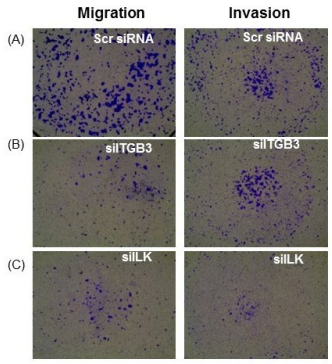
Results: Knockdown of ITGB3 and ILK in our siRNA cell lines resulted in decreased cell proliferation and decreased invasion and migration compared to controls (Image1). We also found significantly decreased cell proliferation and increased apoptosis using each of the small molecule inhibitors in vitro (Image2).

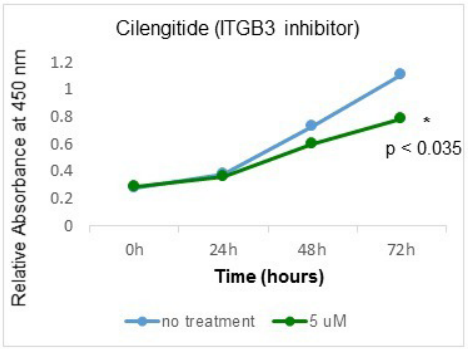
Conclusion: These results support our hypothesis that ITGB3 and its downstream signaling events play a key role in regulating ES metastasis and may serve as a potential therapeutic target. We continue to investigate this pathway in vitro. We are also using our small molecule inhibitors and inducible shRNA and overexpression approaches to study these effects on metastatic tumor development in vivo using our mouse model.

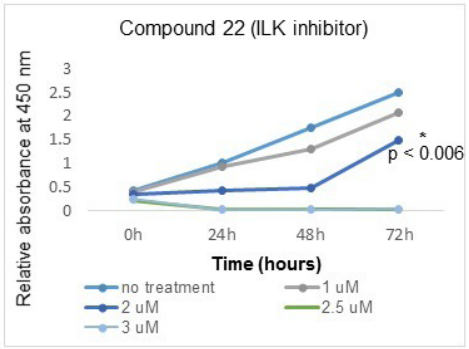
Cell proliferation assay:
Knockdown of ITGB3 or ILK decreases ES cell proliferation

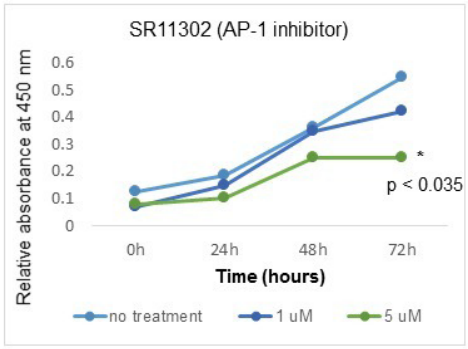


Invasion/migration assay:
Knockdown of ITGB3 or ILK decreases ES invasive and migratory phenotypes









Poster 055 #2790924

CIC REARRANGED SARCOMAS: THE MD ANDERSON EXPERIENCE WITH A RARE, RECENTLY RECOGNIZED ENTITY

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Objective: Recently, primitive small round blue cell tumors that resemble Ewing Sarcoma but are negative for the EWSR1-FLI1 translocation have been found to harbor alternative translocations including CIC-DUX4, which may portend a worse prognosis. We reviewed our institutional experience with this recently described rare disease.

Methods: With IRB-approval. CIC-rearranged round cell sarcomas treated at MD Anderson Cancer Center were identified through the Pathology Database for retrospective chart review. Descriptive statistics, response to treatment and survival analysis were performed.

Results: 10 patients with CIC-rearranged sarcomas were identified. 5 were male and 5 were female. The median age was 19 (Range: 10-35). 8 patients (80%) were Caucasian, 1 was Hispanic (10%), and one was African American (10%). 8 patients (80%) had extraosseous primary sites, and 2 (20%) had osseous primary tumors. 8 patients had treatment data available. All received either VAC/IE or VDI as initial treatment. A complete pathologic response was seen in one patient who went to surgery after neoadjuvant chemotherapy, 2 patients had a partial response . 1 had stable disease, and 1 had progressive disease. 3 patients did not have measurable disease at the time of initial treatment. In the salvage setting, 4 patients received VIT, 1 had stable disease, 2 had progression, and 1 was not assessable. Three patients received gemcitabine and docetaxel, and all 3 had progressive disease as best response.

Conclusion: Though sensitive to Ewing sarcoma directed regimens, with a subset associated with cure, CIC-rearranged sarcomas have less robust responses than in classic Ewing Sarcoma. Further investigation is needed to define optimal treatment for this rare and challenging disease.

Demographic Characteristics of Patients with CIC-rearranged Sarcomas

	Number
Sex	
Male	5
Female	5
Age	
High	35
Low	10
Median	19
Race	
White	8
Hispanic	1
African American	1
Primary Site	
Osseous	8
Extra-Osseous	2
Tumor Size	
Maximum	29 cm
Minimum	3 cm
Median	5.2 cm
Stage at Presentation	
Localized	7
Metastatic	3

Response to regimens administered to patients with CIC-rearranged sarcomas

Regimen	Complete Response	Partial Response	Stable Disease	Progression
VDI or VAC/VDC/IE (n=5)	1	2	1	1
VIT (n=3)	0	0	1	2
Gemcitabine and Docetaxel	0	0	0	3
HD Ifos +/- Etoposide	0	0	0	2

V: vincristine, D: doxorubicin, I: ifosfamide, A: actinomycin D, E: etoposide, VIT: vincristine/irinotecan/temozolomide, Gem/Tax: gemcitabine/docetaxel, HD Ifos: high-dose ifosfamide 12-14 gm/m2.

Poster 056 #2804359

THE EFFECT OF SURGICAL MARGINS ON LOCAL CONTROL FOR THE TREATMENT OF EWING'S SARCOMA: A SINGLE INSTITUTIONAL EXPERIENCE

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Objective: Ewing's Sarcoma is a rare primary bone malignancy, which necessitates both systemic and local treatment. While local control may be effectively rendered using radiation, surgery is often preferred to avoid the potential consequences of radiation, most notably a secondary malignancy. In instances where negative margins are obtained, surgery alone is used to achieve local control. In instances where positive margins are realized, radiation is frequently added. The quantitative surgical margin below which the addition of radiation is beneficial remains unknown. The purpose of this study was to identify a surgical margin threshold, above which effective local control was reliably realized or below which recurrence resulted.

Methods: Between 2005 and 2016, 32 patients with Ewing's Sarcoma were evaluated at a tertiary care medical center. A retrospective review of the electronic medical records, including the pathology reports, chemotherapy and radiation treatment details, and short-term outcomes was performed. Patients were excluded if they underwent surgical treatment elsewhere. Patients who underwent radiation therapy as their planned method of local control were excluded as well. Complete medical records and intermediate outcome data was available for thirteen patients who underwent surgical management.

Results: Three out of thirteen patients (23.1%) experienced local recurrences following surgical resection of the primary tumor. These patients had surgical margins of 0mm, 0.5mm, and 0.6mm. The only patient to receive post-operative radiation therapy (RT) was the patient with positive surgical margins (0mm). There were no local recurrences above margins ≥ 1.0mm while all local recurrences occurred in cases where were margins < 1.0mm. ($p = 0.004$). Two out of the three patients with local recurrences exhibited poor response to neo-adjuvant chemotherapy (necrosis rates < 20%) in their resected tumors. One of the three patients with local recurrences failed to demonstrate the classic EWSR1-FLI1 translocation.

Conclusion: Findings indicate that resection of Ewing sarcoma with a surgical margin ≤ 1.0mm may carry a higher risk of local recurrence and that post-operative RT should be considered in these cases. This study is limited by the small number of patients included. Careful consideration of surgical margin width may be of greater importance in cases where poor response to neo-adjuvant chemotherapy has been observed. Future multi-institutional collaboration may serve to both validate and better define the threshold below which recurrence is likely as well as the use of tumor response to chemotherapy as an indication for post-operative RT.

Poster 057 #2733070

DNA REPAIR DEFICIENCY IN EWING SARCOMA CORRELATES TO TP53 MUTATION STATUS AND CAN BE REVERSED WITH WILD TYPE P53 EXPRESSION

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Objective: Previous data has demonstrated a correlation between increased copy number alterations and global DNA methylation disruption with worse prognosis in patients with Ewing sarcoma (ES). While these aberrations manifest as genomic instability in affected ES cell lines, the underlying pathways contributing to this unstable phenotype are not well-understood. We examined DNA repair following irradiation (IR) in multiple ES and other cancer cell lines. We hypothesized that defective DNA repair in ES is not a function of some unknown pathway unique to ES, but rather, of TP53 (and p53 protein) status.

Methods: We performed immunostaining analysis for γ-H2AX on the following cell types: ES (ES1, ES8, CHLA9, CHLA10, A673, TC252, and CHLA258), osteosarcoma (U2OS and SAOS2), and ovarian adenocarcinoma (SKOV3). Cell lines were examined prior to IR and at four time points after 5 Gy IR: 5 minutes, 2 hours, 8 hours, and 24 hours. For each time point, images of 50 cells were saved. Using ImageJ, images were converted to binary and γ-H2AX foci were counted as a surrogate for DNA damage. The percentage of cells with >20 γ-H2AX foci were compared across all cell lines and time points. A673 cells were transduced with a lentiviral system with either an empty vector vs. human TP53 gene (wild type). Transduced cells were treated and DNA repair was measured as described above.

Results: As illustrated by cell lines U2OS and A673 (Fig. 1), all cells had a significant increase in γ-H2AX foci following IR. However, at 24 hours post-IR, those with wild type p53 (HP53) (Table 1) averaged a 5% increase in cells with >20 γ-H2AX foci vs. 25.7% increase for those with mutated p53 ($p=0.0039$) (Fig. 1 and 2A). When A673 was transduced with wild type HP53, its DNA repair response at 24 hours post-IR markedly improved with nearly twice as less γ-H2AX foci (Fig. 2B).

Figure 1:

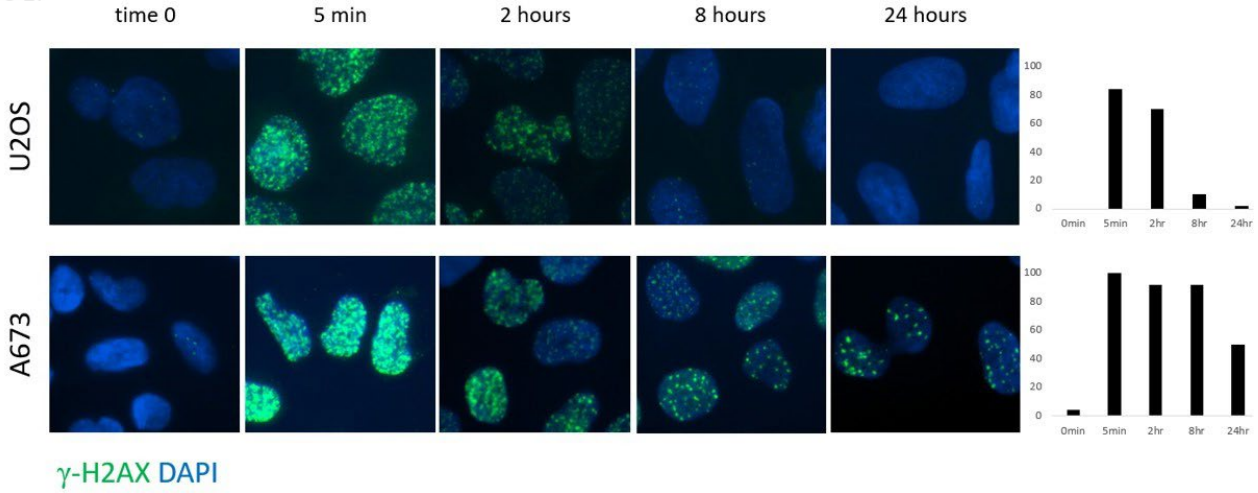

Figure 1. A673 (*TP53 mut*) cells are more defective in repairing double stranded DNA breaks than U2OS (*TP53* WT). Representative images at time points 0, 5 minutes, 2 hours, and 24 hours post IR (5 Gy) showing U2OS and A673 nuclei (blue) stained for γ-H2AX (green). Histograms represent percentage of cells with > 20 foci of γ-H2AX per cell.

Figure 2A:

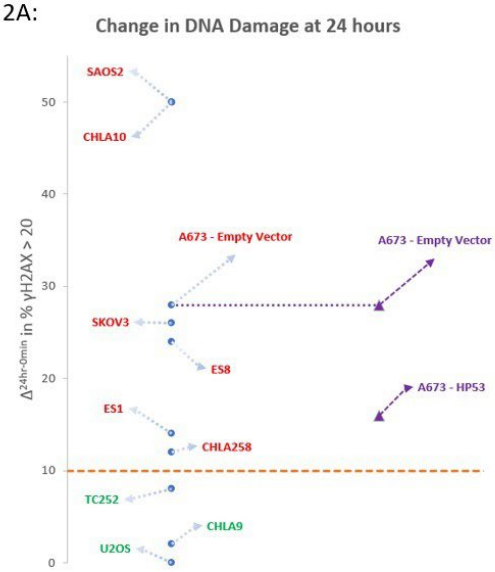

Figure 2B:

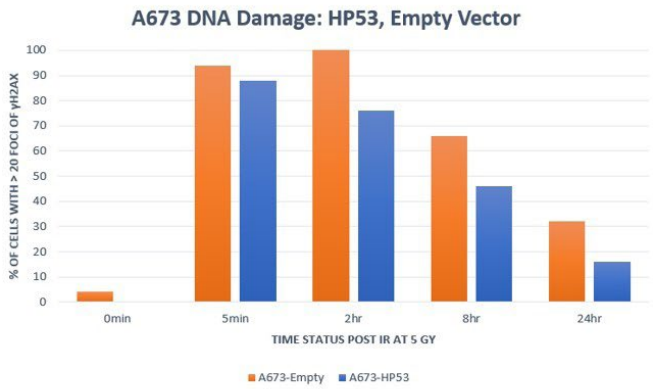

Figure 2. The p53 status of cells is correlated to ability to repair double stranded DNA breaks. A: Percentage of cells with > 20 γ-H2AX foci 24 hours post IR above baseline (pre-IR) is greater in cells with p53 deficiency (red) than cells with WT p53 (green). Mean values for p53 deficient cells and WT p53 cells were 25.7 and 5, respectively (p=0.0039). A, B: When A673 cells are transduced with HP53, their DNA repair significantly improves (A: purple).

Table 1

Cell Line	P53 Status
U2OS	WT
TC252	WT
CHLA9	WT
CHLA10	Mutated
A673	Mutated
CHLA259	Mutated
ES1	Mutated
ES8	Mutated
SAOS2	Mutated
SKOV3	Mutated

Cell lines tested and their corresponding p53 status.
WT = wild type.

Conclusion: The DNA repair mechanism in ES and other cancer cell lines correlates to the p53 status of the cells. Furthermore, introduction of wild type p53 protein expression in p53 mutated cells can rescue deficient DNA damage repair. While the factors contributing to genomic instability in ES remain largely unknown at this time, these data support a potential role of p53 mutation in generating an unstable phenotype through a decreased DNA repair response permissive of genomic alterations. Furthermore, the introduction of novel p53 therapeutics may play an important future role in patients with ES and unstable tumors with p53 mutations.

Poster 058 #2761259

RETROSPECTIVE STUDY OF MAINTENANCE CHEMOTHERAPY IN EWING SARCOMA: SINGLE INSTITUTION EXPERIENCE

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Objective: In the United States, Ewing sarcoma is responsible for 3.5% of cancers in children ages 10-14 years and 2.3% in those of ages 15-19 years. Poor prognosis is found in patients with primary pelvic tumors (50% 5-year survival rate) and those with metastasized disease at time of diagnosis (15-30% 5-year survival rate). This is likely due to progression of disease with a higher rate of relapse after standardized treatment. We reviewed the use of maintenance chemotherapy in high-risk Ewing sarcoma to evaluate for improvement in survival rates.

Methods: Multiple retrospective studies have evaluated the use of irinotecan and temozolomide in treating relapsed and/or progressive Ewing sarcoma with a reported response rate of 55-63%. On literature review, there were no publications studying the use of these chemotherapies in patients to prevent relapse. This study describes patient characteristics, response to standard therapy, and relapse rates with and without the use of maintenance irinotecan and temozolomide.

Results: Chart review of 65 patients diagnosed with Ewing sarcoma/PNET at CHOC from 2000-2016 was completed. Of those patients, 14 did not have records available for review. 29 patients had pelvic or metastatic disease at time of diagnosis. Of these patients, 20 patients (14 metastatic/6 localized pelvic) received only standard therapy, while 9 patients (8 metastatic/1 localized pelvic) received additional maintenance therapy. 13 of the 20 patients who received standard therapy relapsed or progressed, resulting in 11 deaths (55%). Event free survival (EFS) rate of those who received standard therapy was 35%, while overall survival (OS) rate was 45%. Of the 9 patients who received maintenance therapy, 4 patients relapsed/progressed, resulting in 3 deaths (33%). EFS rate of those who received maintenance therapy was 56%, with an OS rate of 67%.

Conclusion: At CHOC, it was found that 65% of patients with primary pelvic tumors or metastatic disease treated with standard therapy alone experienced either relapse or progression of disease. In contrast, 44% of patients with primary pelvic tumors/metastatic disease treated with the addition of irinotecan and temozolomide after completing standard therapy relapsed or progressed. Further study in the use of a maintenance phase of treatment with chemotherapeutic agents such as irinotecan and temozolomide is needed given the small sample size of this study, as well as variation in dosage and length of treatment.

Comparison of results between Standard Treatment vs. Standard Treatment + I/T

	Standard Treatment	Standard Treatment + I/T
Primary pelvic tumor/ Metastatic disease	20	9
Relapse/Progression	13	4
Event-free since EOT	7	5
Event-free survival rate	35%	56%
No. of patients deceased	11	3
No. of patients alive	9	6
Overall survival rate	45%	67%

– GIST –

Poster 059 #2771952

A PHASE 1 PHARMACOKINETIC (PK) AND PHARMACODYNAMIC (PD) STUDY OF PLX9486, ANOVEL KIT INHIBITOR WITH POTENT ACTIVITY AGAINST EXON 17/18 ACTIVATION LOOP MUTATIONS IN PATIENTS WITH GASTROINTESTINAL STROMAL TUMOR (GIST)

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Objective: In GIST, Activating mutations in KIT exon 9 or 11 occur in ~ 80% of patients. Tyrosine kinase inhibitors (TKIs) such as imatinib, sunitinib and regorafenib have transformed the treatment of GIST. Most GIST patients develop resistance mutations commonly in exon (ex) 13, 17 or 18. PLX9486 is a novel TKI with activity against the primary KIT mutations (ex 9 and 11) and against the activation loop mutations in ex 17 and 18. Study objective: determine maximum tolerated dose (MTD) of PLX9486.

Methods: 3+3 dose escalation study with 28-day cycles beginning at 250mg once daily (QD) oral dose in GIST and other solid tumors. BID dosing was studied to increase exposure. PK, PD markers, including circulating tumor DNA (ctDNA), and safety were monitored. Response was assessed by standard criteria.

Results: As of May 31 2017, 23 patients (pts), including 18 with GIST, were enrolled; median age was 54 years (range 39-79 years); GIST pts had a median of 4 prior therapies (range 3-8), and all had progressed (PD) on imatinib. Dose levels were 250-1000mg QD and 500mg BID. QD PK suggested saturable absorption at steady state with a t1/2 of 44-48 hours, Cmax of 1020 ng/mL and a AUC0-24 of 23400 hr*ng/mL at the highest dose (medians). There was no significant PK advantage for BID dosing. Common adverse events (AEs) in ≥25% pts (N=23): nausea(N) (39%), diarrhea (30%), vomiting (V) (26%), fatigue (44%), peripheral edema (30%), anemia (35%), AST increase (48%), ALT increase (35%), and alkaline phosphatase increase (26%). The majority were grade (G) 1-2. G 3+ AEs occurring in ≥5% of pts: N/V, GI hemorrhage, anemia, and fatigue (all 9%). There were 2 G 4 AEs – hyperuricemia and hypophosphatemia. At dose levels ≥ 500mg QD multiple pts had prolonged stable disease and 3 pts had minor responses. A pt dosed at 500mg QD with primary ex 11 and resistance ex 17 mutations in ctDNA had a 14% tumor shrinkage with decreases in circulating KIT mutations. This pt was on study for 9 cycles and had PD on imatinib, sunitinib, regorafenib, pazopanib and ponatinib. Most pts discontinued study drug due to PD and not due to toxicity.

Conclusion: PLX9486 is a novel inhibitor of KIT with activity against difficult to treat ex resistance 17/18 mutations and demonstrates a favorable safety profile. QD dosing is feasible. The recommended phase 2 dose is 1000mg QD. Expansion cohorts in GIST are planned as are combinations with sunitinib and pexidartinib which have complementary activity against KIT resistance mutations.

Poster 060 #2759753

TRIAL IN PROGRESS: A RANDOMIZED PHASE 2 STUDY OF NIVOLUMAB MONOTHERAPY VERSUS NIVOLUMAB COMBINED WITH IPILIMUMAB IN PATIENTS WITH METASTATIC OR UNRESECTABLE GASTROINTESTINAL STROMAL TUMOR (GIST)

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Objective: The vast majority of GISTs are driven by mutations in KIT and PDGFRα and secondary mutations in these genes are felt to confer resistance to tyrosine kinase inhibitors. In advanced/metastatic GIST, the benefit of second line and beyond TKIs is progressively less after imatinib failure. As such, novel non-TKI approaches are important to explore. Preclinical evidence and anecdotal reports have indicated that the immune system is active in refractory GIST.

Methods: This study is a randomized, parallel group, unblinded Phase 2 trial that will evaluate the response rate by RECIST 1.1 criteria in patients with advanced or metastatic GIST treated with nivolumab (240 mg Q2 weeks up to 2 years) or nivolumab (240 mg Q2 weeks up to 2 years) with ipilimumab (1mg/kg Q6 weeks up to 2 years). Eligible patients are randomized 1:1 into the 2 treatment options. The primary objective of this study is to assess the response rate of nivolumab alone and in combination with ipilimumab in subjects with metastatic or locally advanced/unresectable GIST. With a sample size of 20 per group, an exact binomial test with a nominal 0.050 one-sided significance level will have 82% power to detect the difference between the null hypothesis response rate 1.5% and the alternative response rate of 15%. Secondary objectives are to ascertain the PFS, CBR and safety of nivolumab alone and in combination of ipilimumab in subjects with metastatic or locally advanced/unresectable GIST as well as RR by Choi criteria. The main inclusion criteria for the study include age>18, ECOG of 0-1, progression or intolerance of imatinib, measurable disease as assessed by RECIST 1.1 criteria, and standard bone marrow, hepatic and renal parameters. Main exclusion criteria include exposure to any therapeutic agent within 7 days of randomization, previous exposure to PD-1/PD-L1 or CTLA-4 blocking antibodies, palliative surgery, steroids or radiation therapy 28 days prior to treatment or any autoimmune disease within the past 3 years. Blood for circulating tumor cells(CTCs), cell free DNA(cfDNA), pretreatment and on-treatment biopsies for PD-L1 and immune microenvironmental analysis is also being collected.

Results: To date, 10/40 patients have signed consent and started on trial drug. Pretreatment biopsies have been obtained in 9/10 patients and blood has been collected on all patients for analysis of CTCs, cfDNA and TCR repertoire.

Conclusion: The study is ongoing and accruing patients to a total of 40 patients.

Poster 061 #2785215

GENOTYPE AND RISK OF TUMOR RUPTURE IN GASTROINTESTINAL STROMAL TUMOR

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Objective: Tumor rupture is a strong predictor of poor outcome in gastrointestinal stromal tumor (GIST) of the stomach and small intestine. The aim of this study was to determine whether tumor genotype was associated with risk of rupture.

Methods: Tumor rupture was classified according to the definition proposed by the Oslo Sarcoma Group. Data were retrospectively registered for all patients at Oslo University Hospital undergoing surgery for localized GIST of the stomach or small intestine since 1.1.2000. KIT and PDGFRA (platelet derived growth factor alpha) gene mutations were analyzed by Sanger sequencing.

Results: Two-hundred nine patients with available mutation data were identified, of whom 148 (71 %) had gastric GISTs and 61 (29 %) were localized in the small intestine. Tumor rupture occurred in 37 patients (18 %). KIT mutations were found in 167 tumors (80 %), PDGFRA mutations in 29 (14 %), and in 13 tumors (6 %) no mutation was discovered. Rupture was more frequent in KIT-mutated tumors (20 %) compared to tumors with PDGFRA mutation (7 %; P=0.12). Among the 155 patients with KIT exon 11 mutations, an increased risk of rupture was observed with a deletion or insertion/deletion (29 %) compared to substitutions (10 %) or duplications/insertions (11 %; P=0.014). Notably, 17 of 46 (37 %) tumors with deletions involving codon 557 and 558 (del557/558) had rupture, compared to 15 of 109 (14 %) with other exon 11 mutations (P=0.002). This association was confined to tumors localized in the stomach, and 12 of 34 (35 %) gastric GISTs with del557/558 had rupture compared to 6 of 77 (8 %) with other exon 11 mutations (P=0.001). As expected, tumors with del557/558 had a more aggressive phenotype, with a larger median tumor size and higher mitotic count. Still, del557/558 was associated with an increased risk of rupture also when tumors <10 cm were analyzed separately (P=0.009).

Conclusion: Gastric GISTs with KIT exon 11 deletions involving codon 557 and 558 are at increased risk of tumor rupture. This high-risk feature can be identified in the diagnostic work-up and should be included in the assessment when neoadjuvant imatinib treatment is considered.

Poster 062 #2786892

RECHALLENGE IN ADVANCED GIST PROGRESSING TO IMATINIB, SUNITINIB AND REGORAFENIB: AN ITALIAN SURVEY

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Objective: We retrospectively collected data from metastatic Italian GIST patients treated with imatinib or sunitinib reintroduction after progression to conventional three or four lines of therapy.

Methods: 104 eligible advanced GIST patients, previously treated with imatinib, sunitinib and regorafenib, were collected in the present analysis from 6 cancer centres. All patients received all three standard kinase inhibitors. Imatinib dose increase as active second line or 800 mg upfront in exon 9 mutant GIST were allowed. Specific mutations were recorded if available (deletion versus others) and correlated with survival and response according to RECIST 1.1 or CHOI criteria.

Results: Seventy-one patients were evaluable. 63 received Imatinib 400 mg as rechallenge, while 8 patients were treated with sunitinib at personalised dose and schedule according to the physician's choice. Mutational status was available in all patients and in 68 patients details about type of mutation were achievable. The median follow-up was 13 months (range 1-42 months). The median time to progression (TTP) in patients receiving a rechallenge therapy was 5.4 months (95% CI 1.9-13.5) and Overall Survival (OS) was 10.6 months (95% CI 2.8-26.9). Apparently, in this setting a correlation between mutational status and response rate, TTP or OS was not found. On the contrary, considering only exon 11 mutated patients and comparing patients with deletion vs non deleted ones a significant difference was identified both in terms of TTP and OS (respectively, P = 0.04 and P = 0.02).

Conclusion: Our retrospective data confirm that the rechallenge of imatinib or sunitinib is a reasonable option in advanced GIST patients after failure of previous treatments. As expected, imatinib is the most frequently prescribed option in the Italian real-life setting, demonstrating a TTP and OS longer than those observed in previous studies. Also the prognostic value of the specific type of exon 11 KIT mutations has been confirmed in our series.

Poster 063 #2796834

DUAL INHIBITION OF AKT AND KIT IS SYNERGISTIC IN GASTROINTESTINAL STROMAL TUMOR

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Objective: The majority of gastrointestinal stromal tumors (GIST) harbor oncogenic mutations in the receptor tyrosine kinase KIT or platelet-derived growth factor receptor alpha (PDGFRA). Small molecule kinase inhibitors such as imatinib mesylate (IM) have significantly improved the clinical management of GIST by targeting these mutant receptors. Despite strong overall response rates to IM, disease progression generally does occur in time. Therefore, inhibiting targets other than, or in addition to, traditional tyrosine kinases may provide additional therapeutic benefit in GIST. Both KIT and PDGFRA activate AKT and recent studies associate the PI3-kinase/AKT pathway activity with survival of IM-resistant GIST cell lines and tumors. In this study, we performed in vitro and in vivo experiments to assess the potential benefit of combining IM with an ArQule AKT inhibitor, ARQ 092.

Methods: In order to evaluate in vitro drug sensitivity, a panel of IM-sensitive (GIST-T1, GIST882) and resistant GIST cell lines (GIST-T1/829, GIST430) cells were subjected to drug treatment for 72 hours before measuring viability with the Cell Titer Blue Viability Assay. Synergy between IM and ARQ 092 was quantified using the Chou-Talalay algorithm to calculate CI values. CI values <1 are considered synergistic. In vivo studies are currently underway in IM sensitive (GIST-T1) and resistant (GIST430) GIST xenograft models, as well as in an IM resistant GIST PDX model.

Results: The 3:1 molar ratio of ARQ 092:IM demonstrated synergistic CI values in all four GIST lines. Immunoblot assays confirmed that drugs hit their intended targets in each cell line following six-hour drug treatment. Interestingly, a significant decrease in the activation of a downstream signaling protein, p-S6, was observed in combination-treated cells compared to cells treated with single agents. In addition, combination therapy demonstrated significantly greater efficacy, as measured by tumor response, in the IM sensitive xenograft model. In vivo studies in IM resistant models are ongoing and data will be reported in November.

Conclusion: These studies demonstrate that the novel combination of imatinib mesylate with the AKT inhibitor, ARQ 092 provided significantly improved efficacy compared to monotherapy. These results provide justification for development of further pre-clinical and clincal studies evaluating this combination in GIST patients.

Poster 064 #2803663

BASELINE BLOOD NEUTROPHIL-TO-LYMPHOCYTE RATIO IS ASSOCIATED WITH LONG-TERM OUTCOMES OF GASTROINTESTINAL STROMAL TUMORS (GIST) TREATED WITH IMATINIB AND SUNITINIB

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Objective: Neutrophil-to-lymphocyte ratio (N/L) was shown to be prognostic in several solid malignancies. There are limited data about predictive/prognostic value of N/L ratio during targeted therapies of patients with advanced gastrointestinal stromal tumor (GIST). The aim of the study was to asses a clinical value of N/L ratio in patients with advanced GIST.

Methods: Between 2001 and 2016, 686 patients with metastatic/unresectable GIST treated initially with imatinib were included to the analysis. Additionally, 232 of these patients were treated with sunitinib after imatinib failure. In all patients the N/L ratio was assessed at the baseline, and disease progression or last observation. The cut off for ratio N/L was set at 3. The factors influencing the long-term overall survival (OS) and progression-free survival (PFS) were analyzed with Kaplan-Meier survival probability estimation, log rank test, and Cox proportional hazard model.

Results: Median PFS on 1st line imatinib was 39 months (3-year rate 53%), median OS - 75 months (3-year rate 73%, 5-year rate 50%, 10-year rate 27%). N/L ratio >3 at baseline of imatinib therapy was significantly associated with decreased PFS and OS. Median OS time was 86 months (95% CI: 73-99) for N/L ratio <3 vs. 61.5 months (95%CI: 45-82) for N/L ratio ≥3 (p=0.004), median PFS was 51 months vs 29 months, respectively (p=0.002). At 3 months after starting of imatinib therapy, the sustained increase of N/L ratio above 3 was significantly associated with poorer PFS (p<0.001) and OS (p<0.001). In the Cox model adjusted for mutational status (with presence of exon 11 KIT mutations as positive prgonostic factor) and patient age, N/L ratio was independently associated with higher risk of progression (HR 1.078; 95% CI: 1.013-1.147; p=0.017).

Median PFS on sunitinib therapy was 10 months, and OS - 22 months. In this group, median OS was significantly longer (28.2 months) for patients with initial N/L ratio < 3 when compared with 12.7 months for patients with N/L ratio ≥3 (p=0,03) independently of the presence of exon 9 KIT primary mutation recognized as a positive prognostic factor.

Conclusion: Our results demonstrate the usefulness of N/L ratio as a prognostic and predictive marker in patients with advanced GIST receiving tyrosine kinase inhibitors treatment. The monitoring of the N/L ratio over this therapy may be helpful for assessment of the disease progression or response.

Poster 065 #2765297

SURGICAL AND MEDICAL MANAGEMENT OF SMALL BOWEL GASTROINTESTINAL STROMAL TUMORS: A REPORT OF THE DUTCH GIST REGISTRY

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Objective: Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal malignancies of the gastrointestinal tract. Most frequently these tumors originate in the stomach (60%) or small bowel (30%). As not all GISTs have the same clinical behavior, a cohort of patients with small bowel GIST, treated in GIST expertise centers in the Netherlands was analyzed with regard to diagnosis, treatment and outcome.

Methods: Patients with GIST who have been treated in one of the five participating centers (Antoni van Leeuwenhoek Hospital, Leiden University Medical Center, Erasmus Medical Center, Radboud University Medical Center, University Medical Center Groningen) are registered in the Dutch GIST registry (Jan 2009 – ongoing). Patient characteristics, clinical information (surgery, systemic therapy), pathology reports, recurrence and survival data is registered. Patients with small bowel GIST were identified and included in this analysis (Jan 2009 – Dec 2015). Patients are treated according to international guidelines and were analyzed within two groups based on primary treatment intention (curative (localized) vs. palliative (metastatic) at time of primary diagnosis.

Results: 137 patients were identified (baseline characteristics in table 1). Of patients who underwent surgery with curative intent (n=86), 48 had a tumor with high risk properties (>50% risk of recurrence, table 1). Of these patients, 24/48 received adjuvant systemic therapy. The majority of the patients who did not receive adjuvant therapy underwent surgery before 2010. After a median follow-up (FU) of 22.5 (range 0-75) months, 10/48 patients

Table 1

Groups		Curative (n=98)	Palliative (n=39)	p-value
Gender	Male	43 (44%)	25 (64%)	
Age at diagnosis (yr)		61	63	0,16
WHO performance score at BL				
	0-1	55 (56%)	23 (59%)	
	>1	1 (1%)	6 (15%)	
	?	42 (43%)	10 (26%)	
Hb level at diagnosis (mmol/L)		7,9	7,3	0,01
Tumor status at diagnosis				
	Localized	62 (63%)	0	
	Locally advanced	23 (23%)	0	
	Metastatic	13 (13%)	39 (100%)	
Primary tumor size (median)		81,5	102	0,036
Histology				
	Spindle cell	65 (66%)	26 (67%)	
	Epitheloid	7 (7%)	4 (10%)	
	Mixed type	11 (11%)	4 (10%)	
	Not reported	15 (15%)	5 (13%)	
Risk category (Miettinen)				
	Low/medium risk	34 (35%)	9 (23%)	
	High risk	48 (49%)	24 (62%)	
	Unknown	16 (16%)	6 (15%)	
Mutational analysis				
	KIT exon 9	11 (11%)	7 (18%)	
	KIT exon 11	47 (48%)	20 (51%)	
	KIT exon 13	2 (2%)	0	
	KIT exon 17	1 (1%)	1 (3%)	
	PDGFRα exon 18	0	0	
	Not reported	37 (38%)	11 (28%)	

Baseline and pathology characteristics

developed recurrent disease. Nine of those patients had not received adjuvant therapy. After surgery, the time to develop recurrent disease was median 25 (3-44) months.

In 37/86 patients operated in a curative setting, surgeries were performed because of another disease or in an emergency setting (table 2). This resulted in a non-R0 resection in five patients, whereas 3/39 patients who had elective surgery had a non-R0 resection.

Twenty of the 36 patients who received systemic therapy for primary metastatic disease did have disease progression on first line treatment with imatinib after a median of 13 (3-39) months. After a median follow up of 27 (1-54) months, 16 patients have an ongoing response on imatinib. Median PFS of these 36 patients is 21 months and the estimated median OS 46 months (median FU 13 (0 - 69) months).

Table 2

Groups		Curative (n=98)	Palliative (n=39)
Surgeries performed (patients)		88 (86)	28 (20)
Median age at surgery		58,3	58,9
Reason for surgery			
	Planned	39 (44%)	12 (43%)
	Planned because of other tumor	20 (23%)	7 (25%)
	Emergency	17 (19%)	7 (25%)
	Unknown	12 (14%)	2 (7%)
Type of surgery			
	Laparotomy	73 (83%)	26 (93%)
	Laparoscopy	6 (7%)	0
	Unknown	9 (10%)	2 (7%)
Type of resection			
	Local / limited	72 (82%)	17 (61%)
	Multivisceral	5 (6%)	5 (18%)
	Unknown	11 (13%)	6 (21%)
Surgery result			
	R0	68 (77%)	9 (32%)
	R1	7 (8%)	3 (11%)
	R2	1 (1%)	12 (43%)
	Unknown	12 (14%)	4 (14%)
Surgery performed in			
	Center of referral	51 (58%)	9 (32%)
	Center of expertise	26 (30%)	17 (61%)
	Unknown	11 (13%)	2 (7%)

Surgery characteristics. Local/limited resection involved a typical small bowel segment or wedge resection.

Conclusion: In half of the patients, primary surgery was not performed in an elective setting. This may explain that in our national registry, more than expected, patients have high risk tumors or metastatic disease at diagnosis. Response to imatinib, in (neo)adjuvant and palliative setting seems comparable to primary gastric GISTs.

Poster 066 #2771975

SURVIVAL OUTCOMES IN METASTATIC GIST PATIENTS HAVE BEEN DRAMATICALLY IMPROVED BY TYROSINE KINASE INHIBITORS: REAL WORLD DATA FROM MULTIPLE INSTITUTIONS

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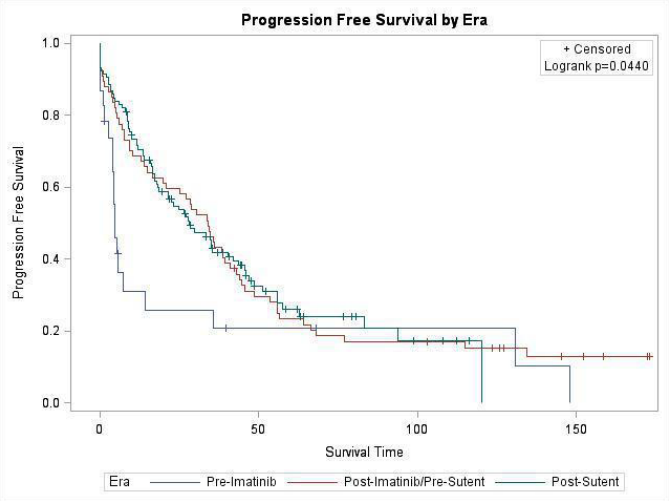
Objective: The treatment of advanced gastrointestinal stromal tumor (GIST) has been revolutionized by the development of tyrosine kinase inhibitors (TKIs). The impact of these treatments on real world outcomes, however, have not been reported. Imatinib was introduced for use in the metastatic setting in British Columbia (BC), Canada, in 2002, and sunitinib has been available for this application since 2007. We sought to evaluate the impact of the introduction of these agents on survival outcomes in patients with metastatic GIST in a real-world, non-clinical trial setting.

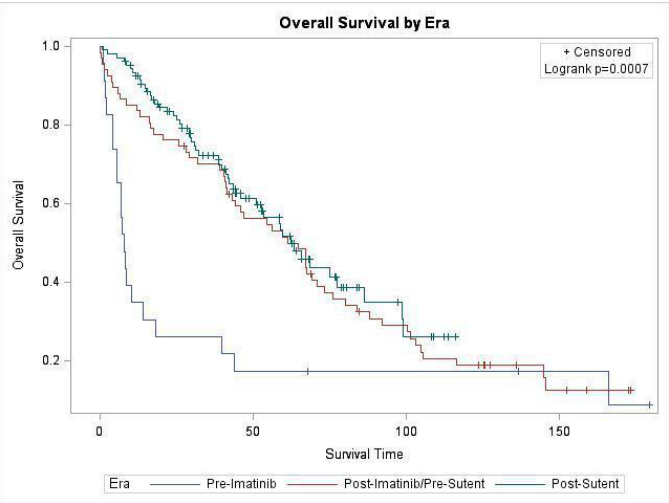
Methods: Patients with advanced GIST treated at any of the 5 tertiary cancer centres in the province of BC between 1997-2013 were identified through the BC Cancer Registry and Sarcoma Outcomes Unit. Patients were divided into three eras: pre-2002, 2002-2007, and post-2007 to reflect treatment availability (pre-imatinib, post-imatinib/pre-sunitinib, and post-sunitinib). Patients enrolled in clinical trials and those with resectable GISTs were excluded. Demographic information, tumour characteristics, and lines of therapy were obtained. Progression-free survival (PFS) and overall survival (OS) were extracted from the outcomes unit data, and were compared across each time cohort.

Results: A total of 657 patients were diagnosed with GIST between 1997-2013. Of these, 196 had metastatic disease; 23 in the pre-imatinib era, 67 in the post-imatinib/

pre-sunitinib era, and 106 in the post-sunitinib era. 47% presented with de novo metastatic disease. Baseline tumour and patient characteristics were similar across all cohorts. The median PFS increased significantly from 4.8 months (95% CI: 3.9-14.4) in the pre-imatinib era to 33.9 months (95% CI: 16.6-41.0) in the post-imatinib/pre-sunitinib era, and 28.0 months (95% CI: 18.3-41.9) in the post-sunitinib era (p = 0.044, see figure 1). There was also a significant 53.6 month increase in median OS over time, from 7.8 months 95% CI: 5.6-14.0) in the pre-imatinib era to 61.4 months (95% CI: 41.5 – 73.2) in the post-imatinib/pre-sunitnib era and 62.2 months (95% CI: 50.9-86.3) in the post-sunitinib era (p = 0.0007, see figure 2).



Progression free survival for patients with metastatic GIST diagnosed in the pre-imatinib, post-imatinib/pre-sutent, and post sutent eras.



Overall survival for patients with metastatic GIST diagnosed in the pre-imatinib, post-imatinib/pre-sutent, and post-sutent eras.

Conclusion: Survival outcomes for patient diagnosed with incurable GIST in BC have improved significantly since the introduction of TKIs 15 years ago. The incremental benefit of other TKIs has been modest in comparison to that seen with introduction of any TKI. This study confirms how the natural history of this disease has been dramatically altered by the development of these therapeutic agents.

Poster 067 #2789694

THE NFC CLONE, A NEUROFIBROMIN C TERMINUS-SPECIFIC ANTIBODY, IS A VALUABLE TOOL FOR THE IDENTIFICATION OF NF1-INACTIVATED GISTS

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Objective: Mounting evidence supports the involvement of NF1 mutations, either constitutional or somatic, in the pathogenesis of GISTs. Due to the large size of the NF1 locus, the existence of multiple pseudogenes and the wide spectrum of mechanisms of gene inactivation, the analysis of NF1 gene status is still problematic for most laboratories. On these grounds, we sought to assess the efficacy of a recently developed neurofibromin-specific antibody (NFC) in detecting NF1-inactivated GISTs.

Methods: NFC reactivity was analyzed in a series of 67 GISTs, 29 of which NF1-associated and 38 NF1-unrelated (NF1 wild-type or carriying non-pathogenetic NF1 variants). Cases were scored as NFC negative when, in presence of NFC positive internal controls, no cytoplasmic staining was detected in the neoplastic cells.

Results: NFC immunoreactivity was lost in 24/29 (82.7%) NF1-associated GISTs and in only 2/38 (5.3%) NF1 unrelated GISTs (p=3.1e-11). NFC loss of staining significantly correlated (p=0.007) with the presence of biallelic NF1 inactivation.

Conclusion: This study indicates that the NFC antibody is a valuable tool for the identification of NF1-inactivated GISTs, thus serving as a surrogate for molecular analysis.

Poster 068 #2789930

INHIBITION OF AUTOPHAGY SENSITIZES GASTROINTESTINAL STROMAL TUMOR CELLS TO TKI/BCL-2 INHIBITORS-INDUCED APOPTOSIS

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Objective: Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumor of the GI tract.

Most GISTs are driven by mutations in KIT or platelet-derived growth factor receptor-α (PDGFRA), which responds well to imatinib, a tyrosine kinase inhibitor (TKI) that blocks KIT and PDGFR-α signaling. Bcl-2 family plays a critical role in the regulation of cell apoptosis in GISTs. ABT-737 as an inhibitor of Bcl-2/Bcl-xL can result in a time and dose-dependent activation of apoptosis. Autophagy is a key mechanism to promote tumor cells survival, inhibition of which can induce the cell death in GISTs. Chloroquine, an antimalarial drug, has been also identified as an autophagy inhibitor. In this study, we assessed the combinational effects of imatinib, ABT-737 and chloroquine in GIST cells.

Methods: Human GIST cell lines, GIST-T1 and GIST882, were used. Cells were treated with imatinib, ABT-737 and chloroquine either separately or in different combinations. Cell viability was tested by MTS assay (Promega Corporation, Madison, WI). The levels of related proteins of apoptosis (PARP) and autophagy (LC3-II) were measured by western blot. Cell apoptosis was tested by flow cytometry (BD Biosciences, San Jose, CA) using Annexin V (Beckman Coulter, France).

Results: Cell viability assay indicated cell survival percentage of double or triple drug combinations (<5%) dramatically decreased compared to single drug treatment (42%, 36% or 12%) (P<0.01). Cell apoptosis percentage of double (32.9% or 36.6%) or triple drugs combinations (66.5%) significantly increased compared to single treatment (6.1%, 6.1% or 13.1%) (P<0.01). Western blot showed drug combinations increased apoptosis, but inhibited autophagy. Compared with inhibition of TKI and/or Bcl-2, inhibiting autophagy simultaneously with TKI and Bcl-2 inhibitors could remarkably reduce cell viability and significantly induce cell death via apoptosis in GIST cells.

Conclusion: The combination of imatinib, ABT-737 and chloroquine has collaborative effects on the treatment of GISTs in vitro. The combined strategy may enhance the clinical efficacy, which provides a rationale for the clinical evaluation of these drug combinations in GISTs treatment.

Poster 069 #2797842

EARLY RESPONSE EVALUATION BY 18F-FDG-PET INFLUENCES MANAGEMENT IN GASTROINTESTINAL STROMAL TUMOR PATIENTS TREATED WITH NEO-ADJUVANT INTENT

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Objective: Early response evaluation by 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) is effective in gastrointestinal stromal tumors (GISTs) treated with imatinib and recommended in GISTs treated with neo-adjuvant intent. Yet, it is unclear whether this effects treatment decisions.

Methods: All patients in the Dutch GIST Registry treated with imatinib with neo-adjuvant intent were identified. Only FDG-PETs made within 8 weeks after initiation or change (in dose or switch) of imatinib were included. Responses were derived from radiological reports and defined in 3 categories: 1) complete response; 2) partial response; 3) no response. Change in management was defined as a difference between pre-PET and post-PET treatment plans. Four categories were defined: change in 1) surgical management; 2) systemic treatment; 3) treatment objective (from curative to palliative); 4) management regarding a second tumor.

Results: Seventy FDG-PETs for early response evaluation in 63 patients treated with neo-adjuvant intent were identified. Forty-one patients (65.1%) had a KIT exon 11 and 22 (34.9%) had a non-KIT exon 11 mutation (15 other and 7 unknown mutations). Of the 70 scans 64 (87.1%) had a baseline, 50 (71.5%) showed metabolic response (partial and complete), and 18 (25.7%) led to change in management. Change in management was strongly correlated with a lack of response (p<0.001) and a non-KIT exon 11 mutation (p<0.001). Mutational status and response were strongly correlated (p<0.001). Out of 29 FDG-PETs conducted in non-KIT exon 11 GISTs, 15 (51.7%) led to change in management: 1 (3.4%) in surgical management, 6 (20.7%) in systemic treatment, 7 (24.1%) in both and 1 (3.4%) regarding a second tumor . Out of 41 FDG-PETs conducted in KIT exon 11 GISTs, change in management was seen 3 times (7.3%): twice in systemic treatment (dose increase after partial response was seen) and once regarding a second tumor. No change in treatment objective was seen.

Conclusion: In contrast to GIST patients harboring a KIT exon 11 mutation, in non-KIT exon 11 mutated GISTs treated with neoadjuvant intent early response evaluation by FDG-PET often leads to change in management.

Poster 070 #2803681

THE OUTCOMES OF TREATMENT OF PATIENTS WITH ADVANCED GASTROINTESTINAL STROMAL TUMOR (GIST) IN ELDERLY

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Objective: Although highest incidence of gastrointestinal stromal tumor (GIST) occurs at the age >65 years, there are limited data on treatment outcomes of patients in elderly, moreover there were under-represented in clinical trials. The aim of the study was to analyze the results of treatment of patients with advanced GIST in the elderly in the largest, homogenous series of patients.

Methods: Between 2001 and 2016, 656 of 686 patients with metastatic/unresectable GIST treated initially with imatinib were included to the analysis. Additionally, 232 of these patients were treated with sunitinib after imatinib failure. We have analyzed the outcomes of patients who have been started the tyrosine kinase inhibitor therapy at the age ≥ 70 years compared to patients younger than 70 yo.

Results: In the group of patients treated with imatinib 136 (21%) started therapy at the age of at least 70 years (median age in the entire group: 60). Median progression-free survival (PFS) on 1st line imatinib did not differ between patients ≥70yo and <70 (38.5 vs 44.9 months), but median overall survival (OS) was significantly better for younger patients (81 months vs. 50; p=0.0001; although disease-specific survival - DSS - was similar). Distribution of primary tumor mutational status was generally similar in elderly and younger patients: 66% vs 67% exon 11 KIT mutants, 16% vs 12% exon 9 KIT, 13% vs 4% PDGFRA and 3% vs 16% wild type, respectively. Permanent dose reduction (300-100 mg/day) was required for 23 patients (16.9 %) and was significantly more frequent for elderly group as compared to younger patients (5%). Drug-related adverse events were mainly of grades 1 and 2 and were medically manageable, but grade 3/4 toxicity occurred more frequently at elderly (14.7%) than in younger patients (3.8%). Similarly in group of patients treated with second-line sunitinib median PFS and DSS were comparable in groups of patients ≥70yo (n=55) and < 70 yo (9.7 months vs 10.3 months; p=0.7, and 21.5 vs 22.9 months). More than 40% of patients in both groups required dose adjustments to 37.5-25 mg daily.

Conclusion: We confirmed that current therapy of advanced GIST with tyrosine kinase inhibitors (both in 1st and 2nd line) in elderly patients can allow to achieve the similar disease control and final outcomes as younger patients, but it demands the close cooperation of experienced oncologist with patients for dose modifications and side effects management.

Poster 071 #2761064

PROGNOSTIC VALUE OF SERUM INFLAMMATION MARKERS IN GASTROINTESTINAL STROMAL TUMOR

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Objective: Treatment of Gastrointestinal Stromal Tumors (GISTs) is mainly driven by well-known tumor characteristics such as size and number of mitosis. Several inflammatory markers have been recently linked to the development and prognosis of GISTs. The aim of the present study was to investigate the value of preoperative serum inflammation markers in determining the prognosis of GISTs.

Methods: Clinical and pathological features of patients who underwent surgery at our institution for primary GIST between 2000 and 2014 were reviewed. For all patients, peripheral blood inflammation markers were calculated: neutrophil-lymphocyte ratio (NLR), monocyte-lymphocyte ratio (MLR), platelet-lymphocyte ratio (PLR), lymphocyte-white cell ratio (LWR), monocyte-white cell ratio (MWR), platelet-white cell ratio (PWR) and lymphocyte-monocyte ratio (LMR). Patients with active infection at the time of surgery were excluded from the study.

Results: A total of 140 patients, 65 females and 75 males, with a median age of 66 (range: 15-88) were included in the study. Most GISTs were located in the stomach (70,7%), while the remaining were found in the duodenum (12,1%), ileum (9,3%), esophagus (2,9%), jejunum (2,9%) and sigmoid colon (2,1%). Ninety-seven patients (69,3%) were asymptomatic at diagnosis; 39 (27,9%) had other concomitant cancers. Neoadjuvant therapy was administered to 9 patients (6,4%). Median follow-up was 58,5 months (range: 1-196). Three and 5-year overall survival (OS) were 83,5% and 78,7%, respectively; 3 and 5-year disease free survival (DFS) were 89,7% and 86,9%. Median OS and DFS were not reached.

On univariate analysis, factors associated to DFS were tumor diameter (p=0,003), gastric location (p=0,024), cell type (p=0,024), mitosis (p<0,001), MLR (p=0,014), NLR (p=0,016), LMR (p=0,029). Independent prognostic factors on multistep multivariate analysis (DFS) were: mitosis (p=0,001), NLR (p=0,015), MLR (p=0,015), PLR (p=0,031), the strongest being MLR. Correlations were found between MLR, NLR, PLR and tumor diameter, and between PLR and number of mitosis.

Conclusion: Serum inflammation indexes such as NLR, MLR and PLR are independent prognostic factors for DFS in GIST. Thus, they can be used as markers to preoperatively stratify patients. Inclusion of NLR, MLR and PLR in the clinical management of GISTs should be considered, since they may improve the accuracy of risk estimation.

Poster 072 #2761990

PATIENT REPORTED TREATMENT RESPONSES IN KNOWN/LIKELY SDH-DEFICIENT GISTS: ANALYSIS OF THE LIFE RAFT GROUP OBSERVATIONAL REGISTRY

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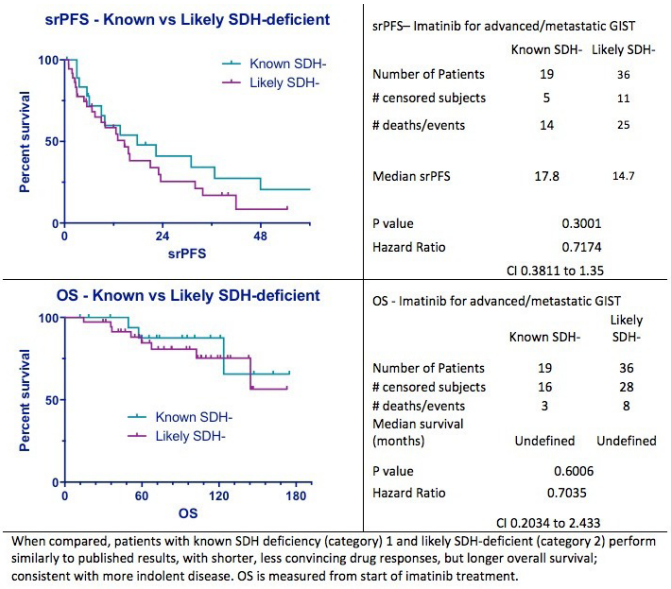
Objective: To date, very few studies have reported the treatment response rates of known/likely SDH-deficient GISTs. We sought to examine patterns of drug utilization and responses in these GIST pts.

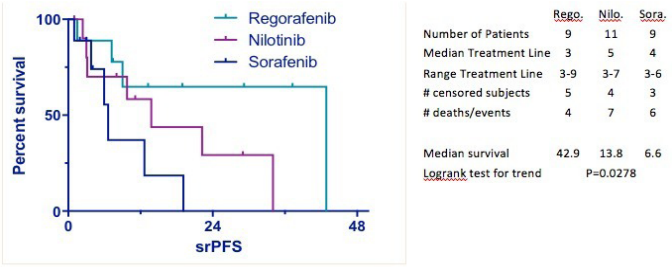
Methods: We performed a retrospective analysis of the Life Raft Group's international patient/member registry. Demographic and disease-specific data were voluntarily supplied by patient members. Patients (pts) with known (i.e., SDHB-negative immunostaining and/or SDHA-D mutation) or likely SDH GIST were included. Due to low numbers of confirmed SDH GIST patients and high numbers of unclassified wild type GISTs, we developed criteria to categorize likely SDH GIST using factors predicting SDH/wild type diagnosis from the LRG registry as well as previously published data, nearly tripling the number of patients available for analysis.

Results: Of 1709 pts in the registry, 741 (43%) had GISTs with known somatic mutations. Twenty-eight (1.6%) pts had known SDH GIST and 58 (3.4%) pts had likely SDH GIST, totaling 86 (5.0%) known or likely SDH GIST pts. The criteria used to define likely SDH GIST are listed in table 2 (category 2). Known (19) and likely (36) SDH GIST pts with advanced/metastatic disease had similar median overall survival (OS; not reached in either case; P=0.6006). Fifty-five (64.0%) pts received 1st line imatinib with self-reported response rate (SR-RR) of 15% and median self-reported progression-free survival (SR-PFS) (13.6 months). The remaining 31 (36.0%) did not receive drug therapy for measurable disease. 37 (43.0%) pts received 49 treatments beyond 1st line. The SR-response rates in later lines of therapy was 11-40%. Median SR-PFS was 17.7 and 9.0 months for 2nd and 3rd+ lines, respectively (logrank test for trend between 1st, 2nd and 3rd+ lines, P=0.30).

Conclusion: In a patient-reported longitudinal registry, we report that pts with known/likely SDH-deficient GIST had long OS, but relatively low SR-response rates to most TKIs, as well as generally short SR-PFSs with the exception of regorafenib. Interpretation of this data should be made with caution due to the small sample sizes and lack of radiological imaging review to confirm for responses. Further studies combining multiple institutional databases from high-volume SDH-deficient GIST referral centers are needed to better define treatment responses rates in these pts.



srPFS and OS for 1st line treatment for advanced/metastatic GIST



srPFS - 3rd line and beyond combined

Table 1 - Patient Reported Treatment Responses on Imaging Studies

Drug	Pts (N)	SR-Response Data (Number with evaluations)	SR-Response Rate (%)	SR-PFS (months)	Treatment Line (TL Median	TL Range
Sunitinib	37	28	10 (36%)	17.7	2	2
Regorafenib	9	9	1 (11%)	42.9	3	3-9
Nilotinib	11	7	1 (14%)	13.8	4	3-7
Sorafenib	9	5	2 (40%)	6.6	4	3-6

Table 2 - SDH Category Criteria

Category	Description	Criteria	# Pts
1	Known SDH-	Negative SDHB stain and/or known SDHx mutation	28
2	Likely SDH-	● Wild type for KIT/PDGFRA, age at diag. ≤35, stomach primary, female ● Unknown mutation, <18 at diagnosis, stomach primary ● Female, wild type, age 35-40 w/ addition of multi-focal stomach primary ● Male pts with unknown mutation, multi-focal stomach primary and 18-35 at diagnosis ● Wild type KIT/PDGFRA, <18 at diagnosis, stomach primary ● Females with diagnosis of Carney's Triad (3 w/unknown mutation, 1 wild type; 37 at diagnosis)	58
3	Possible SDH-	Unk. mutation, age at diag. 18-35, stomach primary, female. By comparison, patients with these criteria and known mutation (n=32) have a SDH or wild type diagnosis 84.4% of the time; a KIT mutation 9.4% and PDGFRA mutation 6.3% of the time.	21
4	Less likely SDH-	Wild type for KIT/PDGFRA, stomach primary, but without all 3 supporting factors or unknown diagnosis, 18-35 at diagnosis, male, stomach primary	33
5	Wild type, very unlikely SDH-	Wild type for KIT/PDGFRA with non-stomach primary and no SDHx mutation and without a negative SDHB stain OR Quadruple wild type	31
6	Unknown	Unknown mutation, does not fit within categories 2, 3 or 4	911
7	Known not SDH-	Known mutation that excludes SDHx	627
		Total	1709

Poster 073 #2765314

REMARKABLE EFFECTS OF IMATINIB IN A FAMILITY WITH YOUNG ONSET GASTROINTESTINAL STROMAL TUMORS AND CUTANEOUS HYPERPIGMENTATION ASSOCIATED WITH A GERMLINE KIT-TRP557ARG MUTATION: CASE REPORT AND LITERATURE OVERVIEW

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Objective: The effect of imatinib in patients harboring a germline KIT mutation has been rarely described.This paper describes the effects of imatinib on the GISTs and the cutaneous hyperpigmentation associated with this syndrome in two related GIST patients. Also, an overview of the literature is given.

Methods: A case study on the effect of imatinib in a family with a mother with mulitple GISTs associated with new onset germline KIT mutation and her two daughters harboring the same mutation is preformed. Additionally, an overview of literature on the effect of imatinib in GIST patients harboring a germline KIT mutation is given. Literature research is conducted by the following search in PubMed: (GIST OR "gastrointestinal stromal tumor") AND "KIT mutation" AND "germline" AND "imatinib".

Results: A 52-year old patient with new onset germline p.Trp557Arg mutation has multiple GISTs throughout the gastrointestinal tract and cutaneous hyperpigmentation. Imatinib treatment showed long term regression of the GISTs and evident pathological response was seen after resection. Remarkably, the hyperpigmentation of the skin also diminished during imatinib treatment. Genetic screening of the family revealed the same mutation in two daughters, both with similar cutaneous hyperpigmentation. One daughter, aged 23, was diagnosed with multiple small intestine GISTs, which were resected. She was treated with adjuvant imatinib which prompted rapid regression of the cutaneous hyperpigmentation. This is the sixth study describing the in vivo effect of imatinib in GIST associated with a germline mutation in KIT exon 11.

Literature search resulted in 30 hits, of whom 5 involved germline KIT mutated GIST patients treated with imatinib. Similar to our findings favorable responses have been described in prior literature outlined in table 1.

Conclusion: Imatinib treatment in GIST patients harboring a germline KIT mutation shows favorable and long-term responses in both the tumor and the phenotypical hyperpigmentation.

Literature overview of in vivo responses to imatinib in GIST patients harboring a germline KIT-mutation

Case	Type of mutation	Age	Effect of imatinib on tumor	Effect of imatinib on cutaneous hyperpigmentation	Follow up
Graham et al. 2007	KIT exon 13, p.K642E	57	SD	Not applicable. Pre-existent vitiligo was unrelated	19 months
Campbell et al. 2009	KIT exon 11, unspecified	45	Not specified	Diminished within 3 months	2 years
Adela Avila et al. 201427	KIT exon 11,				
p.559V>A	27, 29, 32, 33	Not specifically specified.	Reduced melanosis	Unknown	
Bamba et al. 2015	KIT exon 11, p.Val560del	43	CR and PR in most lesions	Not applicable	1 year
Piqueres-Zubiaurre et al. 2017	KIT exon 11, p.Leu576Pro	Unknown (Mother of 11-year old patient)	CR	Lightening of the skin	Unknown
Case 1, this study	KIT exon 11, p.Trp557Arg	52	PR	Diminished within 2 weeks	13 years
Case 2, this study	KIT exon 11, p.Trp557Arg	23	Not applicable	Diminished within 3 weeks	15 months

SD: stable disease; CR: complete remission; PR: partial response; NED: no evidence of disease

Poster 074 #2791377

BASELINE RESULTS AND CENTRAL PATHOLOGY OF THE PROSPECTIVE REGISTRY STUDY OF HIGH RISK GIST AFTER COMPLATE RESECTION (STAR REGISTRY) IN JAPAN

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Objective: Three-year imatinib adjuvant therapy is recommended for patients (pts) with high-risk GISTs by the guidelines, there are a few real world data regarding use of adjuvant therapy and pathological diagnosis. Our prospective registry study examined the present status of adjuvant therapy in Japan.

Methods: Between Dec. 2012 and Dec. 2015, 534 pts with histologically-confirmed high-risk GIST based on the Joensuu classification in local site were registered after informed consent and analyzed. In the central pathology, H&E, immunohistochemistry, and genotyping were done.

Results: There were 294 males and 240 females with median age of 65 yrs. Disease was located in the stomach (n=318), small intestine (163), large intestine (32), esophagus (7) or others (14). Median tumor size was 7.5 cm and median mitosis (local) was 10/50HPF. Tumor rupture was seen in 66 pts (12%), half of which were preoperative. Adjuvant therapy was administered for 416 pts (78%) and withheld for 118 pts (22%). PS was 0 (n=447), 1 (76) and > 2 (7). In the central pathology, KIT was positive in 513 pts (96%) and DOG1 in 514 pts (96%). Mutations were analyzed in 511 pts including 405 KIT exon 11, 38 KIT exon 9, 13 other KIT, 16 PDGFRA exon18 (D842V), 2 other PDGFRA mutations, and 18 wild type. Although KIT expression was consistent between central and local pathology (concordance=93%), 19 tumors (3.6%), which were negative for KIT as well as DOG1 and had no mutation in the both genes in the central examinations, were diagnosed as non-GIST (including leiomyosarcoma, desmoid, or solitary fibrous tumor) in the central pathology. Discordance was more frequent in colonic and extra-GI tumors. By reconsidering central pathological review, ad-

juvant imatinib therapy was stopped in 79% of non-GIST pts and in 57% of D842V-mutated GISTs. There was significant correlation between local and central mitotic counts (r=0.6213; P<0.0001), but mitosis (median 5/50 HPF) in the central pathology was lower than that in local, which resulted in downgrade of the risk classification of 97 tumors (18%).

Conclusion: There are unignorable discordance between local and central pathology. Adjuvant imatinib was used for 78% of high risk GIST pts in real world. The pathological diagnosis by sarcoma pathologists and adjuvant therapy based on the guidelines are still required to improve in real-world clinical practice.

Poster 075 #2792679

LONGITUDINAL FOLLOW UP OF CONTEMPORARY TREATMENT RESULTS IN ADVANCED GIST - A SINGLE CENTRE EXPERIENCE

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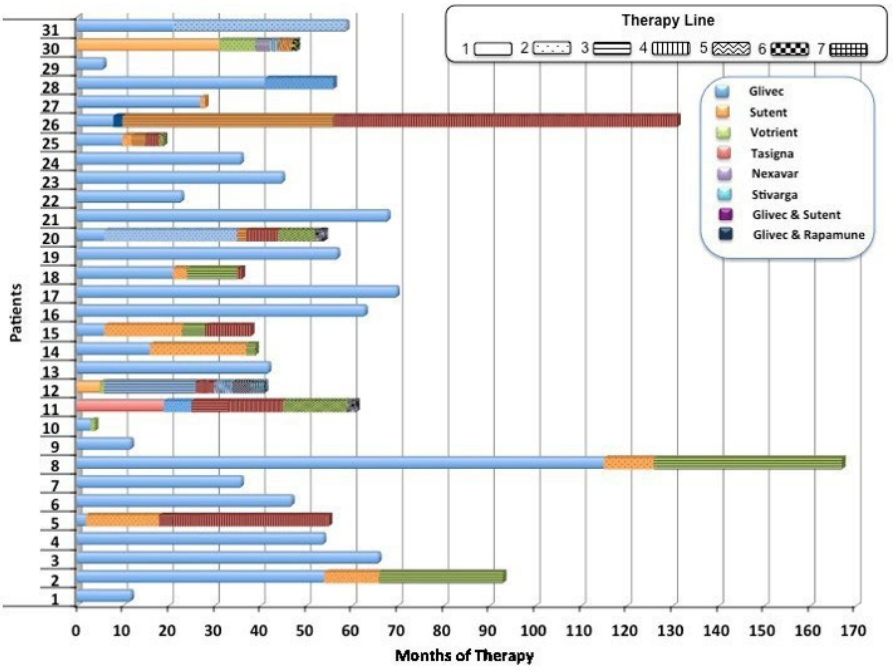
Objective: Gastrointestinal stromal cell tumors (GIST) are the most common mesenchymal tumors in the gastrointestinal tract. Proliferation of GIST is predominantly driven by activating mutations in the c-KIT or PDGFRA gene. Radical surgery previously offered the only possibility of long-term survival. However, the introduction of TKI inhibitors in metastatic disease has dramatically improved the prognosis.The purpose of this abstract is a detailed analysis of clinical data for a contemporary cohort of 31 patients with palliative TKI treatment due to primary metastatic, inoperable or recurrent GIST, thereby providing insight into contemporary treatment results.

Methods: Retrospective analysis of 31 patients who initiated treatment for advanced GIST at the Sarcoma Unit, Sahlgrenska University Hospital from 2012 to 2016. Data were collected on the baseline characteristics of patients and tumors as well as information on the type, duration and tolerability of the different treatment lines.

Results: Baseline tumor characteristics of the patients are presented in Table 1. Median follow-up time from the start of palliative TKI treatment was 48 mon (range 4-167 mon). Median total TKI treatment duration and overall survival had not yet been reached. In first line setting, median treatment duration was 33 mon (range 2-115 mon). 28/31 patients received Imatinib in the first line. 11 patients were still undergoing first line treatment and 20 patients had completed first line treatment at the time of the analysis. The number of TKI therapies received varied between 1-7 with a median of 2 treatment lines (Fig.1). At the time of analysis 18/31 patients were alive and undergoing palliative TKI treatment. 13 patients had died, 11 from progressive disease and 2 from other causes.

Table 1: Baseline characteristics of the patients

Characteristic (n=31)		
Gender	Male	20
	Female	11
Age at diagnosis	<60 y.o.	12
	>60 y.o.	19
Primary tumor localization	Gastric	8
	Small bowel	18
	Duodenum	3
	Rectum	1
	Other	1
Maximal tumor diameter (mm)	<50	7
	50-100	10
	>100	14
Resection of residual tumor during TKI treatment	Yes	8
	No	23
Prior neoadjuvant/adjuvant TKI treatment	Yes	20
	No	11
Initial ECOG performance status	0	25
	1	5
	2	1
Tumor genotype	KIT exon 11	14
	KIT exon 9	3
	KIT exon 13	1
	PDGFRA exon 18	1
	Wild type	1
	c-KIT IHC only	6
	Other	5



Conclusion: This retrospective review of single-centre contemporary treatment results in advanced GIST demonstrate that a majority of patients receive prolonged oncological TKI based treatment and that significant response lengths are also seen in subsequent therapy lines after observed progress in first line treatment. This compares well with available data on overall survival in advanced GIST showing that the introduction of Imatinib and subsequent other tyrosine kinase inhibitors has significantly the likelihood of long-term survival.

– MEDICAL PEDIATRIC AND YOUNG ADULT ONCOLOGY –

Poster 076 #2759178

PRECLINICAL AND EARLY PHASE CLINICAL STUDIES OF SEPREHVIR, AN ONCOLYTIC VIROIMMUNOTHERAPEUTIC, IN PEDIATRIC AND AYA SARCOMAS

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Objective: The first-in-class oncolytic herpes simplex virus, Imlygic (T-VEC), is now FDA-approved for melanoma. We previously reported lytic effects of a similar virus, Seprehvir (HSV1716), in xenograft models of rhabdomyosarcoma, Ewing sarcoma, and malignant peripheral nerve sheath tumor. We sought to determine safety of the virus in young cancer patients with sarcomas and describe any signs of efficacy. Due to known immunostimulatory effects of virus infection, we also sought to determine in mouse sarcoma models if virus can be leveraged to increase therapeutic efficacy of other immunotherapies.

Methods: We launched a clinical trial of Seprehvir (Virttu Biologics, Ltd) in pediatric and young adult patients with solid tumors (www.clinicaltrials.gov: NCT00931931) by both intratumoral and intravenous routes. We also used mouse rhabdomyosarcoma models to test the effects of oncolytic virotherapy on the tumor microenvironment and its effects in combination with checkpoint and other immune inhibitors.

Results: Our clinical results suggest that administration of Seprehvir is safe in young sarcoma patients. We also found evidence of virus replication by detecting delayed appearance of virus genomes in blood following both intratumoral and intravenous administration. Interestingly, direct intratumoral injection of virus induced an inflammatory response in both injected and uninjected lesions. In particular, a patient with rhabdomyosarcoma and another with osteosarcoma showed a transient large increase in 18Fluoro-deoxyglucose in the days and weeks following virus injection that spontaneously resolved without additional therapy. In the male M3-9-M mouse rhabdomyosarcoma model, we found that the combination of intratumoral virus with anti-PD1 antibody increased CD8+ T cells in both spleen and tumor without increased Foxp3+ regulatory T cells. Tumor response was proportional to the effect on T cells; both were most prominent in female animals due to the presence of the immunogenic H-Y antigen on the tumor, though some effects were also present in male mice. We also found inhibitors of TGFβ potentiate the effects of viroimmunotherapy on T cell infiltration and tumor response in this and other mouse rhabdomyosarcoma models.

Conclusion: Oncolytic viroimmunotherapy offers the promise not only of direct cancer-selective cytotoxicity but also of enabling immunotherapy combinations for patients with intractable sarcomas.

Poster 077 #2804816

SAFETY AND EFFICACY OF DENOSUMAB IN PATIENTS WITH GIANT CELL TUMOR OF BONE: RESULTS OF AN OPEN-LABEL PHASE 2 STUDY

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Objective: Giant cell tumor of bone (GCTB) is a rare, progressive osteolytic tumor with proven activity of denosumab in unresectable disease or resectable disease where surgery is likely to carry high morbidity. We report on the primary analysis from an open label phase 2 study.

Methods: Adults or skeletally mature adolescents with GCTB enrolled in 1 of 3 cohorts: unresectable disease (eg, sacral or spinal GCTB or multiple lesions, including pulmonary metastases; Cohort 1), resectable disease with planned surgery associated with severe morbidity (eg, joint resection, amputation; Cohort 2), and transfers from a previous study of denosumab in GCTB (Cohort 3). Patients received denosumab 120 mg SC every 4 weeks with loading doses on study days 8 and 15. Denosumab was continued for 6 additional doses postoperatively, or until disease progression, adverse event, consent withdrawal or loss to follow up in nonsurgically treated patients. The primary endpoint was safety; secondary endpoints included time to disease progression for unresectable Cohort 1 and proportion of patients without surgery for salvageable Cohort 2.

Results: 532 patients enrolled and 526 received ≥1 dose of denosumab; baseline characteristics and safety results are shown in the Table. Median (IQR) follow-up was 54.7 (34.2–74.6) months in Cohort 1 and 43.8 (26.1–58.7) months in Cohort 2. Investigator assessed overall best response rates (CR+PR+SD) were 98.6% in Cohorts 1 and 2. Kaplan-Meier estimates (95% CI) for disease progression or recurrence in Cohort 1 were 1.9% (0.3%–3.6%) at week 25, 4.3% (1.8%–6.8%) at week 49, and 7.0% (3.8%–10.2%) at week 98. 248 patients had planned GCTB surgery, of whom 85 (33.6%) had recurrent disease at enrollment, 157 (63.3%) underwent surgery on-study and 91 (37.4%) continued with denosumab treatment only. Following surgery, 42 (26.8%) of patients experienced a recurrence of GCTB.

Table. Summary of Results

n (%)	Cohort 1 (n=267)	Cohort 2 (n=253)	Cohort 3 (n=12)	All Patients (N=532)
Demographics				
Women	154 (57.7)	142 (56.1)	5 (41.7)	301 (56.6)
Adolescents[a]	14 (5.2)	14 (5.5)	0	28 (5.3)
Age, median (range), y	33 (13–83)	34 (13–82)	31 (22–63)	33 (13–83)
Ethnic group/race				
White/Caucasian	221 (82.8)	208 (82.2)	11 (91.7)	440 (82.7)
Black	17 (6.4)	13 (5.1)	0	30 (5.6)
Hispanic/Latino	13 (4.9	13 (5.1)	1 (8.3)	27 (5.1)
Asian	11 (4.1)	14 (5.5)	0	25 (4.7)
Other	5 (1.9)	5 (2.0)	0	10 (1.9)
GCTB disease type				
Primary resectable	0	168 (66.4)	0	168 (31.6)
Primary unresectable	92 (34.5)	0	2 (16.7)	94 (17.7)
Recurrent resectable	0	85 (33.6)	0	85 (16.0)
Recurrent unresectable	175 (65.5)	0	10 (83.3)	185 (34.8)
Prior GCTB surgery	182 (68.2)	94 (37.2)	0	276 (51.9)
Prior GCTB radiotherapy	44 (16.5)	8 (3.2)	0	52 (9.8)
Adverse Events	**n=264[b]**	**n=250[b]**	**n=12[b]**	**n=526[b]**
All AEs				501 (95.2)
Treatment related[c]				327 (62.2)
Serious AEs				138 (26.2)
Treatment related[c]				42 (8.0)
Fatal AEs[d]				10 (1.9)
Treatment related[c]				2 (0.4)
AEs leading to study discontinuation				46 (8.7)
Treatment related[c]				27 (5.1)
AEs of Interest				
Osteonecrosis of the jaw[e]				28 (5.3)
Atypical femur fracture[e]				4 (0.8)
Malignancy in GCTB				10 (1.9)
Primary Malignant GCTB[f]				5 (1.0)
Secondary Malignant GCTB[g]				1 (0.2)
Sarcomatous transformation				4 (0.8)

AE=adverse event.
[a]Skeletally mature adolescents defined as age ≥12 years with radiographic evidence of at least 1 mature long bone with closed growth epiphyseal plate
[b]Patients who received ≥1 dose of denosumab (safety analysis set)
[c]Treatment-emergent AEs considered by investigator to be possibly related to denosumab.
[d]Fatal AE preferred terms – Respiratory failure (2), Bone giant cell tumor (1), Bone Sarcoma (1), Sarcoma (1), Neoplasm malignant (1), Renal cancer (1), Circulatory collapse (1), Completed suicide (1)
[e]Positively adjudicated by independent reviewers
[f]New malignancy events occurring during the treatment/safety follow-up phase; based on multidisciplinary expert review of clinical history, pathology and radiology
[g]Occurred following radiation therapy for GCTB treatment

Conclusion: Denosumab treatment was generally well tolerated with excellent overall response rates and low rates of disease progression in unresectable patients. Adverse events were consistent with the known profile for denosumab, with malignancy in GCTB events consistent with historical rates in the literature. Several cases of primary malignant GCTB, misdiagnosed as benign GCTB were seen, reinforcing the need for careful expert pathologic evaluation of this rare disease at diagnosis. At this time, denosumab is the only effective therapy in unresectable or metastatic GCTB.

Poster 078 #2747512

COMPREHENSIVE MOLECULAR PROFILING OF UNDIFFERENTIATED EMBRYONAL SARCOMA OF THE LIVER

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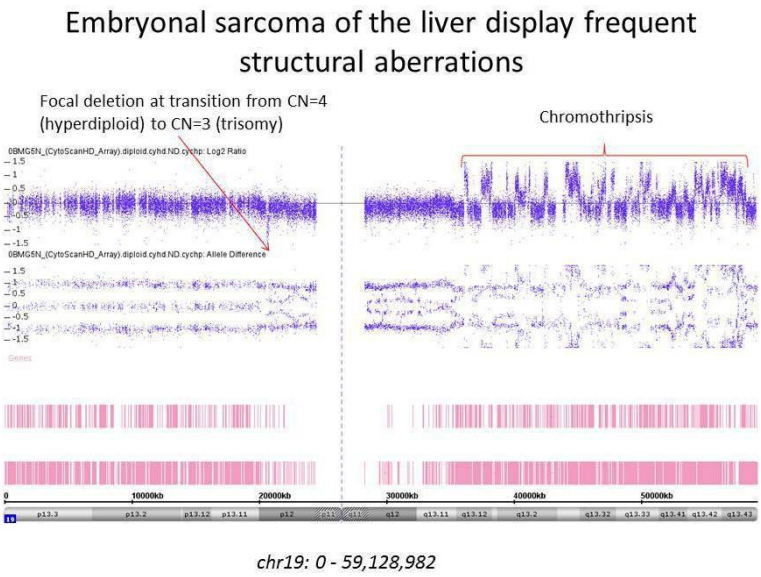
Objective: Undifferentiated embryonal sarcoma (UES) is a rare primary liver malignancy that typically affects younger children. The molecular underpinnings of this cancer have been largely unexplored, though recurrent chromosomal alterations affecting a noncoding region on chr19q13 have been reported in several cases. The prognosis for patients with recurrent or metastatic disease is poor. No disease-specific or molecularly guided therapies are currently known.

Methods: We performed comprehensive molecular profiling on samples from 10 patients diagnosed with UES, including 9 matched tumor-normal pairs and one patient with tumor only. Molecular studies included whole exome sequencing on all tumors and matched normals with whole transcriptome sequencing and high density SNP arrays on all tumors. Data were processed and analyzed using established bioinformatics approaches to evaluate for potentially pathogenic mutations, structural alterations, fusions and expressional changes.

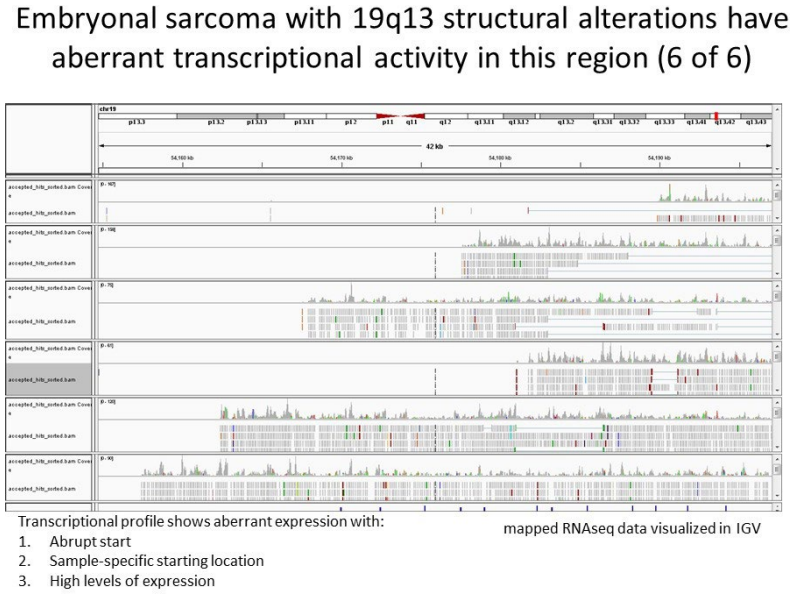
Results: From whole exome sequencing, we observed a median of 28 somatic coding mutations per sample (range: 8-50), placing UES on the low end of the mutational burden spectrum across cancer types, similar to other pediatric malignancies. We note frequent somatic mutation of TP53 in 5 of 9 patients (56%), as well as other potentially pathogenic mutations including singleton mutations in 3 different JAK-STAT pathway genes. Similar to previous case reports, from SNP array data we note frequent structural alterations involving chr19q13 in 6 of 10 cases, including one case with chromothripsis of this region. Strikingly, from RNAseq data, in 6 of 6 samples with 19q13 alteration as compared to 0 of 4 without, we note high levels of aberrant transcriptional activity at this site covering an approximately 100kb region that coincides with the genomic position of a large microRNA cluster, C19MC.

Conclusion: To our knowledge this is the first and only comprehensive molecular analysis of undifferentiated embryonal sarcoma of the liver, utilizing a combination of next-generation sequencing studies and high-density arrays. We observe recurrent mutations and structural alterations including recurrent alterations of chr19q13 in the majority of samples that are uniformly associated with aberrant and striking transcriptional activity of a microRNA cluster, C19MC. Further study to validate C19MC as an oncogenic driver in this disease and to study the down-

stream effects and targetability of this microRNA cluster are ongoing.



Embryonal sarcoma of the liver display frequent structural aberrations



Structural alterations at 19q13 demonstrate aberrant transcriptional activity

Poster 079 #2772790

RESULTS OF A STRATIFIED MULTI-ARM PHASE 2 STUDY EVALUATING EFFICACY AND SAFETY OF HEDEGHOG INHIBITOR, SONIDEGIB (LDE225) IN PATIENTS WITH SELECTED METASTATIC AND/OR UNRESECTABLE SARCOMAS

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Objective: Aberrant activation of the hedgehog (Hh) signalling pathway is a critical oncogenic stimulus implicated in multiple cancers including sarcomas. We investigated the clinical efficacy and safety of sonidegib, an Hh antagonist in a multi-centre, Simon 2-stage, phase-2 study in patients with metastatic and/or unresectable sarcomas.

Methods: Patients (pts) were stratified into three cohorts: osteosarcoma (OST); chondrosarcoma (CS); and an open cohort of treatment-refractory sarcoma subtypes including Ewing sarcoma, desmoplastic small round cell tumour (DSRCT) and rhabdomyosarcoma (RMS). Sonidegib was administered at its recommended dose of 800mg/day. The primary endpoint was clinical benefit defined as complete response (CR), partial response (PR) or maintenance of stable disease (SD) for ≥12 weeks using RECIST criteria. Secondary endpoints included safety, progression-free survival (PFS), overall survival (OS), duration of response and changes in pain level. Biomarkers to explore predictive and pharmacodynamic markers of Hh activation and subsequent modulation were performed on archival specimens, pre- and on-treatment biopsies, and with FDG-PET scans.

Results: A total of 43 pts were treated in three cohorts (OST: n=11; CS: n=19, other: n=13), with the majority hav-

ing progressive disease at study entry. No clinical benefit was seen in OST cohort, with all pts progressing within 12 weeks. Eleven CS pts (61%) achieved clinical benefit via maintenance of SD with no objective response seen. In the open cohort, a pt with metastatic leiomyosarcoma and known Patched (Ptch) mutation achieved a PR, with a complete metabolic response. Median PFS was 1 month in OST cohort, 6.3 months in CS cohort and 1.3 months in the open cohort. Most pts had low baseline pain scores with no significant change at week 12. Sonidegib was well tolerated, with mild to moderate adverse events, consisting primarily of nausea, fatigue and increase in creatine kinase. Initial biomarker analyses of Hh ligand staining and primary cilia revealed no clear association between these biomarkers and objective responses; further analyses including sequencing of the Hh-ome is ongoing.

Conclusion: Single-agent sonidegib at 800mg/day showed limited clinical benefit in these pre-defined cohorts of advanced sarcomas. Interesting activity was seen in one pt with a known Ptch mutation, justifying further investigation in these pts. Ongoing work to elucidate potential biomarkers of Hh signalling is underway and will be presented.

Poster 080 #2798661

PRELIMINARY EVIDENCE OF CLINICAL RESPONSE TO ENTRECTINIB IN THREE SARCOMA PATIENTS

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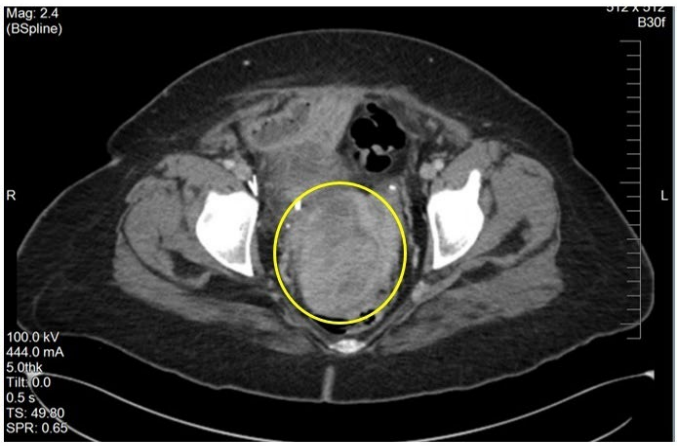
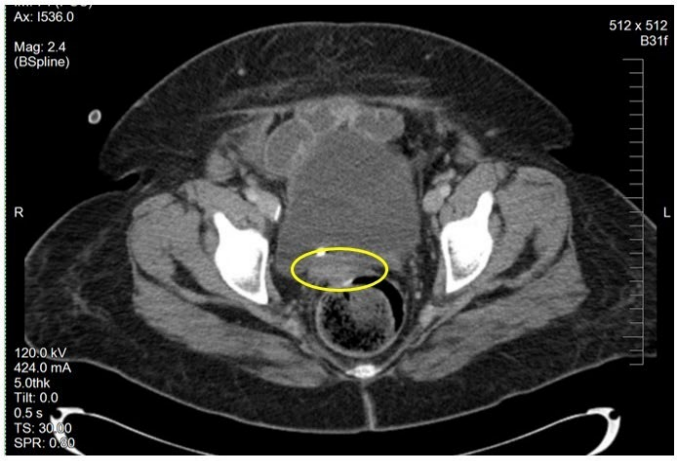
Objective: Entrectinib is a potent, investigational, CNS-active, oral inhibitor of TRK, ROS1, and ALK with IC50 values < 0.2 nM. Phase 1 studies of entrectinib reported a 79% response rate across multiple histologies in patients who were naïve to inhibitors of these targets. Responses were durable with patients remaining on study in response for > 2 years. Entrectinib was well tolerated, with mostly Grades 1 or 2 adverse events that were reversible with dose modification, The STARTRK-2 clinical trial is a registration-enabling Phase 2 global basket study of entrectinib. Patients harboring TRK, ROS1, or ALK gene fusions are generally rare (<3%); however, sarcoma patients may have a relatively higher prevalence. Here, we report on three sarcoma patients enrolled in STARTRK-2, two with ALK and one with NTRK gene fusions, respectively, from Sarcoma Oncology Center, that have experienced preliminary clinical evidence of benefit from entrectinib treatment.

Methods: Patients were identified using a two-step screening process. First, formalin-fixed, paraffin embedded tissue from sarcoma patients was tested for gene fusions by Ignyta, Inc, in San Diego, CA, using next generation sequencing. Second, once an appropriate in-frame NTRK or ALK fusion was identified, the patient was evaluated for enrollment in STARTRK-2. After determination that all study criteria were satisfied, dosing with entrectinib began at 600mg QD. Safety was assessed by monitoring of adverse events, laboratory tests, and clinical visits. Tumor assessments were performed at the end of Cycle 1 and at every 8 weeks thereafter using RECIST v1.1. All scans were also submitted for blinded independent central review assessment.

Results: Patient 1:
Sex: F
Age: 49
Diagnosis: Endometrial stromal sarcoma with metastasis to lung and right kidney
Prior therapies: TAH with BSO. Gemcitabine, doxorubicin and docetaxel
Gene fusion: TPM3-NTRK1
Best response to entrectinib: Partial Response (PR) on Cycle 2 scan (30.2% reduction from baseline)
Status: ongoing, ~12 months on study



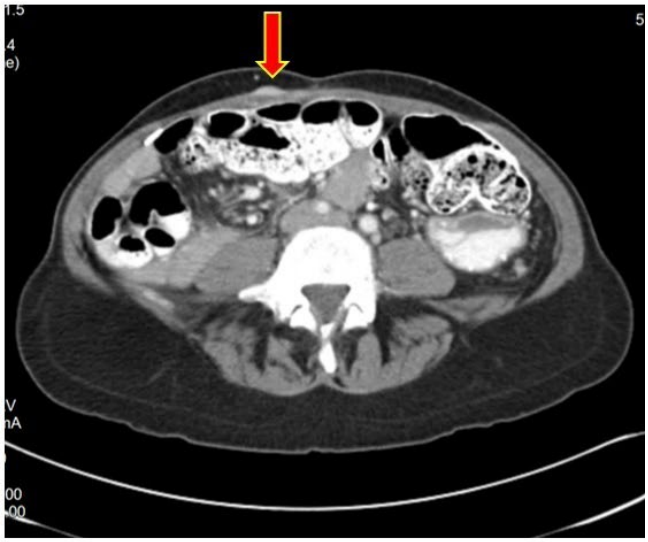
Patient #1 (baseline: 5/20/16)



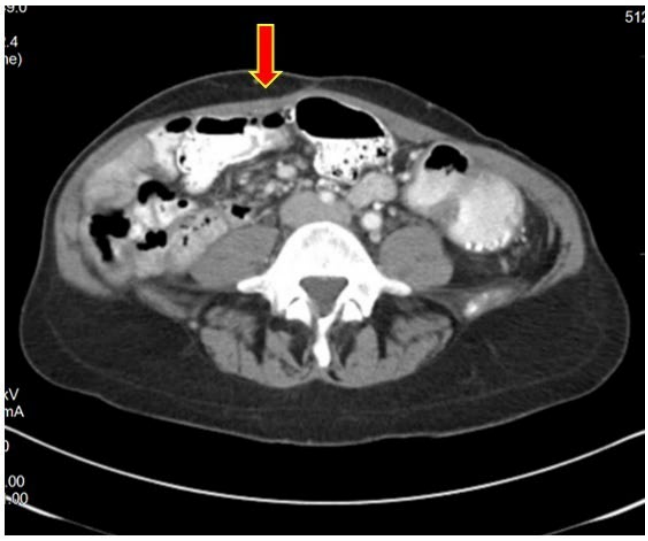
Patient #1 (post C3: 9/1/16)

Figure 1. Patient 1. Significant reduction in size of prerectal mass (circles).

Patient 2:
Sex: F
Age:60
Diagnosis: Metastatic leiomyosarcoma of the abdomen, pelvis, liver and left retroperitoneum
Prior therapies: Debulking surgery, tamoxifen, aldoxorubicin/ifosfamide
Gene fusiont: NPHP3-ALK
Best response to entrectinib: PR on C4 scan (68% reduction from baseline)
Status: ongoing, ~3 months on study



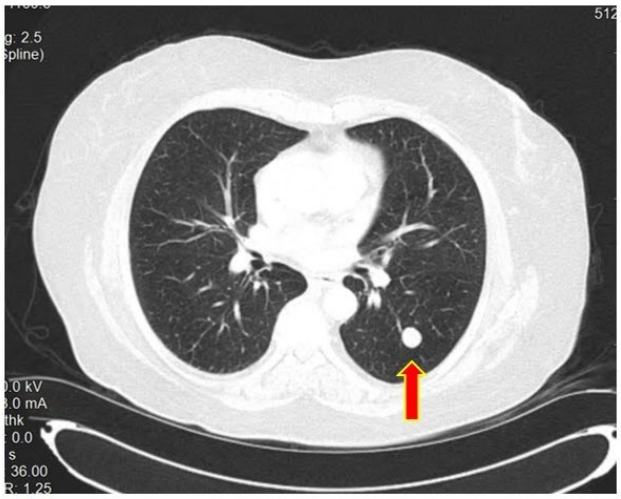
Patient #2 (baseline: 3/23/17)



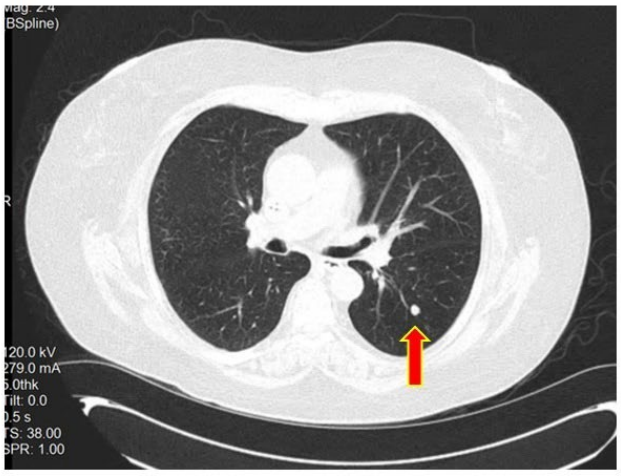
Patient #2 (post C1: 4/25/17)

Figure 2. Patient 2. Complete resolution of lesion on rectus abdominus muscle (arrows).

Patient 3:
Sex: F
Age: 72
Diagnosis: Uterine leiomyosarcoma
Prior therapies: Debulking surgery, XRT with GemCis, Aldox/Gem, Opdivo/Yondelis
Gene fusion: IGFBP5-ALK
Best response to entrectinib: PR on C7 scan (32% reduction)
Status: ongoing, ~9 months on study



Patient #3 (baseline: 9/14/16)



Patient #3 (post C6: 4/18/17)

Figure 3. Patient 3. Significant reduction of left lung nodule.

Conclusion: Three sarcoma patients have had measurable clinical responses to entrectinib treatment. Tumor reductions ranged from 30%-68% by RECIST v1.1 criteria. Entrectinib can be a viable therapy option for sarcoma patients with NTRK, ROS1, or ALK gene fusions. Therefore, all sarcoma patients should be molecularly profiled to identify those who may benefit from entrectinib therapy.

Poster 081 #2804802

METHOTREXATE PLUS VINORELBINE (MTX/VBL) CHEMOTHERAPY FOR THE MEDICAL MANAGEMENT OF DESMOID FIBROMATOSIS (DF)

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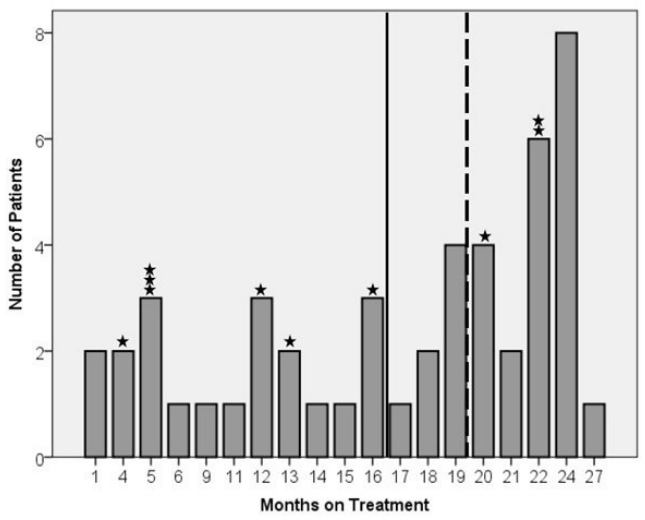
Objective: DF are locally aggressive benign neoplasms that can occur sporadically, in association with familial adenomatous polyposis (FAP), as a result of injury or recent pregnancy. Optimal management of these benign tumors remains controversial. MTX/VBL is systemic therapy which is not associated with any long term sequelae. To date, reports of MTX/VBL have often included patients who have failed prior radiation therapy (RT) or other systemic therapy (ie. doxorubicin). We report our experience in management of patients with progressive DF with MTX/VBL, most of whom are treatment naive.

Methods: Consecutive patients with DF treated between Jan 1994 and Dec 2015 were reviewed. Treatment: MTX 25 mg/m2 IV + VBL 25 mg/m2 IV d1,8,15 q28 d for a planned max duration of 24 cycles. Data including demographics, treatment details and toxicity were collected. A radiologist re-reviewed all available MRI scans to evaluate response by RECIST and T2 changes. PFS was estimated using KM.

Results: Median age of 48 patients was 33 yrs (range 13-73). Thirty seven (77%) patients were treatment naïve and 11 (23%) had residual/recurrent disease. Tumour location was as follows: 16 (33%) extremity, 13 (27%) abdominal wall, 4 (8%) head and neck, 6 (13%) chest wall/back, 7 (15%) mesenteric. Two patients (4%) had multifocal DF at two sites: abdominal wall and mesentery. Prior therapy in the 11 patients included: 6 (55%) surgery alone, 2 (18%) surgery and tamoxifen, 1(9%) surgery and RT, 1 (9%) tamoxifen alone and 1 (9%) tamoxifen and Doxorubicin. Median number of cycles of chemotherapy was 19 mos (range 1 to 27; Figure 1). Schedule modification occurred in 5 patients. The majority of patients (n=27, 56%) had 18 or more cycles of therapy; 9 completed 24 mo. Reasons for early therapy discontinuation before 24 months were: toxicity (n=2, 4%), response achieved (n=28, 58%%), patient preference (n=8, 17%), PD (n=1, 2%). Most severe toxicity was grade 1/2 fatigue, nausea or both in 9 (18%), 12 (25%) and 4 (8%) patients, respectively. Three (6%) patients had neutropenia (grade 1/2). At end of therapy, response was: 8 (17%) SD, 19 (40%) PR, 20 (41%) CR, and 1 (2%) PD for a clinical benefit rate of 98%. Median PFS was 95 mo (range 57.6 to 132.4), and 5-year PFS was 72%. Of the 10 patients who recurred, 5 had had prior therapy. 5-year PFS was 53% in those that completed less than 18 mo compared to 93% in those that completed more than 18 mo.

Figure 1. Months of Therapy and Recurrences in Patients with DF



★ = # of patients who progressed/recurred
┈ = median months on treatment
— = mean months on treatment

Conclusion: MTX/VBL is very safe and very effective in the treatment of patients with DF and should be considered as first-line therapy. Duration of therapy of at least 18 months is likely required to ensure good outcome.

Poster 082 #2789879

LOSS OF MEASLES IMMUNITY IN PEDIATRIC ONCOLOGY PATIENTS: RISK WITH THE RISE OF UNDERVACCINATION

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Objective: Pediatric cancer patients undergoing chemotherapy are at risk of losing immunity to illnesses such as measles. Measles infection in cancer patients has mortality rates up to 50%; up to 35% of children under 7 lose humoral immunity as a result of chemotherapy. Because of volitional vaccine refusal, there has been a dramatic increase in measles infection from 63 in 2010 to 677 in 2014, including a California outbreak (110 cases), a recent Minnesota outbreak, a smaller outbreak in Chicago, and 358 US cases in our study period. Small and medium pediatric oncology practices frequently share floor/clinic space with the general pediatric patients putting them at risk, especially given the virulence of the disease starting 48 hours prior to symptoms. We wished to characterize the risk of measles infection to our patients. Measles protective humoral immune status was checked in all of our patients from January 1, 2015 to June 15, 2017.

Methods: Patients less than 21 years of age receiving chemotherapy between January 2015 - June 2017 in our institution's pediatric oncology department were included

in a retrospective review. Loss of measles immunity according to titer lab results was defined as less than or equal to 0.90.

Results: A total of 46 patients were included. Five patients (10.8%) had non-protective measles antibody levels. Two of our patients had sarcoma, 3 had leukemia/lymphoma and all were seen frequently in both clinic and the floor. For patients who had initial measles immunity, IgG titers trended down in the majority of cases while on chemotherapy. None of the patients developed measles.

Conclusion: Measles outbreaks in the US are potentially fatal to immunocompromised oncology patients. This danger is increased because of shared clinic space with the general patient population. Given the increase in measles cases in the last five years and the vulnerability of oncology patients to this disease, it should be standard practice to check all patients for measles immunity prior to starting chemotherapy and throughout the course of treatment. Patients who are infected with measles should be isolated from this susceptible patient population.

Poster 083 #2804254

INTRAVENOUS HYPERHYDRATION IMPROVES HIGH-DOSE METHOTREXATE EXCRETION, LESSENS TOXICITY AND REDUCES HOSPITAL STAYS IN PATIENTS WITH OSTEOSARCOMA UNDERGOING CHEMOTHERAPY

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Objective: Intravenous high-dose methotrexate (HD MTX) is a cornerstone of osteosarcoma chemotherapy protocols in children, adolescents and young adults. HD MTX administration necessitates serial monitoring of serum methotrexate (MTX) concentrations, leucovorin rescue, urine alkalinization and adequate hydration of the patient to prevent host toxicity. An intravenous hydration rate of 125 mL/m2/hr with titrated sodium bicarbonate is used as a standard infusion to facilitate methotrexate administration and clearance after infusion, with adjustments made based on MTX levels and renal function. Despite this hydration regimen, elevated MTX levels and delayed clearance remain an ongoing complication causing toxicities, prolonged hospital length of stays and delayed therapy cycles. We sought to determine if an institutional policy of increased intravenous hydration could decrease the incidence of these issues.

Methods: In 2013, our institution implemented a policy of hyperhydration, administering IV fluids at 200 mL/m2/hr throughout the entire methotrexate cycle. We have conducted an IRB approved retrospective chart review of patients <21 years old with high grade conventional osteosarcoma treated with HD MTX at our institution between 2007 and 2017.

Results: Thirty five patients (ages 5-21 years old) received 377 cycles of methotrexate; 7 of 25 patients on standard hydration (SH) and 0 of 10 patients on the hyperhydration (HH) protocol experienced grade 3 to 4 methotrexate toxicity (defined as MTX levels of ≥50 μM at 24 hours, ≥5 μM at 48 and 72 hours; P=0.084). We identified eight grade 3-4 toxicities out of 230 HD MTX cycles in the SH group, and none in the 147 of the HH group (P=0.025). In addition, the SH group had a mean time to clearance of 120.0 hours (SD 53.6 hours); the HH cohort a mean of 81.4 hours (SD 18.9 hours). This resulted in a difference of 38.6 hours (95% CI 29.5-47.6 hours; P<0.0001). There were no adverse events of fluid overload in the HH group nor was there a statistically significant difference in tumor histological response between the HH and SH groups after induction chemotherapy.

Conclusion: The HH protocol of 200mL/m2/hr is a potentially superior alternative to SH for reducing MTX toxicity, improving MTX clearance, and reducing hospital stays in patients with osteosarcoma receiving HD MTX chemotherapy.

Poster 084 #2804754

DRUG SENSITIVITY TESTING AND GENOTYPIC SCREEN ON PATIENT-DERIVED SARCOMA CELLS TO GUIDE PRECISION MEDICINE

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Objective: To identify drugs with therapeutic potential for patients with advanced and/or refractory sarcoma as a guide for treatment decisions by performing comprenhensive phenotypic and genotypic screens on patient-derived sarcoma cells. To investigate if this approach has potential to predict patient response to treatment.

Methods: We cultured and characterized patient-derived sarcoma cells and evaluated their sensitivity to dose response series of 525 anti-cancer agents includying approved drugs at five different concentrations. In parallel we sequenced a panel of sarcoma-associated genes to identify mutations and evaluated transcritpion of cancer

driver genes in the patient-derived sarcomas (PDC), their tumor of origin and matched healthy muscle. In total, 15 sarcomas and 5 healthy mesenchymal primary cell cultures were studied. For sarcomas with translocations, we set up proximity ligation assays to identify fusion proteins in situ and determine tumor representativity in the outgrowing cultures.

Results: Soft tissue sarcomas and healthy mesenchymal cell cultures were established from patient biopsies with a success rate of 62%. This comprehensive drug sensitivity testing identified agents that are used in routine sarcoma treatment like anthracyclines and taxanes. It also identified targeted inhibitors specific for each sarcoma subtype. Dasatinib showed a potent inhibition of several sarcoma subtypes. In a case of Ewing sarcoma, the drug sensitivity testing predicted the patient response to taxanes.

Conclusion: Our results show that patient derived sarcoma cells can be culture in vitro and used in phenotypic and genotypic screens to identify potentially efficient drugs to treat sarcoma patients with poor treatment options.

Poster 085 #2800896

PATIENTS WITH SARCOMA DOMINATE ACCRUAL TO THE ICAT2, GAIN CONSORTIUM STUDY: REPORT OF AN ONGOING SEQUENCING STUDY

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Objective: The Genomic Assessment Informs Novel Therapy (GAIN) Consortium is composed of 12 member institutions committed to collaborative investigation of the precision cancer medicine approach in difficult to cure pediatric cancers.

Methods: The GAIN Consortium is conducting a sequencing study titled “Multicenter Cohort Study to Evaluate Outcomes after Receipt of Targeted Therapy Matched to an Individualized Cancer Therapy (iCat) Recommendation: The iCat2 / GAIN Consortium Study (NCT02520713)”. Diagnoses of enrolled patients were reviewed in order to assess accrual of sarcoma patients to the study.

Results: Patient are eligible for the iCat2, GAIN Consortium study if they are age 30 or younger at the time of being diagnosed with a solid extra-cranial malignancy that either lacks a definitive diagnosis after initial pathologic assessment or is at risk for a poor outcome (defined as relapsed/refractory or expected 2-year event-free survival <50%). All patients have tumor sequenced with a targeted DNA sequencing panel. For selected diagnoses including rare and difficult to classify sarcomas, whole exome (WES) and RNA sequencing is performed. Sequencing results obtained in a clinical (CLIA or CAP certified) laboratory which include the targeted panel, WES and validations of RNA sequencing are returned to the consenting oncologist. As of June, 2017 with 9 of the 12 study sites actively enrolling patients, 145 patients have enrolled with 92 (63%) of these patients having sarcoma. The most common sarcoma diagnoses enrolled are osteosarcoma, Ewing sarcoma and rhabdomyosarcoma. Patients enrolled with histologies rarely occurring in those <30 years old include desmoplastic small round cell tumor, alveolar soft parts sarcoma, chordoma and chondrosarcoma.

Conclusion: The iCat2/GAIN consortium study constitutes a research opportunity in which children, adolescents and young adults with sarcoma can both contribute sequencing data to a multi-institution collaborative study and also receive potentially clinically significant sequencing results and recommendations for therapy via their physicians. The consortium is planning to extend participation to sarcoma patients at institutions beyond the GAIN Consortium member institutions.

Poster 086 #2804815

DENOSUMAB THERAPY FOR PEDIATRIC ANEURYSMAL BONE CYSTS: COMPLETE RESPONSE IN 2 PATIENTS WITH CONFIRMATION OF NEW TOXICITY

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Objective: New treatment options are being proposed for Aneurysmal Bone Cysts (ABCs). Recent literature documents tumor responses to minimally invasive or non-operative treatments. The safety and effectiveness

of non-operative ABC treatment remains unclear. More research is needed to inform patient selection for non-operative treatment, particularly ABC presentations that are refractory or difficult-to-resect. We initially reported a complete response to the receptor-activator of nuclear kappaB ligand (RANKL) inhibitor, denosumab, in a 5 year old male (Patient A) who presented with an unresectable sacral ABC (MSTS Annual Meeting, 2014; Pelle et al. Transl Res 2014). The use of denosumab in the pediatric population is not well described. At this time, there are no publications documenting long term follow for ABCs treated with denosumab.

Methods: We conducted a retrospective review of two patients' clinical course in 2012 to provide long-term follow-up. Relevant clinical information was recorded regarding radiographic response to treatment and side effects.

Results: In both of our patients with large or unresectable ABCs, denosumab therapy resulted in early relief of pain and a measurable size decrease within 10 weeks of treatment initiation as determined by MRI and CT. Early lesional ossification and cortical thickening were consistently observed throughout treatment. Patient A received 18 months of denosumab with no evidence of hypocalcemia, atypical femur fractures, or osteonecrosis during treatment. Peri-physeal sclerosis was noted to be widespread by 12 months of therapy. 6 months following cessation of treatment, the patient developed malignant hypercalcemia requiring dialysis support. He fully recovered and remains disease-free at 4.5 years. Patient B was determined to be disease free by MRI and CT after 14 months of denosumab treatment with no apparent side effects to date.

Conclusion: Preliminary evidence suggests that denosumab is an active agent against refractory or difficult-to-resect ABCs. Based on our experience and other recent literature reports, malignant hypercalcemia is now a verified complication of this treatment approach in the pediatric population, and may not be adequately recognized given the typical association of denosumab with hypocalcemia rather than hypercalcemia. Extension of serum calcium monitoring should be considered for 6-12 months after cessation of denosumab treatment.

Poster 087 #2791121

A RETROSPECTIVE COMPARISON OF PAZOPANIB WITH ESTABLISHED THERAPIES FOR DESMOID TUMORS IN PEDIATRIC, ADOLESCENT AND YOUNG ADULT (AYA) PATIENTS

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Objective: Desmoid tumors (DT) lack a reliably effective medical therapy. Surgical resection may be morbid and does not preclude recurrence. Radiation has potentially severe late effects, particularly detrimental in young patients. At our institution, we recently observed encouraging results with pazopanib therapy for DT compared with established therapies.

Methods: Retrospective single-institution chart review comparing treatment outcomes in AYA and pediatric patients with DT treated with pazopanib to those treated with established therapies.

Results: Six DT patients, 3-21 years with previously treated DT, received pazopanib; 33 DT patients received established therapies only. In both groups, the median age at diagnosis was 16 years, female patients comprised 50%, and most common DT site was extremity. In the pazopanib group, there were 4 patients with sporadic DTs, all with CTNNB1 mutations by next generation sequencing, and 2 FAP patients. In the comparison group, 5 sporadic DTs had CTNNB1 mutations and 1 had a somatic APC mutation. Established therapies showed few objective responses and most patients received multiple therapies as a result. Surgical resection had a 68% recurrence rate. One patient who received radiation developed a sarcoma in the radiation field. Of 8 patients who received vinblastine/methotrexate (VM), only 1 had a PR by Response Evaluation Criteria in Solid Tumors v1.1 (RECIST), 5 had SD, 2 not evaluable. Toxicities included fever and neutropenia, peripheral neuropathy, nausea/vomiting. After VM, 5 of 8 required additional therapy. Of 7 patients who received sulindac/tamoxifen, none had objective improvement, 4 had SD, 1 had PD, 2 not evaluable. Five of 7 required additional therapy. All female patients developed ovarian cysts. In contrast, none of the patients progressed while on pazopanib. Best responses by RECIST were PR in 2 of 8 and SD in 6 of 8 tumors, and all extra-abdominal DTs demonstrated dramatically increased fibrosis on T2-weighted MR. A PR of 66% was observed in a patient who had failed multiple prior therapies. A mesenteric DT in a FAP patient also showed PR. Four of 6 patients reported substantial pain relief and improvement in function within 1 month. Pazopanib was discontinued in 1 patient after 18 months due to recurrent facial edema. All other toxicities responded to dose reduction and objective treatment effect was not sacrificed.

Conclusion: In this series, pazopanib offered an effective treatment option for AYA patients with symptomatic DT.

Poster 088 #2804434

THE SPECTRUM OF SARCOMAS IN THE ADOLESCENT AND YOUNG ADULT (AYA) POPULATION - A SINGLE INSTITUTION REVIEW OF 345 PATIENTS

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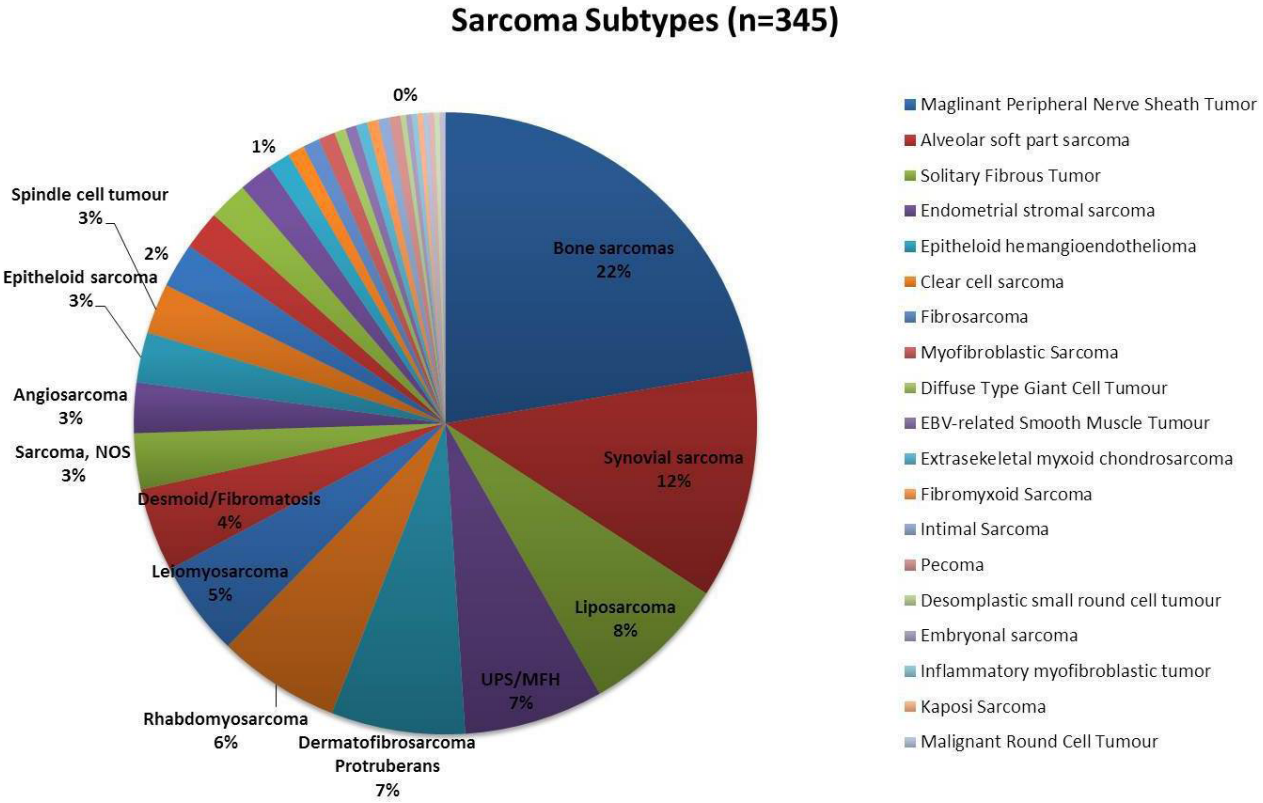
Objective: Sarcomas comprise between 10-15% of adolescent and young adult (AYA) malignancies (patients aged between 16-39 years) compared with 1-2% of adult malignancies (patients aged 40 years and above). We sought to evaluate the distribution of subtypes and treatment approaches for AYA sarcomas.

Methods: We retrospectively reviewed the data on AYA patients presenting to the National Cancer Centre Singapore (NCCS) with a diagnosis of sarcoma between 1 January 2002 and 30 June 2016.

Results: There was even distribution of females (173) and males (172). T (BS)The location of these tumors was axial in 146 patients (pts) (42%), in pts (39%) and in 60 pts (17%), and unknown in 3 pts (0.8%)The distribution of patients across different age subcategories was as follows : 42 between 16-19 years (12%); 66 between 20-24 years (y) (19%); 54 between 25-29 y (16%); 82 between 30-34 y (24%); 101 between 35-39 y (29%). The distribution of histologies is depicted in Figure 1. The most common histologies within the different age groups in were osteosarcoma (16-19 y), osteosarcoma (20-24 y)-, dermatofibrosarcoma protuberans and synovial sarcoma (25-29 y), liposarcoma and synovial sarcoma (30-34 y), and dermatofibrosarcoma protuberans (35-39 y). The majority of patients (81%) presented with localized disease, amongst whom more that 95% underwent attempted surgical extirpation, including amputation in 7 pts. Adjuvant and/or neoadjuvant chemotherapy was administered to 110 (32%) of patients, with almost all patients receiving combination chemotherapy. Amongst 66 patients presenting with metastatic disease, 51 patients received palliative systemic therapy; of these, only 9 patients received 3 or more lines of therapy.

Conclusion: Sarcomas contribute significantly to the burden of care amongst AYA cancer patients. The distribution of sarcoma subtypes amongst AYA patients is unique when compared with pediatric or adult patients. Determination of prognostic factors and clinical outcomes is ongoing.



Poster 089 #2772162

FACTORS ASSOCIATED WITH DISEASE STABILIZATION IN DESMOID-TYPE FIBROMATOSES

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Objective: Spontaneous disease stabilization of desmoid-type fibromatosis (DF) has been demonstrated in many patients. Thus, watchful waiting approach without any front-line treatment is being offered to the patients who present with DF. To provide for the most suitable treatment for each patient, identification of factors predictive of disease stabilization is necessary. The purpose of this study was to assess the disease stabilization rate and identify predictive factors for disease stabilization.

Methods: One hundred and forty-four patients with sporadic, extra-abdominal DF who were managed with front-line conservative treatment and followed for at least 2 years were reviewed. Tumors were radiologically diagnosed as stable when an unchanged or a continual decrease in tumor size by the longest diameter was successively recorded for at least 6 months with no renewed growth at final follow-up. The primary endpoint was tumor stabilization. Possible patient-, disease-, and treatment-related factors predictive of disease stabilization were examined. Kaplan-Meier method was used to estimate time to tumor stabilization, and the Log-rank test was utilized for univariate analysis. Multivariate analysis was performed using the Cox proportional hazards model.

Results: One hundred sixteen (80.6%) out of 144 tumors were stable at final follow-up, with a mean time to stabilization of 17 months (range 0 to 153). Tumor stabilization rates at 1, 2, and 3 years were 59%, 72%, and 77%, respectively. On Kaplan-Meier analysis, patients <40 years (44.9±7.4 months vs. 7.3±1.5 months, p<0.001), with tumors ≥5 cm (40.1±7.4 vs. 15±3.8 months, p=0.005), and with recurrence (49.2±8.2 vs. 9.1±2 months, p<0.001) were found to have significantly longer time to tumor stabilization. After multivariate Cox regression analysis, both recurrent presentation (RR=1.7, p=0.011) and younger age (RR=1.8, p=0.006) were the independent factors associated with disease stabilization. Analysis of recurrent disease showed 48 (67.6%) of the 71 recurrent tumors were stable at final follow-up, with a mean time to stabilization of 27 months (range 0 to 153). Stabilization rates for the recurrent tumors at 1, 2, and 3 years were 46%, 55%, and 62%, respectively.

Conclusion: A front-line conservative treatment seems to be the optimal treatment for majority of patients who present with DF. Younger patients and those presenting with recurrence may require longer periods of initial observation with pain palliation as needed.

Poster 090 #2804791

CLINIC AND MOLECULAR PROGNOSTIC FACTORS IN DESMOID TUMORS TREATED WITH UPFRONT SURGERY. A SPANISH GROUP FOR SARCOMA RESEARCH STUDY

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Objective: Desmoid tumor (DT) management has a wide spectrum of therapeutic options, and even when surgery is currently not recommended for most cases, the fact is that a relevant number of patients still undergo surgery as first option. Clinical behavior is difficult to predict at individual basis, even for those completely resected DT. In sporadic DT, the prognostic role of different missense mutations in CTNNB1 gene has been inconsistent among several publications. Our aim was to analyze the potential prognostic role of genotype in a series of primary DT treated with surgery.

Methods: Patients were selected from GEIS registry, IRBs and ethic committees approved the protocol including molecular tests in paraffin embedded tumor samples. Kaplan–Meier estimations were used for time-to-event variables and the log-rank test was used to compare groups. Tumor tissue was processed with the QIAamp FFPE Tissue Kit (Qiagen, Valencia, CA), according to manufacturers instructions. Exonic primers were used to amplify a sequence within exon 3 of CTNN1B by PCR. Bidirectional sequencing with specific primers was performed in an AB 3500 genetic analyzer, using the BigDye Terminator v3.1 kit (Applied Biosystems).

Results: A subset of 320 patients that underwent upfront surgery was selected. The median age was 37 y (12-89). Primary sites were: limbs 28%, trunk wall 43% and miscellany 29%. The median of size was 6.5 cm (1-27) and the median of Karnofsky index was 90% (50-100). There were 108 (34%) recurrences with a median follow-up of 60 months. Mutations in exon 3 of CTNNB1 gene were found in 142 (88%) out of 162 available blocks, 89 (63%)

in 41A, 31 (22%) in 45F, 22 (15%) in 45P and 20 wild type (12%). Patients harboring 45F showed statistically worse SLR compared with the rest of genotypes: 25.8 m (16.4-35,2) vs not reached, (p=0.035). Patients with DT in limbs had significant worse median of RFS: 38 m (3-73) than trunk wall (149) or miscellany (107), p= 0.001. Likewise, patients with DT ≥ 6.5 cm had significantly worse RFS: 59 m (17-101) vs not reached (p=0.003).

Conclusion: Tumor site, tumor size and type of mutation of CTNNB1 gene has prognostic impact in DT treated with upfront surgery. Genotype 45F entails worse RFS and it justifies further molecular related research in this entity.

Poster 091 #2793719

STABILIZATION OF β-CATENIN: A POTENTIAL THERAPEUTIC TARGET FOR DESMOID TUMORS?

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Objective: To investigate the antitumor effect of a novel agent targeting beta catenin stabilization, BC2059, in desmoid tumor (DT) models.

Methods: A panel of DT cell strains was exposed to increasing concentrations of BC2059 in vitro and evaluated for cell proliferation and colony formation capacity. Antitumor effects were assessed in vitro by cell cycle, apoptosis, and migration and invasion analysis. Cells treated with BC2059 were analyzed the association of β-catenin with TBL1 by immunoprecipitation (IP) analysis. To further understand the effects of BC2059 treatment on DTs we analyzed the expression of β-catenin pathway components in DT cell strains treated with BC2059 using real time PCR and western blotting.

Results: BC2059 markedly inhibited proliferation, capacity of colony formation, migration and invasion of mutated DT cells, but had no effect on wild-type DTs. Comparison of β-catenin mutation between the original tumor and the associated cell strain was the primary method used to differentiate desmoid tumor cell from fibroblast. Therefore, cell strains lacking detectable β-catenin mutation (wild-type) could be comprised of primarily fibroblasts cells and not tumor cells. This is one possible explanation for the lack of effect of BC2059 on DT wild-type cell strains. The decrease in cell viability on mutated DT cells caused by BC2059 was due to apoptosis. Treatment with BC2059 led to a reduction of β-catenin associated TBL1 in all mutated DT cells, resulting in a reduction of nuclear β-catenin. Consequently, levels of genes that are target of b-catenin (e.g MDK, AXIN2) were found to be downregulated after BC2059 treatment.

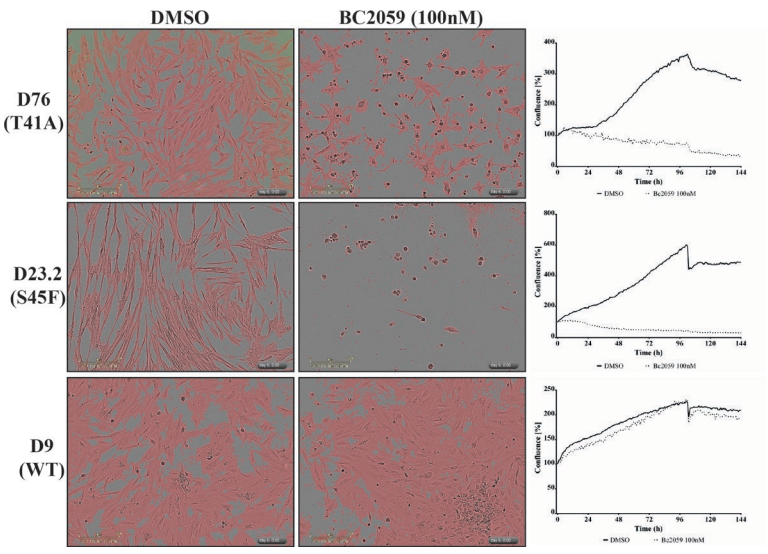
Conclusion: Our findings suggest that BC2059 has significant antitumor activity against β-catenin mutated DTs through stabilization of b-catenin that leads to downregulation of its target genes. Thus, BC2059 may comprise an alternative strategy for the treatment of desmoid tumor patients.

*This work was made possible in part by funding of Beta Cat Pharmaceuticals through the Product Development Award CP130058 from the Cancer Prevention and Research Institute of Texas (CPRIT).

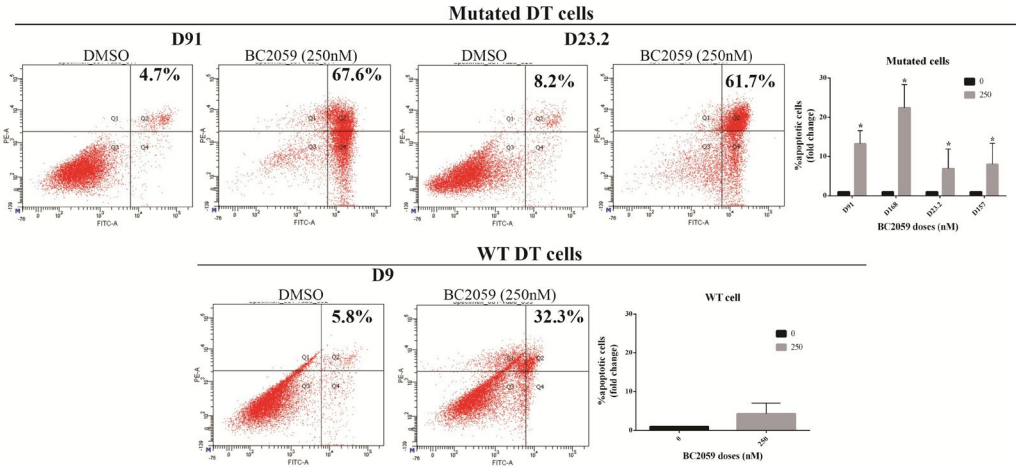
Growth Inhibition of Desmoid Cell Lines by BC-2059

Cell Line	IC50 (nM)	*Mutation Status of CTNNB1*	Treatment duration
D13	47.79	S45F	6 days
D23.2	58.04	S45F	6 days
D180	61.21	T41A	6 days
D91	86.26	T41A	6 days
D76	93.37	T41A	6 days
D186	~ 97.40	S45F	6 days
D14	~98.76	S45F	6 days
D168	103.8	T41A	6 days
D93	166.1	WTa	30 days
D9	191.5	WT	30 days
D38	191.8	WT	30 days
D55	~ 255.1	WT	30 days
D8	~ 284.7	WT	30 days
NDF-α[b]	639.6	normal cell line	30 days
HuMSC[c]	~ 839.4	normal cell line	30 days

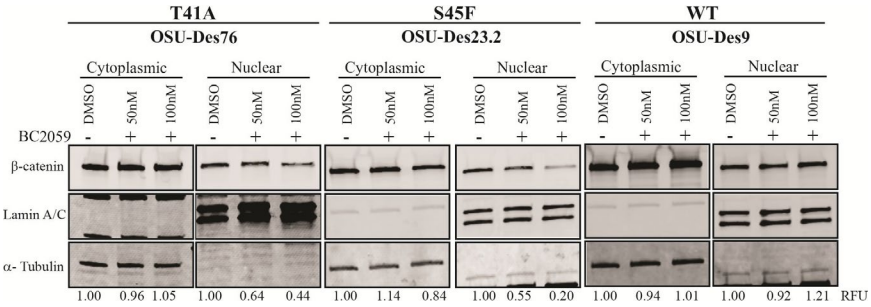
a WT=wild type, no mutation in CTNNB1; b Normal dermal fibroblasts; c Human umbilical mesenchymal stem cells



Representative Images and Confluency Curves from Proliferation Assay



Induction of Apoptosis in Desmoid Cell Lines with BC-2059



Western Blots Showing Effect of BC-2059 on Cytoplasmic and Nuclear β-Catenin

Poster 092 #2753606

POSTOPERATIVE THERAPY FOR SCALP ANGIOSARCOMAS

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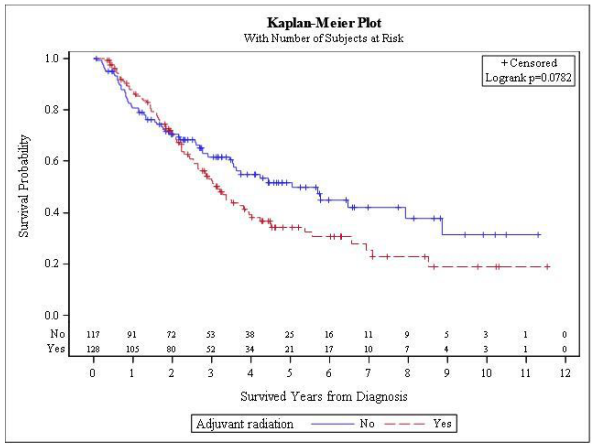
Objective: Angiosarcomas of the scalp are rare with the impact of postoperative therapy based on limited retrospective evidence. The purpose of our study was to determine practice patterns and overall survival (OS) impact of postoperative radiation or chemoradiation among patients with non-metastatic resected scalp angiosarcomas in the National Cancer Data Base (NCDB).

Methods: The NCDB, accounting for 70% of cancer diagnoses in the United States, was queried for non-metastatic definitively resected angiosarcomas of the scalp from 2004 to 2014 with complete treatment records. Univariable and multivariable logistic regression and Cox-proportional hazard models as well as Kaplan-Meier analysis was conducted.

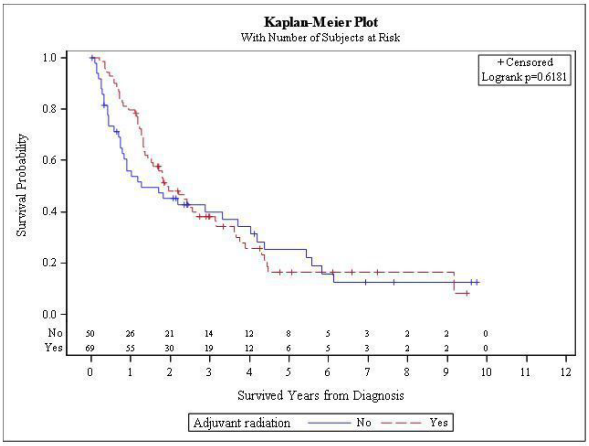
Results: A total of 438 non-metastatic definitively resected scalp angiosarcomas were identified: 226 (51.6%) patients received postoperative radiation with 98 (22.4%) patients also receiving concurrent chemotherapy. On multivariable analysis, only positive surgical margins (OR=11.86, 95%CI: 1.11-3.13) was associated with receiving radiation, but both positive surgical margins (OR=2.77, 95%CI: 1.54-4.98) and treatment at a high-volume center (OR=2.17, 95%CI: 1.17-4.03) were associated with receipt of concurrent chemoradiation. Regarding OS on multivariable analysis, patients 65 years or older at diagnosis (HR=9.88, 95%CI: 2.30-42.41), patients living in a lower-income county (HR=1.78, 95%CI: 1.05-3.02), and tumors ≥5 cm (HR=1.77, 95%CI: 1.27-2.47) had inferior OS. Neither adjuvant radiation, adjuvant chemoradiation, nor elective neck dissection were statistically associated with improved or inferior OS. Radiation did not impact OS in subgroup analysis (see Figures). Two-year Kaplan-Meier estimates for OS for patients receiving RT compared to those who did not was 64.6% (95%CI: 59.8-68.9%) and 57.0% (95%CI: 52.7-61.0%) (p=0.45).

Figure 1: Kaplan-Meier curve of patients with negative margins after definitive resection for scalp angiosarcomas comparing those who received adjuvant radiation and those who did not.



Adjuvant radiation	No. of Subject	Event	Censored	Median Survival (95% CI)	1 Yr Survival	2 Yr Survival	5 Yr Survival
No	117	54 (46%)	63 (54%)	5.1 (3.5, 8.9)	80.6% (72.1%, 86.8%)	70.5% (61.1%, 78.1%)	51.8% (41.0%, 61.5%)
Yes	128	77 (60%)	51 (40%)	3.1 (2.5, 3.9)	87.0% (79.6%, 91.8%)	71.8% (62.8%, 79.0%)	34.1% (24.9%, 43.6%)

Figure 2: Kaplan-Meier curve of patients with positive margins after definitive resection for scalp angiosarcomas comparing those who received adjuvant radiation and those who did not.



Adjuvant radiation	No. of Subject	Event	Censored	Median Survival (95% CI)	1 Yr Survival	2 Yr Survival	5 Yr Survival
No	50	37 (74%)	13 (26%)	1.3 (0.7, 3.7)	56.1% (40.9%, 68.8%)	45.3% (30.8%, 58.7%)	25.2% (12.9%, 39.5%)
Yes	69	52 (75%)	17 (25%)	1.9 (1.4, 2.7)	79.7% (68.2%, 87.4%)	48.2% (35.8%, 59.5%)	16.3% (7.7%, 27.8%)

Conclusion: In this NCDB series, half of resected scalp angiosarcomas received radiation, with a minority receiving concurrent chemotherapy. The receipt of postoperative radiation or chemoradiation was not associated with improved OS. Patients with positive margins at resection were more likely to receive radiation and/or chemoradiation. Patients treated at a high-volume institution were more likely to receive chemotherapy. Older age, living in a low-income county, and tumor size ≥5 cm were poor prognostic factors. Our series represents the largest in the literature examining resected scalp angiosarcomas.

Poster 093 #2793944

β-CATENIN S45F MUTATION RESULTS IN APOPTOTIC RESISTANCE; A POTENTIAL ROLE FOR *RUNX3*

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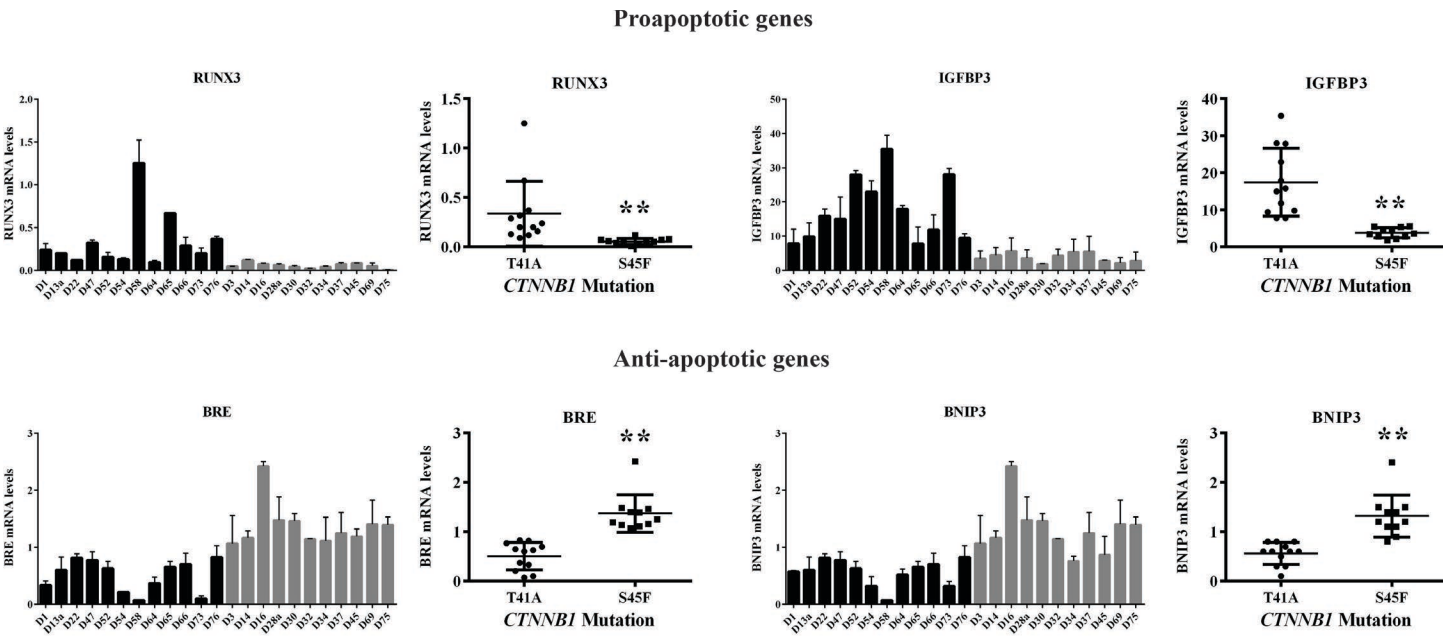
Objective: To investigate molecular driving forces behind the differences between the CTNNB1 S45F and T41A mutations in DTs.

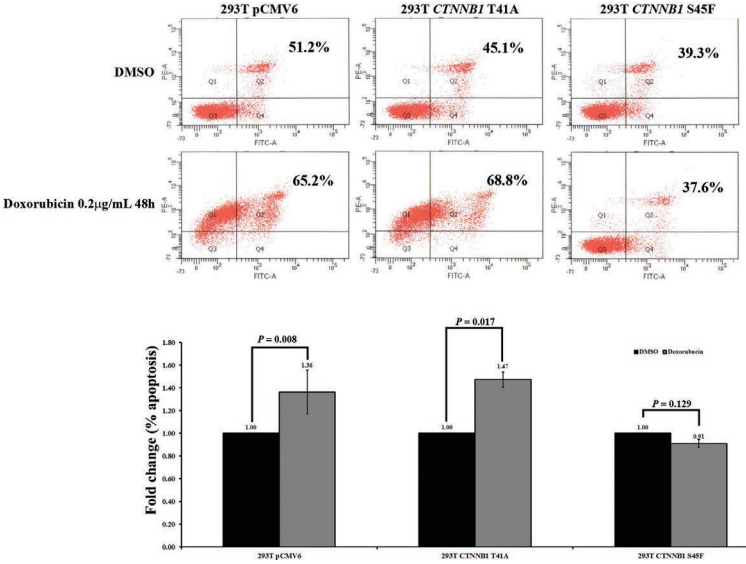
Methods: We conducted a gene array assay including desmoid tissues with CTNBB1 T41A or S45F mutation. The gene array was validated using qRT-PCR. As an artificial system, we also transfected mutated β-catenin genes into normal embryonic cells (293T cells) to recapitulate the biology observed in desmoid cells. The ability of inducing apoptosis between the T41A and S45F mutated/transfected cells were assessed via flow cytometry analysis and via induction of cleaved caspase 3/7 after staurosporine or doxorubicin treatment.

Results: Our gene array analysis showed that proapoptotic genes are downregulated and anti-apoptotic genes are upregulated in the cells with the S45F mutation when compared to the T41A mutation. Moreover, we showed that there is no significant induction of apoptosis in the S45F-mutated desmoid cell strains or in the transfected 293T cells after staurosporine or doxorubicin treatment when compared to the T41A-mutated/transfected cells. Furthermore, our results showed a higher expression of nuclear β-catenin in the S45F-mutated cells when compared to the ones harboring the T41A mutation. Further investigating into these differences, we found that one of the pro-apoptotic genes downregulated in S45F-mutated tumors, RUNX3, has been shown to attenuate WNT signaling activity, suggesting that this gene could have an important role in the cross-talk between apoptosis and β-catenin pathway. To analyze the role of RUNX3 in the response to apoptosis of S45F mutated desmoids we overexpressed RUNX3 in the transfected 293T cells and then treated those cells with doxorubicin. Our results showed that the 293T CNTNNB1 S45F transfected with RUNX3 have a higher induction of apoptosis when compared to the parental cells, suggesting that RUNX3 plays a role in the resistance to apoptosis observed in the S45F mutated cells.

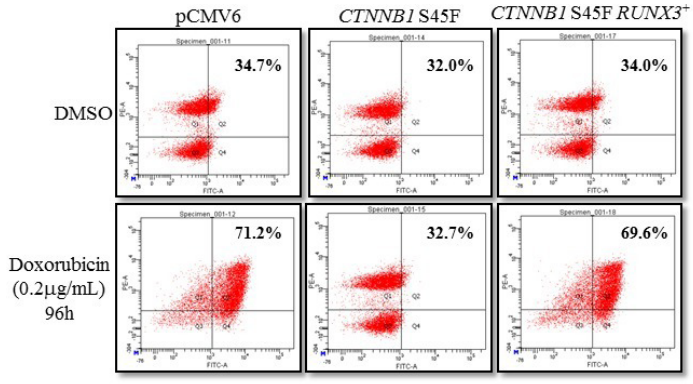
Conclusion: Taken together our results suggest that apoptosis is downregulated in desmoid tumors harboring the CTNNB1 S45F mutation, and that cells with the CTNNB1 S45F mutation are less able to undergo apoptosis than T41A-mutated cells. The impairment of apoptosis appears to be specific to the CTNNB1 S45F mutation and not to desmoid tumors per se. Moreover, our results also showed that RUNX3 may play a role in the resistance to apoptosis of S45F mutated cells and may be the cross-talk between the β-catenin and apoptosis pathway in desmoid tumors.

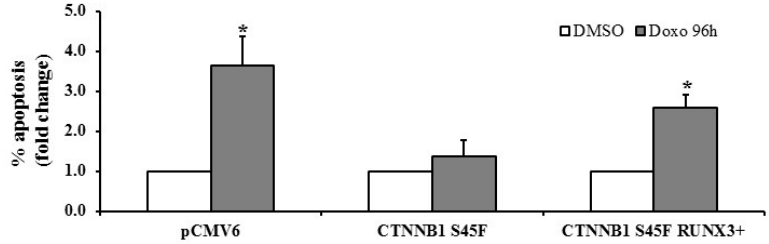


Apoptosis is downregulated in the S45F β-catenin mutated desmoids compared to the T41A mutated cells



The decrease in apoptosis activation is specific of β-catenin S45F mutation and not desmoids tumors per se





293T CNTNNB1 S45F transfected with RUNX3 have a higher induction of apoptosis when compared to the parental cells

Poster 094 #2798520

INVESTIGATION OF NOVEL *EX VIVO* TISSUE DRUG SCREENING TO PREDICT THERAPEUTIC RESPONSE IN DESMOID TUMORS

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Objective: To investigate ex-vivo fresh tumor sensitivity as a predictor of tumor responsiveness in desmoid tumors and compare to standard of care.

Methods: Fresh DT tissue have been thinly sliced and exposed to different drugs and combinations ex-vivo and evaluated for viability. The expression and activation of downstream markers were analyzed in DT ex-vivo tissue slice culture by western blot.

Results: Ex-vivo tissue culture is used to test tissue responsiveness to chemotherapeutic options in DT fresh tissue. Confirmation of appropriate downstream protein inhibition through western blot shows appropriate targeting and modality of cell death.

Conclusion: Ex-vivo tissue culture drug testing exhibits significant predictive effects on DT tissue with appropriate downstream effect in patient specific manner compared to in-vivo data. This data suggests that ex-vivo fresh tissue drug testing may be an appropriate drug selection technique in addition to pathology and genomic data in predicting adjuvant and salvage therapy after surgical treatment. This data suggest that quick and easy personalized treatments can be tested and selected through ex-vivo culture and testing to allow optimal treatment selection. Furthermore, our results suggest that along with previous therapies, novel treatment can be tested as well.

Poster 095 #2793308

HIGH LOCAL RECURRENCE RATE FOR GIANT CELL TUMOR OF BONE AFTER NEOADJUVANT DENOSUMAB TREATMENT

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Objective: Neoadjuvant denosumab for giant cell tumor of bone can lessen the extent of surgery, with salvage of the native joint. However, the risk of local recurrence using this strategy remains unknown. The primary aim of this study is to determine the local recurrence rate after neoadjuvant denosumab and curettage for giant cell tumor of bone. The secondary aim is to determine whether neoadjuvant denosumab would aid in preservation of the native joint.

Methods: A retrospective chart review was performed evaluating all patients who received neoadjuvant denosumab treatment for giant cell tumor of bone followed by curettage of the lesion. Date of diagnosis, number of denosumab treatments, date of surgery and type of surgical treatment were reviewed. In addition, if there was a recurrence, date of diagnosis, date of surgery, and type of surgical treatment were reviewed.

Results: Between 2013 and 2016, five patients were identified as being treated with neoadjuvant denosumab. These patients had significant destruction of subchondral bone for which the optimal surgical treatment was wide resection followed by fusion, arthroplasty, or amputation. Denosumab was administered in 3 weekly loading doses followed by 4-5 monthly maintenance doses. Surgery was performed 6 months after the first loading dose. All 5 patients received curettage of the lesion followed by argon beam coagulation and allograft packing at the subchondral bone. Four patients had polymethymethacrylate (PMMA) placed in the defect. Two patients had plate stabilization.

Four of 5 patients (80%) had local recurrence an average of 19 months (range 7-29 months) after curettage. The fifth patient is 3 months postoperative. The subsequent procedures performed on 3 patients included wide resection: one required wrist fusion, one underwent distal femur replacement, and one had a below knee amputation. The fourth patient had repeat curettage and allograft packing. Of these 4 patients, none have had a local recurrence in initial follow-up (mean 2 month, range 0-3).

Conclusion: Neoadjuvant denosumab ultimately did not enable long-term joint preservation. There appears to be an unacceptably high recurrence rate when utilized as neoadjuvant treatment. In this series, denosumab delayed the original planned surgery by 1-2 years, resulting in patients undergoing two operative procedures. One possible reason for the high local recurrence rate is that preoperative use may limit the ability to recognize active disease and perform adequate curettage.

Poster 096 #2790456

TUMOR REDUCTION AND SYMPTOM RELIEF AFTER ELECTROCHEMOTHERAPY IN A PATIENT WITH AGGRESSIVE FIBROMATOSIS

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Objective: Aggressive fibromatosis also known as desmoid tumors constitute 3% of soft tissue tumors. It is a monoclonal (myo-) fibroblastic proliferation derived from

mesenchymal progenitor cells. These tumors commonly develop in the fibrous (connective) tissue of the body that forms tendons and ligaments, usually in the arms, legs or midsection but also in the head and neck area. Electrochemotherapy (the use of brief electric pulses to enhance uptake of chemotherapy) is increasingly being used to treat cutaneous and subcutaneous tumors of different histologies, however the use for aggressive fibromatosis has not previously been reported in humans.

Methods: This case report describes a 63-year old woman with subcutaneous aggressive fibromatosis in the neck region of which the main symptom was severe pain, despite medication. At diagnosis, surgery was not feasible and radiotherapy not performed due to the diagnosis of familial adenomatous polyposis. Previous treatments included NSAID, endocrine therapy and sorafenib, which the patient had to stop due to severe side effects. After thorough consideration and discussion of various treatment options, the patient was referred for consideration of electrochemotherapy. She was informed that electrochemotherapy was considered experimental treatment in her particular case and consented to treatment. The patient was treated twice with electrochemotherapy with a 5 month interval, with 26.000 international units (IU) of bleomycin (15.000 IU/m2) and 64 pulse sequences of each eight pulses were administered using a square wave pulse generator (Cliniporator, IGEA, Carpi, Italy), and linear array electrodes. See figure 1.

Results: At one year follow-up substantial tumor reduction (7.1 x 2.2 cm to 2.9 x 1.7 cm) was observed both clinically and on MRI, and the patient went from reporting severe pain, NRS (numeric rating scale) score 7 to mild pain, NRS score 2 without pain medication. See figure 2. Side effects to the treatment with electrochemotherapy were considered mild and consisted of pain, inflammation and hyperpigmentation of the treated skin area.

Conclusion: This case study opens up the possibility of treating aggressive fibromatosis close to the skin with electrochemotherapy, and warrants phase II studies to investigate clinical outcomes in greater detail.

Figure 1: Electrochemotherapy treatment and follow-up. The left and middle panel are from the first electroporation procedure. A linear array electrode was used, coupled to a square wave pulse generator. Treatment commenced 8 minutes after iv bleomycin infusion, and the tumor was manually palpated after which electrodes were sequentially applied to cover the tumor volume. Right panel: At one-year follow-up hyperpigmentation in the treated area is just visible.

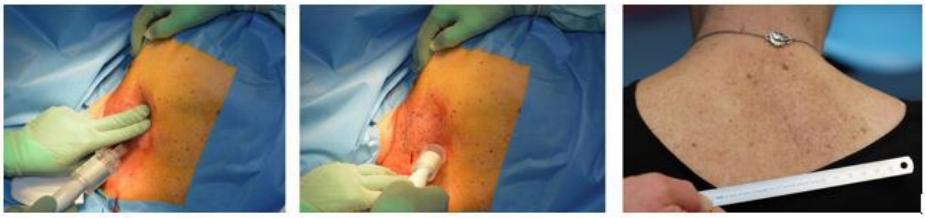
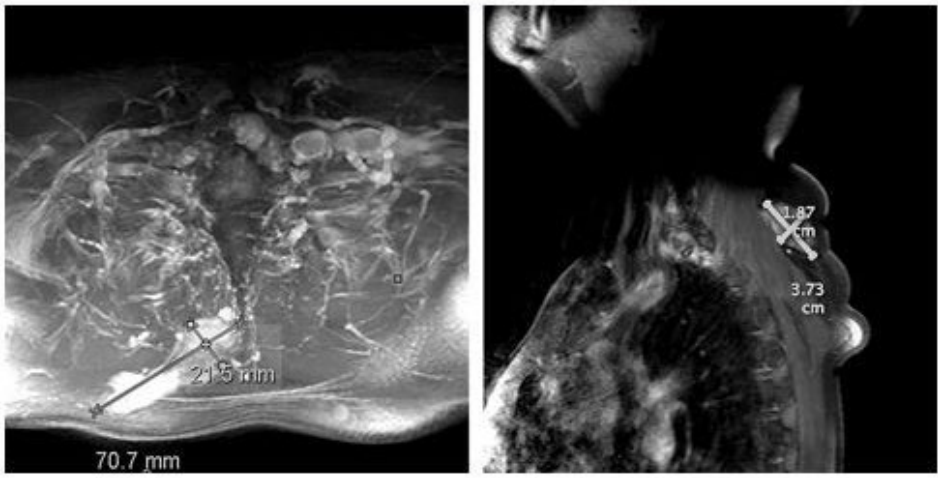
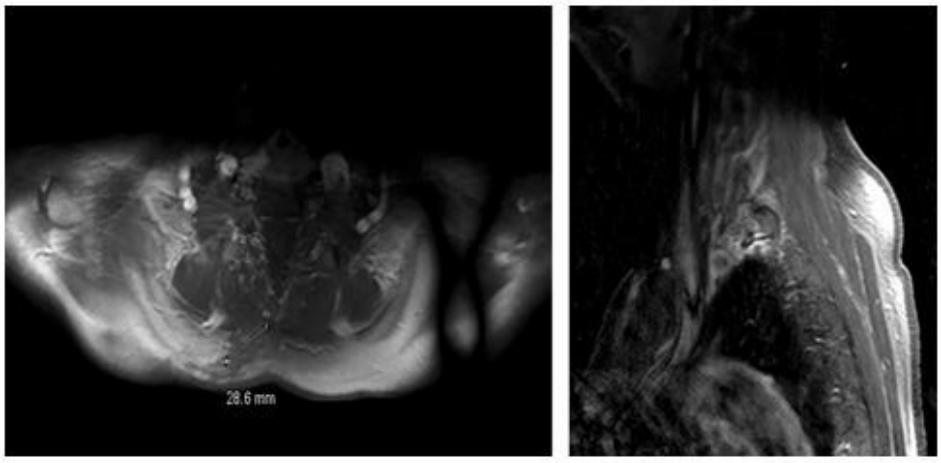


Figure 2.

A. MRI (January 2016). Before first treatment with electrochemotherapy, after treatment with sorafenib.



B. MRI (January 2017). After second treatment with electrochemotherapy. One year clinical follow-up.



Poster 097 #2785289

IL-6 MEDIATED SELF-SEEDING 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. Our work focuses on understanding the mechanisms that drive OS specifically to the lung and on developing interventions that target metastasis. Oncologists have long observed that metastases tend to appear after removal of a primary tumor. Recently, we and others have described how circulating tumors return to the primary tumor in a process called “self-seeding.” We hypothesized that upon removal of a primary tumor, circulating cells redirect toward metastatic colonization of the lung. Since self-seeding depends on the production of chemoattractants by primary tumors to direct trafficking of circulating cells back to the primary tumor, identification of the responsible cytokines could facilitate development of therapeutic modalities that leverage this biology.

Methods: We compared the percentage of OS cells which traffic to the lungs after amputation of an orthotopic tumor to that in mice which retained their primary tumor. We compared levels of OS cells that traffic to the lung after tail vein injection in mice bearing primary orthotopic tumors to that in mice without primary tumors and sought to identify the inoculated cells within the primary tumor. We evaluated production of a number of candidate mediators of this process by ELISA of conditioned OS supernatants, and performed transwell migration assays using the same candidates as chemoattractants to identify responses to cytokine gradients.

Results: Amputation triggers an increase in the number of OS cells resident within the lung. Lower numbers of OS cells introduced intravenously traffic to the lungs in mice bearing primary tumors than in mice without primary tumors. Of the several candidates tested, we have identified cytokines that are reliably produced by OS tumor cells across multiple models. A subset of those cytokines induces potent chemoattraction in all OS cell lines tested.

Conclusion: These results suggest that removal of a primary tumor terminates self-seeding, redirecting circulating tumor cells toward colonization of the lung. Given that specific, identifiable cytokines are produced by most OS cells and that these cytokines also reliably mediate chemoattraction, we suspect that they are primary, mechanistic drivers of OS self-seeding. We are exploring ways to leverage this biology in the development of novel therapies that prevent metastatic disease.

Poster 098 #2795749

GRM4 AND IL23 ARE NOVEL THERAPEUTIC TARGETS IMPLICATED IN OSTEOSARCOMA SUSCEPTIBILITY AND PROGRESSION

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Objective: There is a need for novel therapies for osteosarcoma. Multiple lines of evidence support the role of immunotherapy in bone cancer. Genome-wide association studies have identified the GRM4 (glutamate metabotropic recptor 4) locus as the strongest assocaition with susceptibility to osteosarcoma. Although the mechanisms are not known, emerging evidence suggests a link to immune regulatory functions. Here we use genetic models to demonstrate that Grm4 and Il23 are epistatically linked and rate-limiting to spontaneous osteosarcoma development in mice. Because there are emerging and established drugs that target both IL23 and GRM4, we use our model systems to study pharmacologic interdiction of the GRM4-IL23 axis on tumor development in vivo.

Methods: We have used a radiocarcinogen-induced osteosarcoma model to study the dependence of tumor development on Grm4 and Il23 in mice. The relationship between activation of GRM4 and expression of IL23 was studied in mouse and human monocytic cells. A panel of human osteosarcomas was studied for expressiom of IL23A. Finally, we conducted therapeutic studies using syngenic murine osteosarcoma cell lines, using an agonist for GRM$ (PHCCC) and an antagonist of IL23.

Results: In both human and murine monocytes, activation of Grm4 suppressed expression of Il23, while murine Grm4 -/- dendritic cells expressed markedly increased amounts of Il23 transcript and protein. Interestingly, the levels of Il12, a tumor suppressor cytokine linked to Il23, were reciprocally increased by activation of Grm4. These data suggest that GRM4 promotes an effective immune suppressor response by activating IL12 and suppressing IL23. Consistent with opposing roles in tumor development, the Grm4 -/- mice appear predisposed to earlier onset osteosarcoma development, while Il23 -/- mice were strikingly protected from the development of osteosarcomas ($P<0.0001$). In both mouse and human osteosarcomas, IL23 was expressed by infiltrating macrophages and dendritic cells. Using either an agonist for GRM4 (PHCCC) or an antagonist of IL23, we show that we can suppress tumour growth, an effect which appears synergistic with doxorubicin-based chemotherapy.

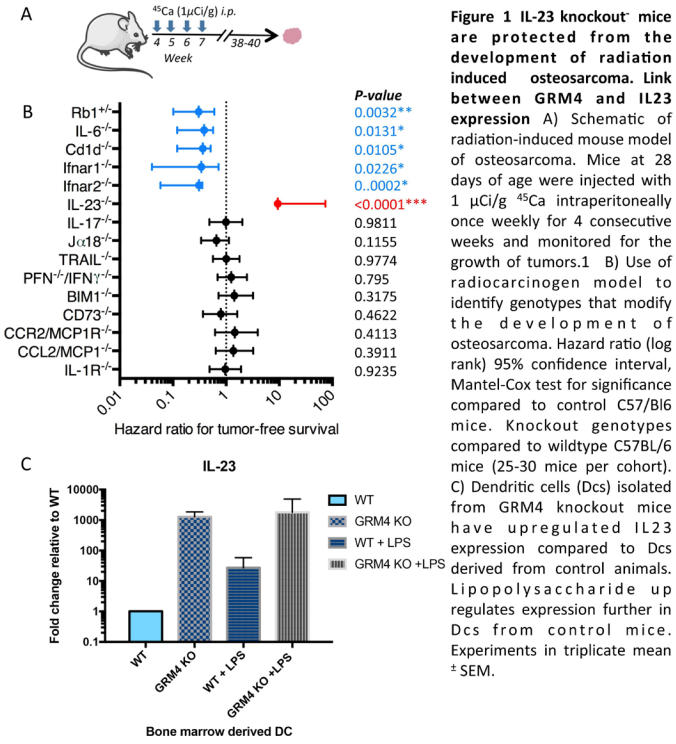

Figure 1 IL-23 knockout mice are protected from the development of radiation induced osteosarcoma. Link between GRM4 and IL23 expression A) Schematic of radiation-induced mouse model of osteosarcoma. Mice at 28 days of age were injected with 1 μCi/g ^{45}Ca intraperitoneally once weekly for 4 consecutive weeks and monitored for the growth of tumors.1 B) Use of radiocarcinogen model to identify genotypes that modify the development of osteosarcoma. Hazard ratio (log rank) 95% confidence interval, Mantel-Cox test for significance compared to control C57/Bl6 mice. Knockout genotypes compared to wildtype C57BL/6 mice (25-30 mice per cohort). C) Dendritic cells (Dcs) isolated from GRM4 knockout mice have upregulated IL23 expression compared to Dcs derived from control animals. Lipopolysaccharide up regulates expression further in Dcs from control mice. Experiments in triplicate mean ± SEM.

Conclusion: Taken together, these data provide a mechanistic basis for the genetic association between GRM4 and human osteosarcoma via IL12/IL23. More importantly, as agents targeting both GRM4 and IL23 are in clinical development, these genes represent promisign novel therapeutic targets for patients with osteosarcoma.

Poster 099 #2767401

DISULFIRAM VERSUS DOXORUBICIN TREATMENT IN AN ORTHOTOPIC MODEL OF METASTATIC OSTEOSARCOMA

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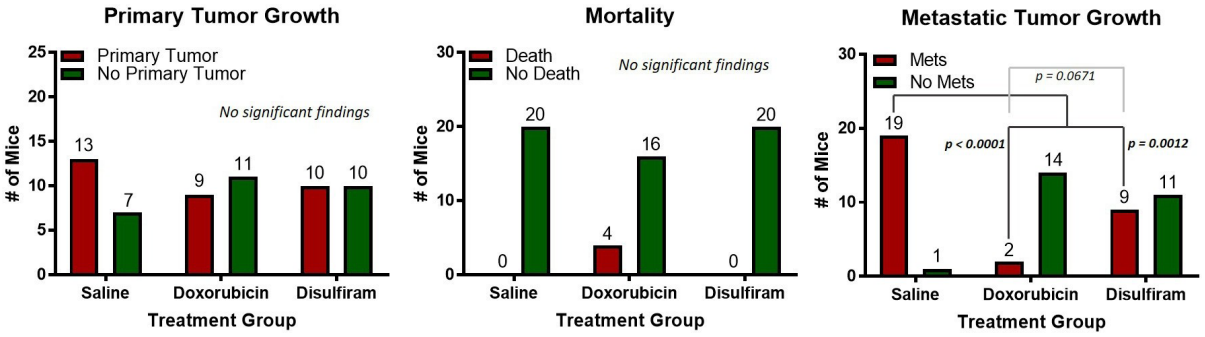
Objective: The 5-year survival of osteosarcoma (OS) patients with lung metastases is as low as 15%. Our group has shown that disulfiram (DSF), an FDA-approved aldehyde dehydrogenase inhibitor, inhibits OS proliferation and metastatic behavior in vitro. Here we compare the molecular effects of DSF and DXR treatment of OS and its metastases in an orthotopic, immunocompetent mouse model.

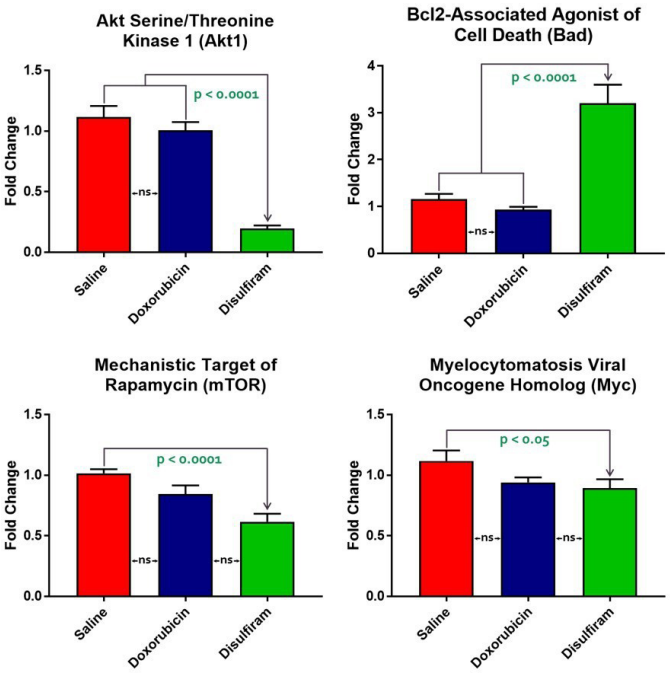
Methods: Sixty 4-6-week-old immunocompetent Balb/C mice were administered proximal tibial para-physeal injections of 500,000 K7M2 mouse OS cells. Systemic treatments with Saline, DXR or DSF began 3 weeks after injection. Hindlimbs were amputated at 4 weeks. Mice were euthanized with ex vivo lung retrieval at 10 weeks. mRNA transcript analysis was performed on all samples for targets of tumorigenic interest, including Akt serine/threonine kinase (Akt1), Bcl2-associated agonist of cell death (Bad), mechanistic target of Rapamycin (mTOR), and myelocytomatosis viral oncogene homolog (Myc). Indocyanine green (ICG) fluorescence measurements were performed to confirm primary tumor growth as well as presence of lung metastases at the time of study completion.

Results: Of the 60 mice, 32 (53%) developed primary tumors and 30 (54%) demonstrated evidence of pulmonary metastases. Four mice (20%) from the DXR treatment group died before completion of the study. Primary tumors were used for subsequent analysis. DSF-treated mice had significantly reduced rates of metastasis as compared to saline-treated mice (Fig. 1). DSF-treated mice demonstrated significant reductions in mRNA transcripts of pro-tumorigenic targets Akt1, mTOR, and Myc as compared to saline-treated mice. DSF-treated mice demonstrated significant elevation in mRNA transcripts of the anti-tumorigenic target Bad as compared to saline-treated mice (Fig. 2). There was no significant difference between DSF- and DXR-treated mice in their rates of mortality (Fig. 1). Both DSF- and DXR-treated mice had significantly reduced rates of metastasis as compared to saline-treated mice. There was no significant difference between the two treatment groups (Fig. 1). DXR-treated mice had no significant difference from saline-treated mice in expression of any of the four tumorigenic targets Akt1, Bad, mTOR, and Myc. DSF-treated mice had significantly lower expression of Akt1 and significantly higher expression of Bad as compared to DXR-treated mice (Fig. 2).

Conclusion: DSF has potent anti-metastatic properties and may be better tolerated than traditional anthracycline chemotherapy.



Comparison of primary tumor growth, mortality, and metastatic tumor growth among three treatment groups. In the metastatic tumor growth, the black lines signify differences compared to the saline group and the gray line signifies difference between DXR and DSF.



Comparison of mRNA transcript expression among four tumorigenic targets of interest *Akt1*, *Bad*, *mTOR*, and *Myc*. Fold change is normalized to expression levels of saline, subtracted from its geometric mean of three housekeeper genes: *Rps17*, *Rpl30*, and *Nono*.

Poster 100 #2779078

BONE SARCOMA AND TIME TO TREATMENT: AN ANALYSIS OF THE NATIONAL CANCER DATABASE

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Objective: To determine the current national standard in the United States for time to treatment interval (TTI), defined as the period from diagnosis to first definitive treatment, in bone sarcoma, and to identify the characteristics associated with TTI variability.

Methods: A retrospective analysis of the National Cancer Database identified 15,083 patients with primary bone sarcoma diagnosed from 2004-2013. Patient exclusions included pediatric patients <18 years old (not available from this database), patients that did not receive definitive treatment (n = 1,720) in the form of surgery, systemic therapy or radiotherapy, and outliers with a TTI > 365 days (n = 34). Final analysis included 13,329 patients. Kruskall-Wallis tests identified differences within the variables regarding TTI, and a zero-inflated, negative binomial regression model identified the patient, tumor, and treatment variables that were independent risk factors for delayed TTI.

Results: The median TTI was 22 days. Approximately 60% of patients were definitively treated in the same center where the index diagnosis was made. The most common initiating treatment modality was surgery (67%), followed by systemic therapy (26%) and radiotherapy (6%). Longer TTI was correlated with the following patient and tumor factors, by descending influence: having a transition in care (Incidence rate ratio [IRR]=1.89; P<0.001), being uninsured (IRR=1.36; P<0.001), a primary tumor site of the pelvis (IRR=1.26; P<0.001), Medicaid insurer (IRR=1.22; P<0.001), seeking care at an academic center (IRR=1.14; P<0.001), non-white race (IRR=1.12; P=0.002), and Medicare insurer (IRR=1.08; P=0.017). Shorter TTI was correlated with the following tumor and treatment factors, by descending influence: a diagnosis of chondrosarcoma (IRR=0.85; P<0.001), having surgery as the index treatment (IRR=0.88; P<0.001), a primary tumor site of the lower extremity (IRR=0.91; P=0.001), stage II or stage III disease (IRR=0.91; P=0.010), and a primary tumor site of the upper extremity (IRR=0.92; P=0.023).

Conclusion: The national median for TTI of bone sarcoma is 22 days. Delays in TTI in bone sarcoma are associated with socio-economic, healthcare, and tumor characteristics. Transitions in care between institutions are responsible for the greatest delays in bone sarcoma TTI. Physicians need to be aware of the causes for delays in TTI as we work to improve national delays in diagnosis and treatment initiation.

Table 1. Time to Treatment Initiation and Patient Demographics

	Number of Patients (%)	Median TTI, (IQR)	P-Value
Total Number of Patients	13329	22 (4 - 43)	
Age, years			<0.001
Median [Range]	49 [18-90]		
18-30	3220 (24)	19 (8, 35)	
31-50	3882 (29)	22 (0, 44)	
51-70	4248 (32)	23 (1, 47)	
71+	1979 (15)	24 (3, 48)	
Sex			0.002
Male	7439 (56)	22 (6, 43)	
Female	5890 (44)	21 (0, 43)	
Race			<0.001
White	11277 (85)	21 (3, 42)	
Black	1228 (9)	25 (6, 49.75)	
Other/Unknown	824 (6)	21 (3, 45)	
Charlson/Deyo Score			0.509
0	11433 (86)	22 (4, 43)	
1	1493 (11)	21 (1, 45)	
≥ 2	403 (3)	24 (0, 54)	
Histology			<0.001
Osteosarcoma	3979 (30)	24 (10, 42)	
Chondrosarcoma	5608 (42)	19 (0, 43)	
Ewing's Sarcoma	1313 (10)	19 (9, 32)	
Chordoma	1354 (10)	30 (1, 63)	
Other	1075 (8)	25 (7, 49)	
Facility Type			<0.001
Community Cancer Program	303 (2)	22 (0, 43)	
Comprehensive Community Cancer Program	2026 (15)	19 (0, 41)	
Academic Center	5652 (42)	26 (5, 49)	
Integrated Network Cancer Program	544 (4)	20 (0, 44)	
Other/Unknown	4804 (36)	20 (6, 38)	
Insurance			<0.001
Uninsured	674 (5)	24 (5.75, 48)	
Private Insurance	7488 (56)	20 (1, 41)	
Medicaid	1372 (10)	23 (8, 46)	
Medicare	2983 (22)	24 (3, 47)	
Other/Unknown	812 (6)	28 (9, 52)	
Income			0.460
< $38,000	2216 (17)	22 (5, 46)	
$38,000 - $47,999	3130 (24)	22 (4, 44)	
$48,000 - $62,999	3504 (26)	21 (3, 42)	
$63,000+	4236 (32)	22 (2.25, 42)	
Unknown	243 (2)	21 (6, 40)	
Distance from Facility			<0.001
< 21 miles	6238 (47)	21 (1, 42)	

Table 1. Continued			
21-50 miles	2846 (21)	22 (5, 42)	
51-100 miles	1808 (14)	21 (5, 43)	
>100 miles	2212 (17)	25 (6, 48.75)	
Unknown	225 (2)	21 (6, 39.5)	
Transition in Care			<0.001
Yes	5309 (40)	34 (17, 58)	
No	8020 (60)	14 (0, 33)	
Year of Diagnosis			<0.001
2004	1189 (9)	22 (3, 43)	
2005	1339 (10)	20 (0, 42)	
2006	1258 (9)	20 (2, 41)	
2007	1307 (10)	21 (2, 45)	
2008	1290 (10)	21 (3.75, 42)	
2009	1393 (11)	21 (2, 43)	
2010	1370 (10)	22 (5, 46)	
2011	1349 (10)	21 (4, 43)	
2012	1451 (11)	22 (4, 43)	
2013	1383 (10)	26 (7, 48)	
Primary Tumor Site			<0.001
Upper Extremity	1743 (13)	20 (0, 40)	
Lower Extremity	4482 (34)	20 (7, 37)	
Pelvis	2543 (19)	30 (13, 56)	
Other	4561 (34)	20 (0, 46)	
Tumor Size			<0.001
≤ 8.0 cm	6397 (48)	21 (0, 44)	
> 8.0 cm	6932 (52)	22 (7, 43)	
Grade			<0.001
1, Well Differentiated	2488 (19)	11.5 (0, 40)	
2, Moderately Differentiated	2246 (17)	26 (3, 49)	
3, Poorly Differentiated	2491 (19)	23 (9, 41)	
4, Undifferentiated	1809 (14)	23 (12, 41)	
Unknown	4295 (32)	22 (4, 45)	
Clinical Staging			<0.001
Stage I	4419 (33)	24 (0, 49)	
Stage II	2518 (19)	25 (12, 42)	
Stage III	216 (2)	23.5 (10.25, 45)	
Stage IV	1288 (10)	21 (10, 38)	
Unknown	4888 (37)	19 (0, 42)	
First-Line Treatment Modality			<0.001
Surgery	8949 (67)	19 (0, 44)	
Radiation	765 (6)	37 (18, 68.5)	
Systemic	3500 (26)	24 (14, 38)	
Other	24 (0.2)	30.5 (2.5, 68.25)	
Multi-modal	91 (0.7)	23 (6, 49)	

Table 2. Multivariable Model

	Incidence Rate Ratio on TTI (95% CI)	P-Value
Age (>30 years)	1.07 (1.00, 1.14)	0.051
Sex (Female)	0.99 (0.94, 1.04)	0.612
Minority Race	1.12 (1.04, 1.19)	0.002
Charlson/Deyo Score ≥ 1	0.98 (0.92, 1.06)	0.677
Histology		
Osteosarcoma vs all other diagnoses	1.03 (0.97, 1.09)	0.316
Chondrosarcoma vs all other diagnoses	0.85 (0.79, 0.92)	<0.001
Facility Type		
Academic Center vs any other institution	1.14 (1.08, 1.21)	<0.001
Insurance		
Uninsured vs Private Insurance	1.36 (1.21, 1.53)	<0.001
Private Insurance vs all others	0.87 (0.83, 0.92)	<0.001
Medicaid vs Private Insurance	1.22 (1.12, 1.33)	<0.001
Medicare vs Private Insurance	1.08 (1.01, 1.16)	0.017
Distance to facility ≥21 miles	0.98 (0.93, 1.03)	0.520
Transition in Care	1.89 (1.80, 1.99)	<0.001
Primary Tumor Site		
Upper Extremity	0.92 (0.85, 0.99)	0.023
Lower Extremity	0.91 (0.86, 0.96)	0.001
Pelvis	1.26 (1.19, 1.35)	<0.001
Tumor Size		
> 8.0 cm	1.00 (0.95, 1.05)	0.923
Grade		
Overall grade	0.99 (0.97, 1.01)	0.265
Grade 3 or 4	0.95 (0.89, 1.00)	0.059
Clinical Staging		
Stage overall	0.98 (0.98, 0.99)	<0.001
Stage II or III	0.91 (0.85, 0.98)	0.010
First-Line Treatment Modality		
Surgery vs other treatment	0.88 (0.84, 0.94)	<0.001

****Incidence Rate Ratio means for every 1 point increase in the independent variable, the rate of time to treatment initiated (in days) would change by a factor of that value while holding all of the other variables in the model constant.**

Poster 101 #2802255

INHIBITION OF REGULATED INTER-MEMBRANE PROTEOLYSIS ENHANCES CHEMOSENSITIVITY IN 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 only 15-30% and has remained unchanged for over three decades. One of the contributing factors to the lack of improvement in survival is the development of chemoresistance. Hence elucidating the mechanisms that contribute to chemoresistance and implementing strategies to overcome it will likely be pivotal to improving survival for these patients. ER stress response has been shown to promote chemoresistance in several cancer cells by enhancing prosurvival and suppressing pro-apoptotic pathways. Our objective here is to examine how ER stress promotes chemoresistance in patients with OS.

Methods: We used immunohistochemistry, Western blotting, qPCR, siRNA immunofluorescence and bioinformatic tools and techniques to examine the effects of UPR in OS tumors and cell lines (U2OS, 143b).

Results: In silico analysis of gene expression datasets of primary tumors from OS patients showed that ER protein processing and stress machinery were enriched in OS tumors. We confirmed the activation of ER stress pathways IRE-1, PERK and ATF6α (activating transcription factor 6α) in human OS cell lines and found that only ATF6α activation had a functional role in the chemoresistance of OS cells to cisplatin and irinotecan. This was mediated by ATF6α regulation of folding of NOTCH protein and not its mRNA levels. Additionally, we found that the sensitivity of OS cells to a combinatorial treatment of γ-secretase inhibitor and cisplatin was significantly enhanced in the absence of ATF6α. In agreement with our in vitro findings, retrospective analysis of primary tumors from OS patients showed that high nuclear (active) ATF6α served as an independent prognostic indicator irrespective of the metastatic status and tumor site. As ATF6α is activated by site-1 and site-2 proteases (S1P and S2P) via RIP (Regulated intermembrane proteolysis), we found that both genetic (siRNA) and pharmacologic (Nelfinavir) inhibition of RIP, significantly enhanced chemosensitivity in OS cells. In agreement with the role of RIP in chemoresistance we found that downregulation of RIP activated, osteoblast specific transcription factor OASIS, also contributed to the chemoresistance in OS cells.

Conclusion: Our findings highlight a novel mechanism of chemoresistance in OS. Hence combinatorial treat-

ment with drugs that inhibit RIP holds promise as an innovative and effective treatment strategy for OS.

Poster 102 #2804794

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

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Objective: Osteosarcoma is the most frequent primary bone tumor in pediatric and young adults. Understanding the genomic alterations (GA) that define the disease might assist in stratification of molecularly guided clinical trial design and inform new treatment opportunities. We analyzed the GAs and used the results to sub-classify the disease and uncover potential new routes to precision therapy for patients suffering from advanced and refractory disease.

Methods: Tissue from 348 osteosarcoma patients was assayed by hybrid-capture based comprehensive genomic profiling (CGP) in the course of clinical care to evaluate GAs, including base substitutions, indels, amplifications, copy number alterations, fusions/rearrangements) and targeted therapy opportunities. Tumor mutational burden (TMB) was calculated from a minimum of 1.11 Mb sequenced DNA and reported as mutations/Mb. Microsatellite instability status (MSI) was determined by a novel algorithm from the sequencing data.

Results: CGP identified several genomically defined subgroups. Chromosome 4q12 amplicon GA's, primarily amplification in PDGFRA, KIT, and KDR, were seen in 10% of the cohort. Chromosome 8 altered FGFR1 patients (5%) were predominantly male (75%) and frequently co-occurred with MYST3 (44%) and MYC (38%; males only). An FGFR1 altered cohort, a MCL1 defined subgroup (6%) and an MDM2 subgroup (7%)were mutually exclusive, with 1 exception. The majority of ATRX GA's were associated with CDKN2A/B GA's. TP53 and RB1 GAs were identified in 55% of patients. The majority of GAs seen in patients were copy number changes; older patients had more base substitutions than young patients (82% vs. 68%, respectively, p value 0.02). Other notable targetable alterations identified included NTRK2 (5% - fusions, copy number, and single base alterations) BRAF, and BRCA1/2 (1%). Profiling also identified different patterns in GAs between younger and older patients, including but not limited to C17orf39 (29% vs. 2.7%,), MYC (23% vs. 7%), and AURKB (8% vs. 0%), respectively. TMB High (H, ≥20 mut/Mb) was seen in only 1% of patients, while TMB Intermediate (I, ≥6 and <20 mut/Mb) was seen in 12% of patients, more frequently in older patients.

Conclusion: Genomic profiles of tumors from patients with osteosarcoma reveal genomicallly distinct subgroups, which would likely inform clinical trials and different treatment options. Taking into account the heterogeneity and defined subgroups, when targeted therapies are studied in osteosarcoma, it will be important to take the patients' molecular profiles into consideration (for example, reanalysis of anti-PDGFRA and pan-TKIs inhibiting FGFR in the context of a patient's genomics, to further delineate response or lack thereof.) These findings may contribute to a better understanding of different pathways of oncogenesis of osteosarcoma and may ultimately define novel systemic treatment options through informed clinical trial development.

Poster 103 #2796479

TARGETING THE F-BOX PROTEIN SKP2: IMPLICATIONS IN HUMAN OSTEOSARCOMA

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Objective: Osteosarcoma (OS) is the most common primary bone cancer with a high propensity for local invasion and distant metastasis. The F-box protein S-phase kinase-associated protein 2 (Skp2) has been shown to regulate cellular proliferation through its E3 ligase activity and cancer metastasis via RhoA transcription. Currently, the involvement of Skp2 in OS pathobiology is not known. We intend to investigate the role of Skp2 in OS and the use of flavokawain A (FKA), a novel chalcone from kava extract with low toxicity, as a potential Skp2 targeting agent for OS treatment.

Methods: The expression of Skp2 in standard OS cell lines, patient-derived OS cell lines, and OS patient tumor samples were assessed by qRT-PCR and Western blotting. Kaplan-Meier analysis and log-rank test were used to correlate the expression of Skp2 with the prognosis of OS patients. Raw Skp2 expression data were retrieved from GEO dataset and correlated with survival data obtained from R2 platform for survival analysis. The expression of Skp2 was knocked down by shRNA and by treatment with FKA; Suppression of Skp2 was validated by qRT-PCR and Western blot. OS cell lines were treated with increasing dosages of FKA and tested for cell motility, proliferation, and invasion by wound healing, MTT, and Matrigel invasion assays. Cell cycle analysis was performed using flow cytometry. Cell cycle analysis was performed and Skp2-induced RhoA expression was examined after FKA treatment. The effects of Skp2 depletion by shRNA and by treatment with FKA on lung metastasis were evaluated after injection of OS cells into SCID mice. Confirmation of Skp2 knockdown in lung tissue was done by immunohistochemistry.

Results: Skp2 is overexpressed in 13 tested OS cell lines, including 5 standard and 8 patient-derived OS cell lines compared to normal human osteoblasts. Survival analysis using R2 platform showed that patients whose tumors expressed high levels of Skp2 had a significantly poorer metastasis-free survival (p=0.0095) and overall survival (p=0.0013). Skp2 knockdown by shRNA significantly reduced in vitro cell motility (p=0.035), invasion (p=0.018), RhoA expression, and in vivo lung metastasis, suggesting an important role for Skp2 in OS progression. Treatment of several OS cell lines with FKA suppressed Skp2 in a dose-dependent manner, suggesting that Skp2 is an important target of FKA. Concurrently, RhoA expression is inhibited by FKA, confirming that FKA exerts the same effects on RhoA as Skp2 knockdown. Similar to Skp2 knockdown, FKA also inhibits the growth, motility, and invasion of multiple OS cell lines. Flow cytometry confirms that FKA induces cellular apoptosis and cell cycle arrest at the G2/M phase. Finally, oral treatment with FKA markedly reduced the formation of lung nodules in an orthotopic model of OS.

Conclusion: Taken together, these findings suggest that the F-box protein Skp2 is commonly overexpressed in OS and targeting Skp2 is a novel and important therapeutic strategy for OS. Our studies also identify the kava chalcone FKA as an effective Skp2 targeting agent for OS with potential broad implications for other cancers that overexpress Skp2. Studies are ongoing to elucidate the mechanisms by which FKA influences the levels of Skp2.

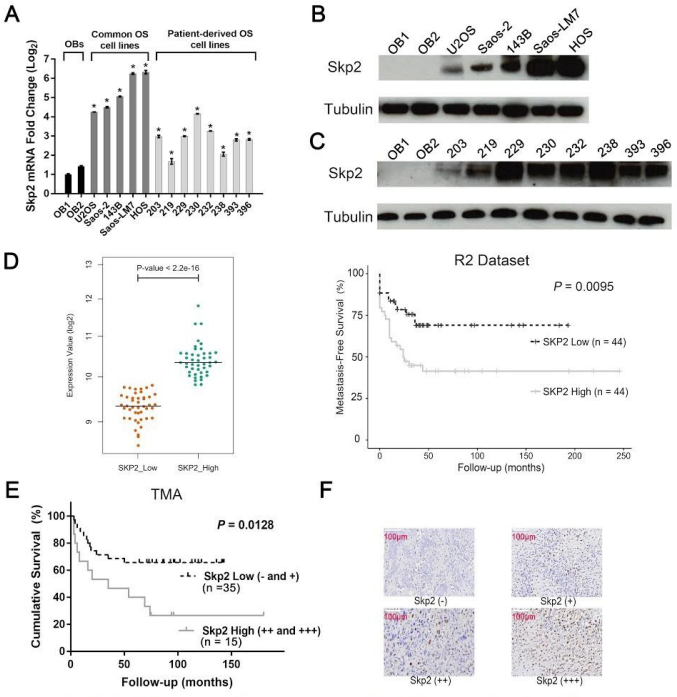

Fig. 1 Skp2 is commonly overexpressed in OS tumor cells at mRNA level (a) and protein level (b,c) and associated with poor survival of the patient (d,e). IHC staining of Skp2 in an OS tissue microarray (f).

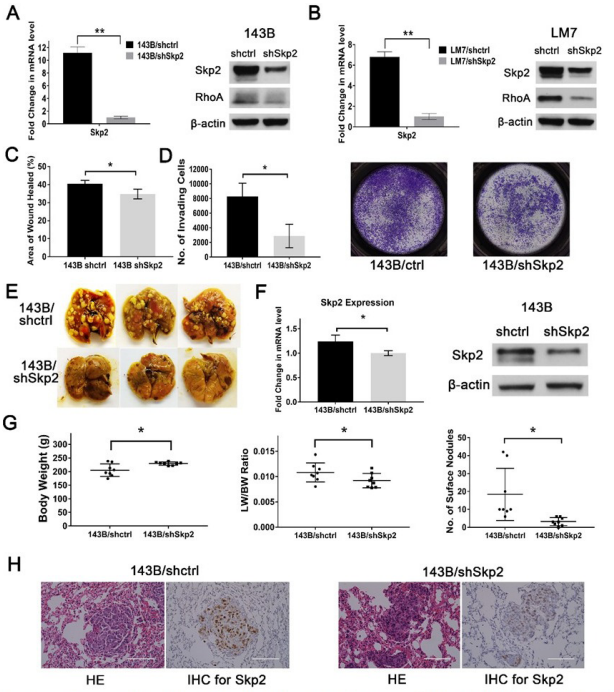

Fig. 2 Knockdown of Skp2 in 143b cells (a) and SaOS-LM7 cells (b). Inhibition of 143b cell motility (c) and inhibition of *in vitro* 143b cell invasion (d) after Skp2 knockdown. Metastatic nodules on the surface of gross mouse lung specimens represented (e) and Skp2 expression in respective lung tissues (f). Skp2 knockdown significantly reduced the normalized lung weight and number of metastatic lung nodules (g), IHC staining confirmed Skp2 knockdown (h).

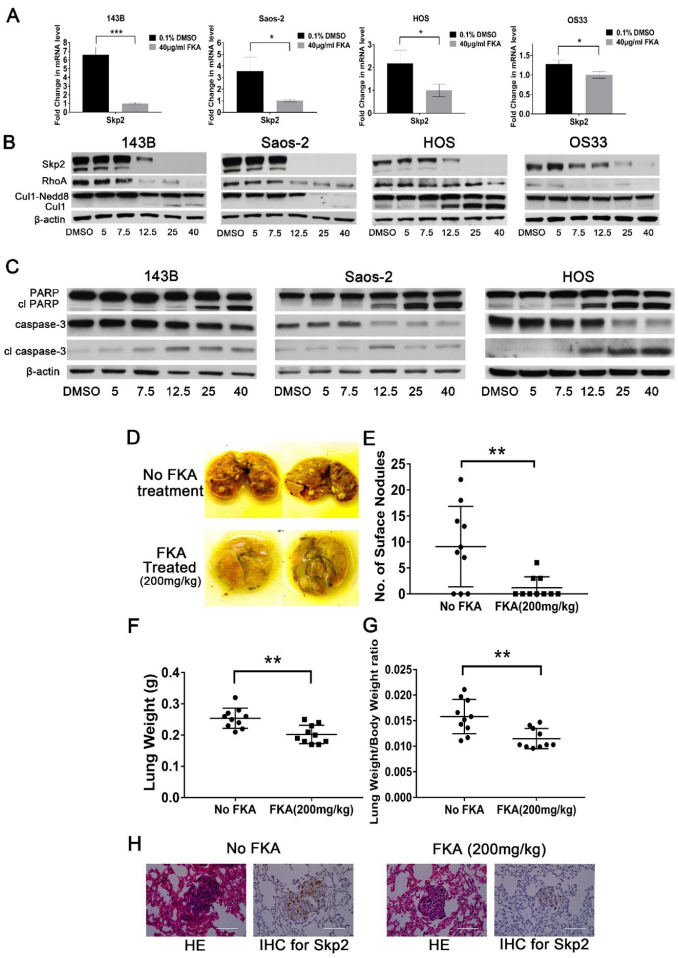

Fig. 3 FKA suppressed Skp2 expression in OS cell lines 143b, SaOS-2, HOS and OS33 at mRNA level (a) and protein level (b) in a dose-dependent manner. The expression of Cul1-Nedd8, which inhibits the degradation of Skp2, was also decreased by FKA in a dose-dependent manner (c).Dietary feeding of FKA inhibits tumor metastasis *in vivo* depicted by gross mouse lung specimen (d), significantly less surface nodules (e), lung weights (f) and normalized lung weights (g). HE and IHC staining for Skp2 of lung tissues in mice treated with FKA and 0.1% DMSO (h).

Poster 104 #2777637

DEEP LEARNING NEURAL NETWORK TO INTERPRET TUMOR NECROSIS IN HIGH-GRADE OSTEOSARCOMA

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Objective: The EURAMOS international study that randomized treatment by tumor necrosis, was unsuccessful in improving the outcome for patients with high-grade osteosarcoma. The development of new drugs, critically needed for patients, will be dependent on an effective biomarker. We propose to develop such a biomarker utilizing advances in digital imaging and machine learning.

Methods: Fifty patients diagnosed with high-grade osteosarcoma at Children's Medical Center Dallas between 1995-2015 were identified. At the time of definitive surgery and using standard procedures, resected specimens were processed to provide the largest surface area for histology evaluation of tumor response. Using a pre-determined grid, each area within the grid was harvested to produce a single histology slide, which was then digitized at up to 40X magnification as whole slide image (WSI) for further analysis. A random set of 1024x1024 pixel tiles were selected from multiple patients WSIs and algorithms based on color threshold and shape features were used for a preliminary segmentation based on which a deep learning algorithm to separate tumor classes (viable tumor, non-viable tumor and non-tumor) using convolutional neural networks (CNN) was developed.

Results: Nine-hundred and forty-two histology slides, representing 50 patient tumors (mean 19 slides/patient; 4-51) were digitized, representing approximately 3.8x106 tiles at 20x magnification. We identified 2,500 tiles, based on stratified random sampling and annotated by 2 pathologists, to train and validate a deep learning CNN algorithm. As an initial validation, the neural network was trained with 900 tiles. The neural network model was able to identify viable tumor regions with 84% accuracy, non-viable tumor (necrotic regions) with 81% accuracy and non-tumor with an accuracy of 93%.

Initial validation of CNN

	Number of Annotated Tiles(size 128*128)	Number of Training Tiles (size 128*128)	Number of Test Tiles (size 128*128)	Accuracy %
Viable Tumor	17513	13722	3791	83.61
Non-Viable Tumor	16691	13353	3338	81.22
Non-Tumor	22725	18180	4545	93.43

Conclusion: We have completed the 1st step in validating the implementation of a CNN deep learning tool to interpret tumor necrosis in osteosarcoma. Next steps for this phase of biomarker development include optimization and validation with all 2,500 tiles and performing the algorithm on all 942 WSI. We will compare the CNN output to the conventional tumor necrosis estimate by two pathologists blinded to each other's estimation of necrosis and to the clinical value generated at the time of surgery. Future steps will include development of a CNN algorithm to examine MRI features and then compare outputs from MRI and histology data.

Poster 105 #2782492

COMBINATION THERAPY FOR OSTEOSARCOMA BONE FORMING METASTASES: 223-RADIUM WITH DENOSUMAB + SBRT AND PAZOPANIB, ORAL CYCLOPHOSPHAMIDE OR IFOSFAMIDE

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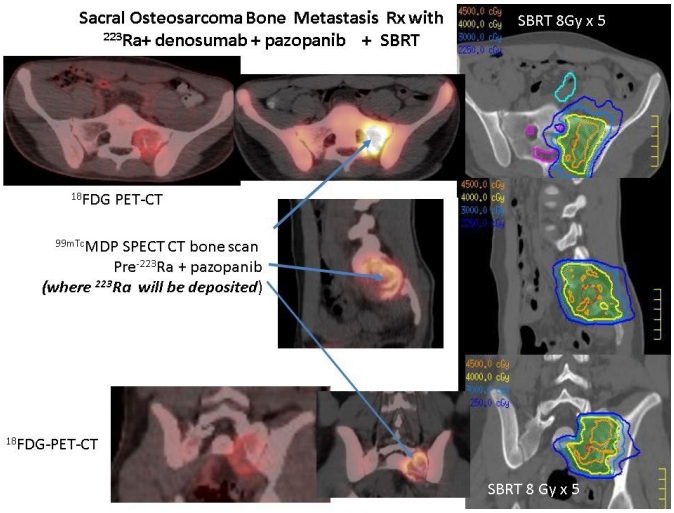
Objective: 223RaCl2 is an alpha emitting bone -seeking radiopharmaceutical. Our previous experience in relapsed osteosarcoma with 223-Ra as a single agent showed safety when given at 3 microCi/kg, 2x the standard dose. Current NCCN osteosarcoma guidelines for 2nd relapse recommend 223-Ra as an option; we report other treatments including denosumab + SBRT, and chemotherapy in combination with 223-Ra

Methods: Patients with unresectable metastatic osteosarcoma and avid uptake on 99mTc-MDP bone scan were treated with 1.5 microCi/kg 223-Ra monthly for up to 6 doses with denosumab, SBRT, and chemotherapy.

Results: As of June 2017 13 patients received 223-Ra and additional therapy. Time from request for prior authorization until insurance approval of 223-Ra ranged from 2 days to 2 months. Patient characteristics and other treatments are summarized in table 1. Two patients had disease in sacrum only- both had SBRT and were able to get 6/6 223-Ra infusions. One patient had denosumab stopped because of hypocalcemia that could not be controlled with oral calcium supplementation. Another discontinued denosumab because it was previously ineffective as a single agent but already had markedly increased ^{99m}Tc-MDP uptake in pulmonary metastases associated with denosumab. The patient with highest metastatic burden (>100 bone metastases) had significant reduction in pain that corresponded to alkaline phosphatase decrease

from 6447 to 147 and improved Na18F-PET. She also regained ability to walk on 223-Ra with pazopanib, radiotherapy, and oral cyclophosphamide without significant hematologic toxicity before progression in non-osseous sites. One patient with prior cranial-spinal radiation had persistent thrombocytopenia and was the only patient that needed transfusions. All others had platelets >40K at all times. Hematologic toxicity was modest; 0/4 on denosumab +pazopanib needed granulocyte growth factor. In contrast 2/2 patients with oral cyclophosphamide required dose adjustment and 2/2 patients treated with CI ifosfamide +mesna (1 gm/m2/d x 14 days) received Neulasta. The most common reason to receive <6 planned doses of 223-Ra was relapse.



Imaging of osteosarcoma bone metastsis in the left sacrum showed avid 18FDG uptake, but even more AVID bone formation using ^{99m}Tc-MDP bone scan SPECT CT imaging after treatment with denosumab+ pazopanib. The high amount of new bone formation showed that this patient was an excellent candidate for ^{223}Ra uptake into the metastasis. After 3 monthly doses of ^{223}Ra, SBRT (8Gy x 5) was done. A total of 6 doses of ^{223}Ra - with monthly denosumab and daily pazopanib were given entrely outpateint with an excellent QOL.

223-Radium + SBRT and Chemotherapy in Metastatic Osteosarcoma: Patient Characteristics and Treatments

Patient Characteristic (N=13)			
Age (median, range)	19	10-34	
223-Ra Doses (median, range)	3	1-6	
Persistent metastatic disease vs new metastases	4	9	
Number of metastases (1, 2-9, >10)	2	5	6
SBRT sites (extremity vs axial)	4	9	
Denosumab (1 dose vs monthly)*	2	11	
Sorafenib	1		
Pazopanib**	8		
Oral cyclophosphamide	2		
Ifosfamide/mesna***	2		
methotrexate	2		

*120 mg sc monthly+ calcium and vitamin D BID;
600-800 mg po daily;* 1gm/m2/day via continuous infusion

Conclusion: Denosumab can possibly increase 223-Ra bone-seeking radiopharmaceutical uptake and is a safe and tolerable adjunct. Additional palliation of osteosarcoma metastases with SBRT, pazopanib, oral cyclophosphamide, and even ifosfamide (via slow continuous infusion) can be safely done concurrently.

Poster 106 #2784812

PRECISION MEDICINE FOR THE TREATMENT OF OSTEOSARCOMA: ATRX DEFICIENCY PREDICTS ENHANCED SENSITIVITY TO HUMAN RECOMBINANT TRAIL

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Objective: Recent comparative oncology research has identified ATRX (α thalassemia /mental retardation X-linked) as one of a few genes commonly mutated in osteosarcoma of dogs and humans. Genome sequencing has demonstrated mutations of ATRX in up to 30% of human osteosarcoma. Given the association of ATRX mutations in osteosarcoma across species, we believe it plays an important role in the pathogenesis of disease, and can be leveraged to identify new, targeted therapies. We screened and validated candidate drugs to which loss of ATRX may confer sensitivity.

Methods: Using the database “Genomics of Drug Sensitivity in Cancer,” we analyzed the effects of various drugs stratified by ATRX mutation status. We validated individual drugs using human osteosarcoma cell lines expressing ATRX (143B and MG-63), and created two different ATRX knockdown conditions (using two independent siRNAs), to compare to a non-silencing siRNA control. Knockdown (KD) conditions were confirmed with western blot. Cell conditions were incubated with candidate drugs for 48h, and viability was assessed in comparison to vehicle control using CellTiter-Glo assay.

Results: The bio-informatics screen identified four drugs with apparent increased effectiveness in ATRX deficient cell populations: ZM-447439 (Aurora kinase B inhibitor), Avagacestat (γ-secretase inhibitor), human recombinant TRAIL (rTRAIL; Death Receptor 4/5 agonist), and Linifanib (VEGF/PDGF antagonist). For individual validation, ATRX KD was considered sensitizing if a statistically significant difference in cell viability, also reported as % inhibition, was observed between the non-silencing and both ATRX siRNA KD conditions. rTRAIL showed a consistently significant decrease in cell viability in the ATRX KD conditions as compared to the non-silencing controls of both the 143B ($p<0.01$) and MG-63 ($p<0.001$) osteosarcoma cell lines (Figures 1 and 2).

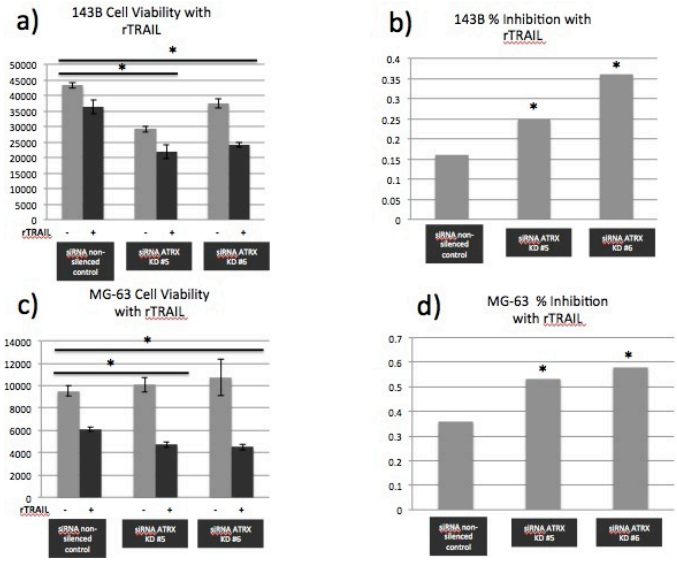

Figure 1: Cell viability of human osteosarcoma cell lines after treatment with human recombinant TRAIL (rTRAIL) in two independent ATRX knockdown conditions (right two columns) compared to non-silencing control (left). rTRAIL was added and compared to each cell condition against PBS control. Cell viability (a,c), also expressed as % inhibition (b,d), was assessed using the CellTiter-Glo assay. Significantly greater cell inhibition (noted by asterisk) is seen with treatment in the ATRX deficient cell populations compared to the non-silencing control.

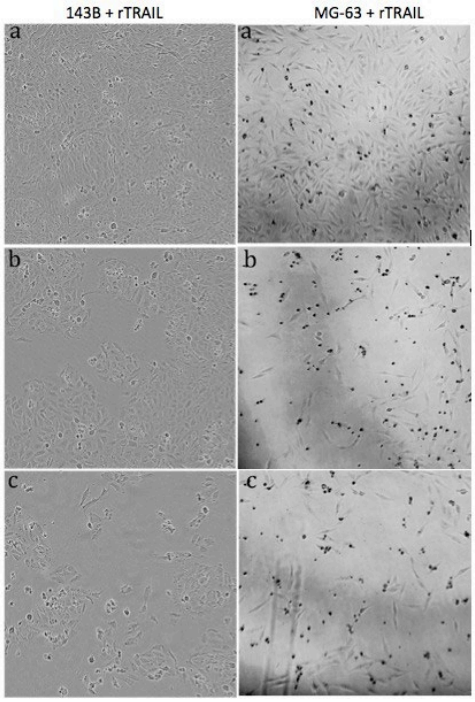

Figure 2: Microscopic images of osteosarcoma cells treated with rTRAIL after 48hrs. (a) siRNA non-silencing control, (b) siRNA ATRX #5 knockdown, (c) siRNA ATRX #6 knockdown

Conclusion: Our cross-species platform for drug discovery identified ATRX as a targetable genetic mutation, important in the pathophysiology of osteosarcoma. ATRX deficiency was shown to confer increased sensitivity to the pro-apoptotic drug rTRAIL. Unlike many existing chemotherapeutic agents, the high specificity and minimal systemic toxicity of rTRAIL are highly coveted properties of a potential anti-cancer drug. These findings provide a framework for clinical development of rTRAIL in a patient subset for which ATRX is lost, and support further efforts for a precision approach to the treatment of osteosarcoma.

Poster 107 #2785232

D-3-PHOSPHOGLYCERATE DEHYDROGENASE (PHGDH) EXPRESSION NEGATIVELY CORRELATES WITH OVERALL SURVIVAL IN OSTEOSARCOMA

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Objective: Osteosarcoma is the most common type of primary malignant bone tumor found in both children and adults. Currently, curative regimens involve the use of high-dose methotrexate (HD-MTX). MTX targets the folate pathway in osteosarcoma by inhibiting dihydrofolate reductase, as part of a pathway that converts serine to purines and thymidylate. Previously, we have demonstrated that osteosarcoma cell lines have an upregulated serine biosynthesis pathway when compared to breast cancer and osteoblast precursors. We hypothesized that inhibition of PHGDH, the first and rate-limiting step in this pathway, with the small molecule inhibitor NCT-503, would be active for the treatment of osteosarcoma.

Methods: Immunohistochemistry analysis of an osteosarcoma TMA was performed in a blinded fashion on 392 clinically annotated samples from 260 patients. Scoring of the TMA was correlated to patient outcomes data. MNNG and NOS1 (osteosarcoma), as well as MDA-MB-231 and MDA-MB-468 (breast cancer) and hMSC (human mesenchymal stem cell) cell lines were treated with NCT-503, a small molecule PHGDH inhibitor. Cell death was measured using propidium iodide (PI) Fluorescence-Activated Cell Sorting (FACS), and cell growth and viability assays were conducted using YOYO-1 fluorescent probes. Glucose, serine, glycine, and glutathione were supplemented into experimental medium to test the effect of metabolite ratios on inhibitor activity. Cells were also cultured with biological concentrations of glucose or higher concentrations of glucose, treated with NCT-503, and metabolite levels were quantified by capillary electrophoresis mass spectrometry (CE-MS).

Results: We found that over 50 % of clinically annotated samples are high expressers of PHGDH (moderate to strong intensity), and have identified an inverse correlation between expression of PHGDH and relapse-free survival ($p < 0.006$), as well as overall survival ($p < 0.016$). We demonstrated that PHGDH-high osteosarcoma cell lines

were highly susceptible to high-dose treatment with single agent NCT-503. Furthermore, we found that low-dose treatment with NCT-503 caused stasis of tumor growth. In the presence of serine and glycine, the effect of NCT-503 was increased as compared to medium containing serine alone. As expected, we found that higher amounts of glucose in experimental medium caused greater flux through glycolysis, as well as increased production of lactate. This was corroborated by CE-MS analysis of metabolite levels.

Conclusion: We have identified PHGDH as a poor prognostic marker in patients with osteosarcoma. High expression of PHGDH is associated with significantly worse relapse-free and overall survival. We have also found that osteosarcoma cell lines have up regulated serine biosynthesis pathways are more susceptible to treatment with HD-MTX. PHGDH thus serves as an attractive target for the future development of treatments in osteosarcoma, in the hopes that we can replace HD-MTX with PHGDH inhibition.

Poster 108 #2785656

INTERIM- AND POSTTREATMENT RESPONSE TO NEOADJUVANT CHEMOTHERAPY ASSESSED BY ^{18}F-FDG PET/CT FOR THE PREDICTION OF OUTCOME IN OSTEOSARCOMA OF THE EXTREMITIES

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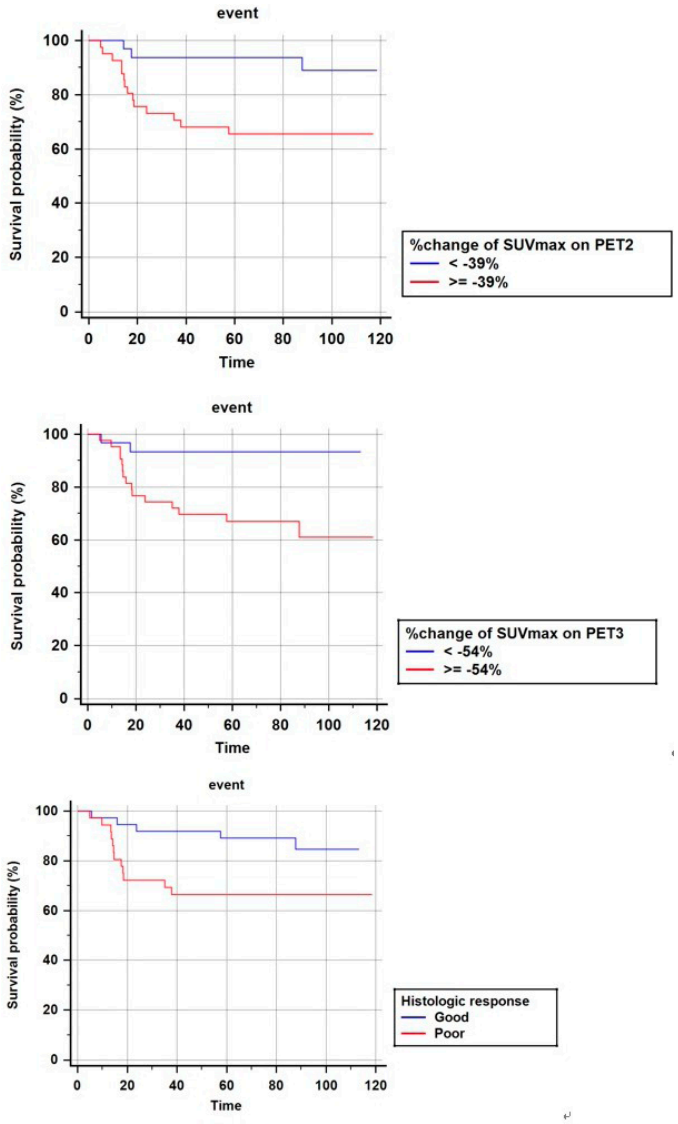
Objective: We assessed whether sequential ^{18}F-FDG PET/CT (PET/CT) could predict the outcome of patients with osteosarcoma of the extremities after one cycle and two cycles of neoadjuvant chemotherapy.

Methods: A total of 73 patients with American Joint Committee on Cancer (AJCC) stage II extremity osteosarcoma treated with two cycles of neoadjuvant chemotherapy, surgery and adjuvant chemotherapy were prospectively enrolled in this study. All patients underwent PET/CT before (PET1), after one cycle (PET2), and after the completion of neoadjuvant chemotherapy (PET3), respectively. PET parameters [maximum standardized uptake value (SUVmax), metabolic tumor volume (MTV), and total lesion glycolysis (TLG)] and their % changes were calculated, and histological responses were evaluated after surgery. ROC curve analyses and the Cox proportional hazards model were used to analyze whether imaging and clinicopathologic parameters could predict event (metastasis or local recurrence)-free survival.

Results: A total of 36 patients (49%) exhibited a poor histologic response and 17 patients (23%) had experienced events (metastasis in 16 and local recurrence in 1). Both on PET2 and PET3, the % change of SUVmax most accurately predicted events by ROC curve analysis (area under the curve = 0.667 for PET1 and 0.685 for PET2, respectively). By multivariate analysis including the % changes of SUVmax on PET2, PET2, histologic response, age, sex and AJCC stage (A or B), only the % change of SUVmax on PET3 > -54% independently shortened event-free survival (relative risk, 6.39; 95% confidence interval, 1.45-28.10). Patients with the % change of SUVmax on PET3 > -54% had worse 3-y (72% vs. 93%) and 5-y (67% vs. 93%) metastasis-free survival rates than the others (P = 0.005).



Conclusion: The %changes of SUVmax both on PET2 and PET3 could predict the outcome of patients with osteosarcoma of the extremities. The %changes of SUVmax on PET3 better predicted the outcome than histologic response.

Poster 109 #2796802

THE MOST CITED ARTICLES IN ORTHOPAEDIC ONCOLOGY

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Objective: Rank lists of the most cited articles serve to identify important studies that have influenced practice, generated discussion, and advanced the sciences of their respective fields. The purpose of this study was to analyze the characteristics of the 50 most cited articles overall and by decade in orthopaedic oncology.

Methods: We searched the Science Citation Index Expanded database from 1965-2016 and analyzed each article for the following characteristics: topic, type of article (basic science vs. clinical research), authorship, institution and country of first author, journal and year of publication, and level of evidence per *Clinical Orthopaedics and Related Research (CORR)* guidelines.

Results: The overall top 50 articles were published between 1966-2016, cited an average of 282 times, and 29 (58%) were level IV evidence. Compared over time, level of evidence of the more cited papers improved from 0% level II and 82% level IV from 1966-1979, to 6% level II and 38% level IV from 2010-2016. In addition, the number of articles and average level of evidence contributed by decade to the overall top 50 list improved, 8 (3.875) between 1966-1979, 15 (3.67) between 1981-1989, 18 (3.69) between 1990-1999, and 9 (3.14) between 2000-2009. There was only 1 level I study included in the top 50 list from any decade.

Table 2. Levels of Evidence of the Top 50 Most Cited Articles in Orthopaedic Oncology by Decade

Level of Evidence	Time Period	1	2	3	4	5	Review Article	Basic Science
	1966-1979							
Number of Publications		0	0	2	41	4	2	1
Percentage (%)		0	0	4	82	8	4	2
	1980-1989							
		0	0	7	34	1	8	0
		0	0	14	68	2	16	0
	1990-1999							
		1	2	10	33	0	3	1
		2	4	20	66	0	6	2
	2000-2009							
		0	5	12	21	0	8	4
		0	10	24	42	0	16	8
	2010-2016							
		0	3	16	19	0	4	8
		0	6	32	38	0	8	16

Conclusion: This list of the most cited articles in orthopaedic oncology demonstrate an increase in high quality studies published and cited between 1966-2016. Nevertheless, there still is a significant lack of higher level of evidence research (Level I and II) in the area of musculoskeletal oncology.

Collaborative studies, a national MSTS registry, international registries, and prospective studies are necessary to improve the quality of published literature in orthopedic oncology.

Top 1-25 Most Cited Articles

Rank	Article	Number of Citations
1	Enneking WF, Dunham W, Gebhardt MC, Malawar M, Pritchard DJ. A system for the functional evaluation of reconstructive procedures after surgical treatment of tumors of the musculoskeletal system. Clin. Orthop. 1993:241–246.	1114
2	Enneking WF, Spanier SS, Goodman MA. A system for the surgical staging of musculoskeletal sarcoma. Clin. Orthop. 1980:106–120.	882
3	Goldenberg RR, Campbell CJ, Bonfiglio M. Giant-cell tumor of bone. An analysis of two hundred and eighteen cases. J. Bone Joint Surg. Am. 1970;52:619–664.	565
4	Dahlin DC, Coventry MB. Osteogenic sarcoma. A study of six hundred cases. J. Bone Joint Surg. Am. 1967;49:101–110.	516
5	Campanacci M, Baldini N, Boriani S, Sudanese A. Giant-cell tumor of bone. J. Bone Joint Surg. Am. 1987;69:106–114.	501
6	Barr JD, Barr MS, Lemley TJ, McCann RM. Percutaneous vertebroplasty for pain relief and spinal stabilization. Spine. 2000;25:923–928.	455
7	Tomita K, Kawahara N, Kobayashi T, Yoshida A, Murakami H, Akamaru T. Surgical strategy for spinal metastases. Spine. 2001;26:298–306.	414
8	Mankin HJ, Lange TA, Spanier SS. The hazards of biopsy in patients with malignant primary bone and soft-tissue tumors. J. Bone Joint Surg. Am. 1982;64:1121–1127.	361
9	McKenna RJ, Schwinn CP, Soong KY, Higinbotham NL. Sarcomata of the Osteogenic Series (Osteosarcoma, Fibrosarcoma, Chondrosarcoma, Parosteal Osteogenic Sarcoma, and Sarcomata Arising in Abnormal Bone) AN ANALYSIS OF 552 CASES. J. Bone Joint Surg. Am. 1966;48:1–26.	344
10	Mankin HJ, Gebhardt MC, Jennings LC, Springfield DS, Tomford WW. Long-term results of allograft replacement in the management of bone tumors. Clin. Orthop. 1996:86–97.	337

11	Enneking WF, Mindell ER. Observations on massive retrieved human allografts. J. Bone Joint Surg. Am. 1991;73:1123–1142.	331
12	Marcove RC, Miké V, Hajek JV, Levin AG, Hutter RV. Osteogenic sarcoma under the age of twenty-one. A review of one hundred and forty-five operative cases. J. Bone Joint Surg. Am. 1970;52:411–423.	323
13	Mankin HJ, Mankin CJ, Simon MA. The hazards of the biopsy, revisited. Members of the Musculoskeletal Tumor Society. J. Bone Joint Surg. Am. 1996;78:656–663.	311
14	Gerszten PC, Burton SA, Ozhasoglu C, Welch WC. Radiosurgery for spinal metastases: clinical experience in 500 cases from a single institution. Spine. 2007;32:193–199.	303
15	Rosenthal DI, Hornicek FJ, Wolfe MW, Jennings LC, Gebhardt MC, Mankin HJ. Percutaneous radiofrequency coagulation of osteoid osteoma compared with operative treatment. J. Bone Joint Surg. Am. 1998;80:815–821.	297
16	Tokuhashi Y, Matsuzaki H, Oda H, Oshima M, Ryu J. A revised scoring system for preoperative evaluation of metastatic spine tumor prognosis. Spine. 2005;30:2186–2191.	296
17	Simon MA, Enneking WF. The management of soft-tissue sarcomas of the extremities. J. Bone Joint Surg. Am. 1976;58:317–327.	271
18	Tokuhashi Y, Matsuzaki H, Toriyama S, Kawano H, Ohsaka S. Scoring system for the preoperative evaluation of metastatic spine tumor prognosis. Spine. 1990;15:1110–1113.	266
19	Schmale GA, Conrad EU 3rd, Raskind WH. The natural history of hereditary multiple exostoses. J. Bone Joint Surg. Am. 1994;76:986–992.	263
20	Enneking WF, Spanier SS, Goodman MA. Current concepts review. The surgical staging of musculoskeletal sarcoma. J. Bone Joint Surg. Am. 1980;62:1027–1030.	262
21	Tomita K, Kawahara N, Baba H, Tsuchiya H, Fujita T, Toribatake Y. Total en bloc spondylectomy. A new surgical technique for primary malignant vertebral tumors. Spine. 1997;22:324–333.	259
22	Rougraff BT, Simon MA, Kneisl JS, Greenberg DB, Mankin HJ. Limb salvage compared with amputation for osteosarcoma of the distal end of the femur. A long-term oncological, functional, and quality-of-life study. J. Bone Joint Surg. Am. 1994;76:649–656.	258
23	Rao AS, Vigorita VJ. Pigmented villonodular synovitis (giant-cell tumor of the tendon sheath and synovial membrane). A review of eighty-one cases. J. Bone Joint Surg. Am. 1984;66:76–94.	258
24	Mirels H. Metastatic disease in long bones. A proposed scoring system for diagnosing impending pathologic fractures. Clin. Orthop. 1989:256–264.	257
25	Enneking WF, Campanacci DA. Retrieved human allografts. A clinicopathological study. J. Bone Joint Surg. Am. 2001;83-A:971–986.	231

Top 26-50 Most Cited Articles

26	McDonald DJ, Sim FH, McLeod RA, Dahlin DC. Giant-cell tumor of bone. J. Bone Joint Surg. Am. 1986;68:235–242.	231
27	Boriani S, Weinstein JN, Biagini R. Primary bone tumors of the spine. Terminology and surgical staging. Spine. 1997;22:1036–1044.	223
28	Parrish FF. Allograft replacement of all or part of the end of a long bone following excision of a tumor. J. Bone Joint Surg. Am. 1973;55:1–22.	221
29	Sung HW, Kuo DP, Shu WP, Chai YB, Liu CC, Li SM. Giant-cell tumor of bone: analysis of two hundred and eight cases in Chinese patients. J. Bone Joint Surg. Am. 1982;64:755–761.	214
30	Rock MG, Pritchard DJ, Reiman HM, Soule EH, Brewster RC. Extra-abdominal desmoid tumors. J. Bone Joint Surg. Am. 1984;66:1369–1374	207
31	Malawer MM, Chou LB. Prosthetic survival and clinical results with use of large-segment replacements in the treatment of high-grade bone sarcomas. J. Bone Joint Surg. Am. 1995;77:1154–1165.	193
32	Lee FY, Mankin HJ, Fondren G, Gebhardt MC, Springfield DS, Rosenberg AE, Jennings LC. Chondrosarcoma of bone: an assessment of outcome. J. Bone Joint Surg. Am. 1999;81:326–338.	187
33	O'Donnell RJ, Springfield DS, Motwani HK, Ready JE, Gebhardt MC, Mankin HJ. Recurrence of giant-cell tumors of the long bones after curettage and packing with cement. J. Bone Joint Surg. Am. 1994;76:1827–1833.	184
34	Harrington KD. The use of methylmethacrylate for vertebral-body replacement and anterior stabilization of pathological fracture-dislocations of the spine due to metastatic malignant disease. J. Bone	180
35	Campanacci M, Capanna R, Picci P. Unicameral and aneurysmal bone cysts. Clin. Orthop. 1986:25–36.	178
36	Larsson SE, Lorentzon R, Boquist L. Giant-cell tumor of bone. A demographic, clinical, and histopathological study of all cases recorded in the Swedish Cancer Registry for the years 1958 through 1968. J. Bone Joint Surg. Am. 1975;57:167–173.	177
37	Boriani S, Bandiera S, Biagini R, Bacchini P, Boriani L, Cappuccio M, Chevalley F, Gasbarrini A, Picci P, Weinstein JN. Chordoma of the mobile spine: fifty years of experience. Spine. 2006;31:493–503.	174
38	Rock MG, Pritchard DJ, Unni KK. Metastases from histologically benign giant-cell tumor of bone. J. Bone Joint Surg. Am. 1984;66:269–274.	166

39	Han CS, Wood MB, Bishop AT, Cooney WP 3rd. Vascularized bone transfer. J. Bone Joint Surg. Am. 1992;74:1441–1449.	165
40	Harrington KD. Metastatic disease of the spine. J. Bone Joint Surg. Am. 1986;68:1110–1115.	166
41	DiCaprio MR, Enneking WF. Fibrous dysplasia. Pathophysiology, evaluation, and treatment. J. Bone Joint Surg. Am. 2005;87:1848–1864.	161
42	Kelly CM, Wilkins RM, Gitelis S, Hartjen C, Watson JT, Kim PT. The use of a surgical grade calcium sulfate as a bone graft substitute: results of a multicenter trial. Clin. Orthop. 2001:42–50.	161
43	Fuchs B, Dickey ID, Yaszemski MJ, Inwards CY, Sim FH. Operative management of sacral chordoma. J. Bone Joint Surg. Am. 2005;87:2211–2216.	160
44	Greenspan A. Benign bone-forming lesions: osteoma, osteoid osteoma, and osteoblastoma. Clinical, imaging, pathologic, and differential considerations. Skeletal Radiol. 1993;22:485–500.	160
45	Kneisl JS, Simon MA. Medical management compared with operative treatment for osteoid-osteoma. J. Bone Joint Surg. Am. 1992;74:179–185.	160
46	Tang N, Song W-X, Luo J, Haydon RC, He T-C. Osteosarcoma development and stem cell differentiation. Clin. Orthop. 2008;466:2114–2130.	160
47	Coley WB. The treatment of malignant tumors by repeated inoculations of erysipelas. With a report of ten original cases. 1893. Clin. Orthop. 1991:3–11.	157
48	Pritchard DJ, Dahlin DC, Dauphine RT, Taylor WF, Beabout JW. Ewing's sarcoma. A clinicopathological and statistical analysis of patients surviving five years or longer. J. Bone Joint Surg. Am. 1975;57:10–16.	155
49	Wise JJ, Fischgrund JS, Herkowitz HN, Montgomery D, Kurz LT. Complication, survival rates, and risk factors of surgery for metastatic disease of the spine. Spine. 1999;24:1943–1951.	152
50	Berrettoni BA, Carter JR. Mechanisms of cancer metastasis to bone. J. Bone Joint Surg. Am. 1986;68:308–312.	152

Poster 110 #2804671

INFERIOR ONCOLOGIC OUTCOMES OF RADIATION-ASSOCIATED OSTEOSARCOMA COMPARED TO SPONTANEOUS OSTEOSARCOMA

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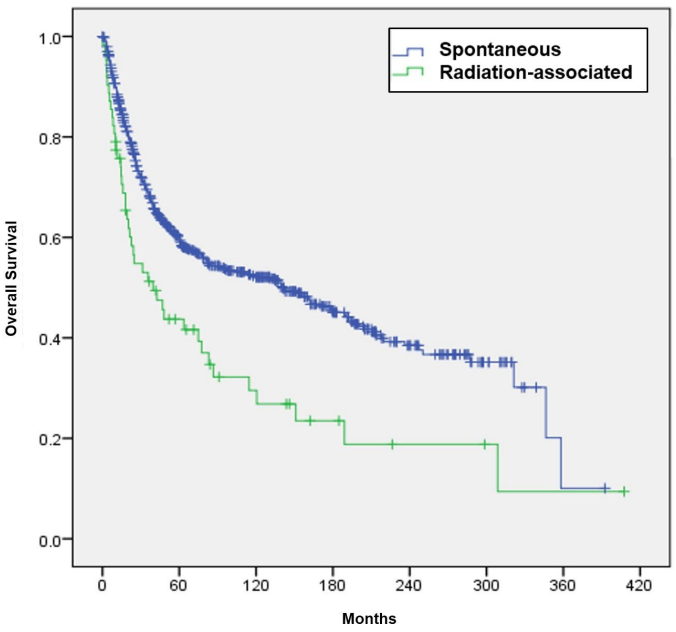
Objective: Second malignancies are among the most serious complications of radiation therapy (RT), but it remains incompletely characterized how they differ from primary malignancies of the same disease site or histology. We sought to describe the clinical characteristics, patterns of care, and outcomes of radiation-associated osteosarcomas (RAOS) as compared with those of spontaneous osteosarcomas (SOS).

Methods: We classified an IRB-approved single-institution retrospective cohort of 703 osteosarcoma patients (diagnosed 1960-2015) as having either RAOS (n=62) or SOS (n=641). Osteosarcomas were defined as radiation-associated if they occurred in a prior RT field at least 1 y after RT.

Results: Primary malignancies in patients who later developed RAOS occurred at a median age of 30 y (range: 2 mo-73 y) and included diverse histologies. Median time from diagnosis of primary malignancy to diagnosis of RAOS was 11 y (range: 1-41 y). Compared with SOS, RAOS patients were older (median 47 y vs. 28 y, p=0.0004) and more often female (59.7% vs 45.2%, p=0.033). RAOS were more centrally distributed (trunk 58.1% vs. 25.7%, extremity 21.0% vs. 60.4%, p<0. 0001) but not higher-grade or later-stage (p=ns for each). Like SOS, RAOS were most commonly treated by surgery alone (53.2% vs. 65.1%, p=ns), with a significant minority receiving RT pre- and/or post-operatively (35.5% vs. 24.3% p=ns). However, with a median follow-up of 4.2 y, RAOS showed worse overall survival (OS, median 3.3 y vs. 11.7 y, log-rank p=0.0003), progression-free survival (PFS, median 2.0 y vs. 6.9 y, p=0.005), and local recurrence-free survival (LFS, median 5.3 y vs. not reached,



p=0.001. On Cox multivariate analysis, among the 568 patients without distant metastatic disease at presentation, RAOS vs. SOS remained significant for worse OS (HR 1.75, p=0.004), PFS (HR 1.54, p=0.04), and LFS (HR 1.74, p=0.03) after adjusting for other variables.

Conclusion: Despite identical histologic diagnoses, RAOS display distinct clinical characteristics and suffer worse outcomes compared to SOS. These findings argue for further investigation into the biological basis of these differences as well as treatment strategies to address them.

Poster 111 #2804714

MULTIMODALITY MANAGEMENT OF HEAD AND NECK OSTEOSARCOMA: OUTCOMES FROM A SINGLE INSTITUTION

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Objective: The optimal management of osteosarcomas of the head and neck (OSHN) is not known. Surgery is the mainstay of treatment, with margin status being an important prognostic factor for disease free survival and overall survival. The benefit of additional treatment including systemic chemotherapy and radiation therapy is unclear, with conflicting outcomes reported in the literature. The purpose of this study is to perform a retrospective review of our experience at Massachusetts General Hospital in treating OSHN patients.

Methods: IRB approval was obtained to retrospectively identify 105 patients within our sarcoma database with OSHN referred to our institution between 1979 and 2015. Overall survival (OS), disease-free survival (DFS), and local control rates (LC) were calculated using the Kaplan-Meier method with log-rank tests. Differences between proportions for categorical variables were analyzed using the chi-square statistic or Fisher exact test as appropriate. Variables affecting survival were analyzed by Cox's proportional hazard model. To account for other factors, Kaplan-Meier method and Cox model was constructed adjusting for a propensity score accounting for the covariates of grade, site, tumor size, chemotherapy, with the outcome being the propensity for receipt of margin and therapy types (surgery only vs surgery + RT).

Results: Median follow up for all of the patients treated in our institution was 40.4 months. OS, DFS, and LC for the entire group at 5 years was 58.6%, 43.9%, and 71.4% respectively. Patient, tumor characteristics can be seen in Table 1. Prognostic factors included younger age, surgery, margin status, tumor size, tumor grade, chemotherapy, and mandibular subsite. Patients who had surgery as part of management had improved DFS (HR 4.75, CI 2.2-10.4, p= 0.001) and OS (HR 3.12, CI 1.5-1.6, p=0.002). On propensity score analysis patients with negative margins had OS (HR 0.33, 0.12-0.89, p=0.03), DFS (HR 0.35, 0.16-0.78, p=0.01), and LC (HR 0.23, 0.07-0.78, 0.02). Radiation was not associated with OS or DFS(HR 1.15, 0.6-2.2, p=0.7; HR 0.96. 06-1.7, p=0.9). When margins were negative there was no benefit of combined surgery and radiation with no statistical difference in OS, DFS, and LC (p=0.43, p=0.60, p=0.67). When margins were positive/close (<1 mm), there was no difference in OS and DFS between patients who received surgery and radiation versus surgery alone (HR 1.68, p=0.4; HR 1.66, p=0.3); however, LC was improved by RT, (HR 3.19, CI 1.03-9.9, p=0.045), with 5 yr LC of 67% versus 50, respectively. There was no dose response seen with radiation dose in respect to LC, DFS and OS. When radiation was given alone without surgery outcome was poor, and 5 year OS and DFS of 22.2% and 12.5%. Chemotherapy was not associated with improved LC (HR 0.74, CI 0.29-1.90, p=0.5). There were 16 radiation induced toxicities, all occurred with combined modality surgery plus radiation therapy. 8 radiation toxicities occurred with photon therapy, and 8 radiation toxicities occurred with proton

Characteristics	N
Male	57 (54.3%)
Female	48 (45.7%)
Age (Median)	36 (3-87)
Primary	98 (93.3%)
Recurrence	6 (5.7%)
Metastases	1 (1.0%)
Radiation-Induced	14
Mandible Site	28 (26.7%)
Other Site	77 (73.3%)
Osteosarcoma NOS Histology	73 (69.5%)
Low Grade	48
High Grade	44
Size (Median)	4 (1.2-14)
Surgery	82 (78.1%)
Negative Margin	42 (51.2%)
Positive Margin	31 (37.8%)
Undetermined Margin	9 (11.0%)
Chemotherapy	61 (57.5%)
Radiation Therapy	58 (54.7%)
Radiation plus Surgery	46
Radiation Alone	12
Median Radiation Dose	66.6 Gy (25.8 Gy-80 Gy)
Photons	48
3D Protons	31
Photons plus Protons	24

therapy. There was one radiation induced malignancy. The mean dose associated with toxicity for photons was 60 Gy (Range 45.1Gy-66Gy), and the mean dose associated with toxicity for proton therapy was 72 Gy (Range 66-80 GyE).

Conclusion: Complete surgical resection of the tumor is the mainstay of treatment in patients with OSHN. Radiotherapy improved LC rates in patients with OSHN who have positive/uncertain resection margins after surgery, and should be given when margins are positive or very close. Chemotherapy does improve OS and DFS, but does not impact LC. Adjuvant therapy increases long term toxicity, and proton therapy can be considered to potentially reduce long term effects.

Poster 112 #2804716

GENOME WIDE METHYLATION AND GENE EXPRESSION PATTERNS IN HUMAN AND CANINE OSTEOSARCOMA

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Objective: Human osteosarcoma is a rare sarcoma of the bone. This disease is very heterogeneous and characterized by high genome instability and a high propensity to metastasize. These traits, combined with low incident rate, make it a difficult disease to study. Canine osteosarcoma is common in large breed dogs, shows high rates of metastasis, and shares many other clinical and molecular features making it a good model for human disease. Global changes in DNA methylation patterns have been seen across many cancer types and can serve as biomarkers for diagnosis, disease progression and outcome. Previously, we showed that the response of osteosarcoma to DNA and chromatin modifying drugs (5-azacytidine and suberoylanilide hydroxamic acid) is heterogeneous. Our goal for this project is to understand the genome wide DNA methylation landscape in human and canine osteosarcoma.

Methods: We used capture based method to measure genome wide DNA methylation levels from human (n=24) and canine (n=45) osteosarcomas at single CpG resolution. A canine osteosarcoma cell line, cultured without and with DNA and chromatin modifying drugs, was used for validation of the canine baits. Unsupervised methods are being used to interrogate methylation patterns within each species to identify epigenetic subclasses of osteosarcomas. Gene expression (RNAseq) are being integrated with the methylation data for all the human samples (n=24) and a subset (n=10) of the canine samples.

Results: Samples have passed quality control and a pipeline has been developed for methylation quantification and comparative analysis. Validation experiments confirmed an overall decrease in methylation, as well as regional alterations in methylation, in canine cells treated with DNA and chromatin modifying drugs. Ongoing analyses seek to define methylation patterns shared between species to understand the main drivers of disease onset and progression. We will also investigate the interaction between DNA methylation levels and gene expression and how those interactions are conserved and/or unique between human and canine disease.

Conclusion: We have developed and validated a resource to study genome-wide methylation in dogs, and are applying this resource to define the contribution of the epigenome to the molecular heterogeneity of osteosarcoma, as well as its evolutionary conservation across species. This information will enable improved disease classification and highlight new avenues of treatment, including the application of DNA and chromatin modifying drugs for this disease.

Poster 113 #2782563

THE CLINICAL OUTCOME OF "DEDIFFERENTIATED" LOW-GRADE OSTEOSARCOMAS

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Objective: It is known that low-grade osteosarcomas, including low-grade central and parosteal osteosarcoma, occasionally progress to high-grade osteosarcomas, which is called "dedifferentiation." However, the optimal treatment and prognosis of "dedifferentiated" low-grade osteosarcoma (DOS) are unclear. The purpose of this study is to clarify the clinical outcome of DOS.

Methods: Eleven patients (male, n=5; female, n=6) who received the treatment for DOS in our institution between 2004 and 2016 were retrospectively reviewed. The median age of the patients was 32 (range, 16-50) years. We investigated the location and histology of the tumor, treatments, clinical course and disease status at the final follow-up examination.

Results: The locations were the distal femur (n=5), proximal humerus (n=2), proximal tibia (n=2), and maxilla (n=2). In all cases, we confirmed dedifferentiated osteosarcoma. The ratio, in comparison to the whole tumor, ranged from

5% to 95%. In all cases there was at least one section of low-grade osteosarcoma component. Immunohistochemistry detected the co-expression of MDM2 and CDK4 in all cases. A genetic examination, either by FISH or an RT-PCR, revealed the amplification of MDM2 in 10 cases. No metastasis was recognized at the initial presentation in any of the cases. All patients underwent surgery, including marginal resection (n=3), wide resection (n=7), and amputation (n=1). Ten patients received preoperative and/or postoperative adjuvant chemotherapy, mostly according to regimens that are used to treat conventional high-grade osteosarcoma. The histological evaluation of 7 surgical specimens revealed that the responses to chemotherapy were grade 1 (n=5), grade 2 (n=1) and grade 3 (n=1). There was 1 instance of local recurrence and 3 cases of distant metastasis. The median disease-free and overall survival period was 21 (range, 6 - 126) months and 39 (range, 6 - 126) months, respectively. The disease statuses were CDF (n=8), AWD (n=1), and DOD (n=2).

Conclusion: Recently, improvements in relation to the knowledge on the histological findings and genetic abnormalities of DOS have facilitated the precise diagnosis of the subtypes of osteosarcoma. In the current study, DOS patients underwent surgery and chemotherapy, similarly to conventional osteosarcoma, and showed relatively good clinical outcomes. We should consider the establishment of diagnostic standards, the accumulation of a greater number of cases and the development of treatment strategies for DOS.

Poster 114 #2791472

A NOVEL FORMULATION OF NICLOSAMIDE TREATS METASTATIC OSTEOSARCOMA IN VIVO

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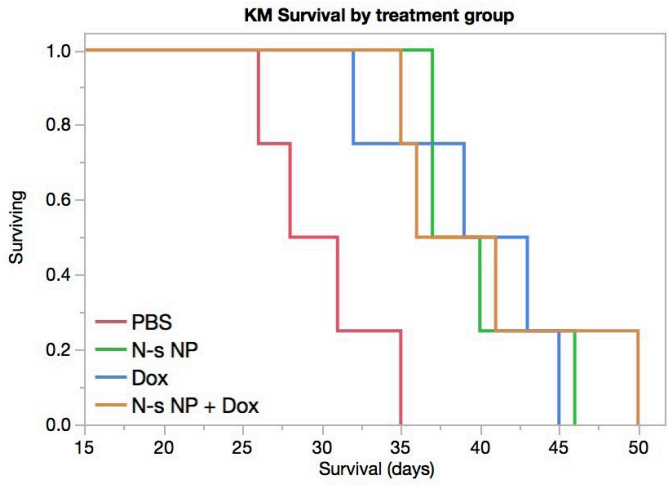
Objective: Osteosarcoma treatment has seen few advances in the last three decades. Current therapy for OS includes adjuvant chemotherapy, frequently based on agents that are associated with significant treatment-related morbidity, such as doxorubicin. As with other cancer types, the search for new drugs that are effective against OS has revealed a number of agents that appear to be effective in vitro but lack a pharmacokinetic profile useful for treatment of in vivo disease. One such drug is niclosamide, which targets a number of pathways known to be dysregulated in OS, such as the Wnt/b-catenin and Akt/mTOR pathways. However, when given as an oral tablet it has poor bioavailability, requiring exceedingly high doses or a solubilizing agent such as DMSO or DMA to achieve a therapeutic response in orthotopic models. Thus, an effective mechanism of delivery for this drug and similar agents would mark an important step in providing new treatment options for patients. In this study, we tested a novel formulation of niclosamide, in which an esterified form of niclosamide becomes the pure-drug core within a synthetic, lipid-coated nanoparticle for delivery to metastatic osteosarcoma.

Methods: Twelve-week-old SCID/beige mice were inoculated via tail-vein injection with 1x106 143B human osteosarcoma cells. The mice (n=4 per group) were treated as follows: 1) phosphate-buffered saline (200ul i.v. weekly), 2) niclosamide-stearate nanoparticles (35nm diameter; 200ul of 100uM, i.v. weekly), 3) doxorubicin (1.2 mg/kg i.p. biweekly), and 4) combined therapy. Nanoparticles were prepared by a solvent exchange method, precipitating the nanoparticles from acetone solution into an excess of water (1:9 v/v). Mice were euthanized when they presented with signs of morbidity. Kaplan-Meier survival curves were compared using log-rank tests.

Results: Mice treated only with niclosamide-stearate nanoparticles did not experience any early side effects, though both the doxorubicin-only and combined-therapy groups demonstrated early treatment-related weight loss, and treatment with doxorubicin was held for these groups at day 21. Treatment with the niclosamide-stearate nanoparticles significantly prolonged survival in mice with metastatic osteosarcoma compared to the saline-treated control group (mean 40 vs 30 days, p=0.0067), and there was no significant survival difference between groups treated with niclosamide-stearate nanoparticles, doxorubicin, or combined-therapy.



Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	14.8388	3	0.0020*
Wilcoxon	14.4938	3	0.0023*

Fig. 1 - All drug-treated groups demonstrated significantly improved survival compared with PBS-treated control mice. There was no significant difference in survival between drug-treatment groups.

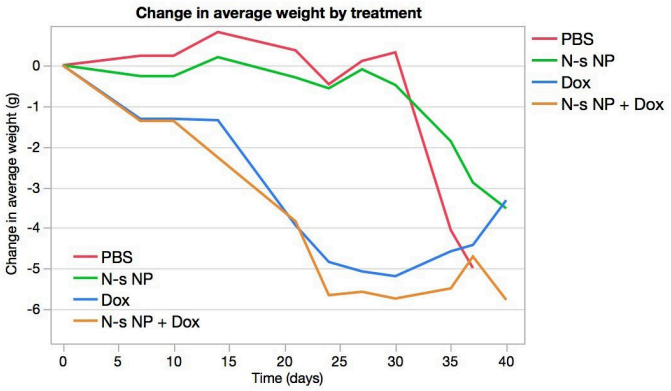


Fig. 2 – Change in average weight for each treatment group (n=4) for the first 40 days of treatment. At day 21, doxorubicin treatment was held for the remainder of the study due to toxicity. At day 40, all PBS-treated mice and 2/4 in each other treatment group had been euthanized due to signs of morbidity.

Conclusion: Niclosamide-stearate nanoparticles appear to be an effective chemotherapeutic agent against metastatic osteosarcoma cells in vivo, with a survival benefit comparable to doxorubicin but without the treatment-related toxicity associated with doxorubicin therapy. This may represent a new modality for treating osteosarcoma in patients with or without known metastatic disease, as well as a potential method for in vivo delivery of other pharmacokinetically-similar hydrophobic drugs.

Poster 115 #2804356

DEVELOPMENT OF A NOVEL SODIUM FLUORIDE-PET RESPONSE CRITERIA FOR SOLID TUMORS (NAFCIST) IN A CLINICAL TRIAL OF RADIUM 223 IN OSTEOSARCOMA: FROM RECIST TO PERCIST TO NAFCIST

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Objective: Drug developmet in osteosarcoma has been challenging, in part because of the lack of appropriate criteria to evaluate responses. Since fluoride is taken up avidly by the bone, we hypothesized that $Na^{18}F$-PET-CT scan can better image the qualitative bone response to a bone targeted alpha particle therapy with Radium-223. We analyzed the qualitative and quantitative approaches to metabolic tumor response assessment with $Na^{18}F$ and ^{18}F-FDG PET and developed a framework for **Na^{18}F** PET response **C**riteria **i**n **S**olid **T**umors (NAFCIST), a new way to evaluate treatment response in osteosarcoma.

Methods: Patients received 1-6 cycles of $^{223}RaCl2$, and cumulative doses varied from 6.84 MBq to 57.81 MBq. Molecular imaging with technetium (Tc)-99m phosphonate scintigraphy, fluorine-18-fluorodeoxyglucose (FDG) positron emission tomography (PET) or sodium fluoride-18($Na^{18}F$)PET was used to characterize the disease. Correlation of biomarkers and survival was analyzed with NAFCIST measure from $Na^{18}F$-PET with PERCIST.

Results: Of the 18 patients, 17 had bone lesions visible in at least one of the imaging studies. In 4/7 patients with multiple skeletal lesions (>5), FDG-PET and NaF-PET studies could be compared. The skeletal tumor locations varied in our patient population: [Cranium =2, extremities =7, pelvis =10, spine =12, and thorax= 9]. The ^{18}F-FDG-PET and $Na^{18}F$-PET studies could be compared in all four patients who had multiple lung lesions (>5). Overall RECIST response was seen in one patient, but four patients experienced mixed responses better defined by $Na^{18}F$-PET. Changes in NAFCIST were correlated with changes in bone alkaline phosphatase levels($r = 0.54$), and negatively with cumulative dose of $^{223}RaCl_2$. ($r = -0.53$). NAFCIST correlated with survival (p value 0.037), versus PERCIST did not (p-value 0.19).

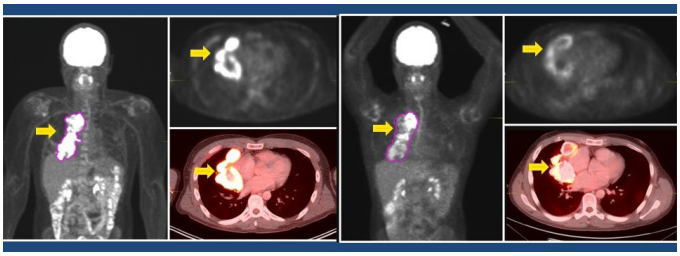

Figure 1: Sodium Fluoride PET/CT scan pre and post Radium 223 alpha particle therapy in a patient with osteosarcoma.

Conclusion: Our results indicate that $Na^{18}F$-PET should be used in osteosarcoma staging. NAFCIST may be a promising criteria for high-risk osteosarcoma response evaluation, and correlates with survival. Further validation studies are needed.

Poster 116 #2761829

LOW AND HIGH LINEAR ENERGY TRANSFER RADIATION EFFECT AGAINST IN VITRO AND ORTHOTOPIC IN VIVO MODELS OF OSTEOSARCOMA BY ACTIVATION OF CASPASE 3 AND 9

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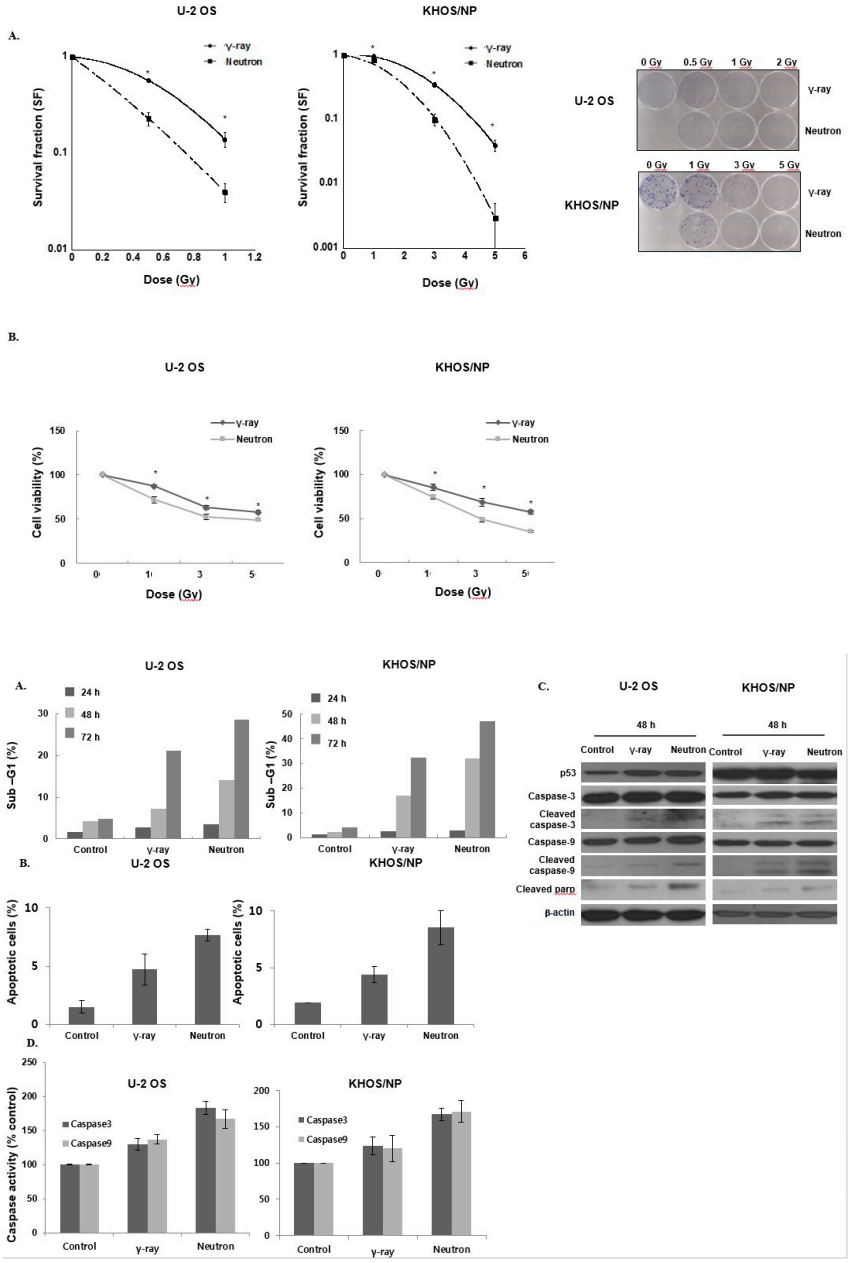
Objective: Osteosarcoma (OS) is a malignant tumor of the bone derived from primitive transformed cells of mesenchymal origin. Local low-linear energy transfer (LET) radiotherapy has limited benefits for OS because of its radioresistance. High-LET radiation has several advantages for treating radioresistant human cancers because of its

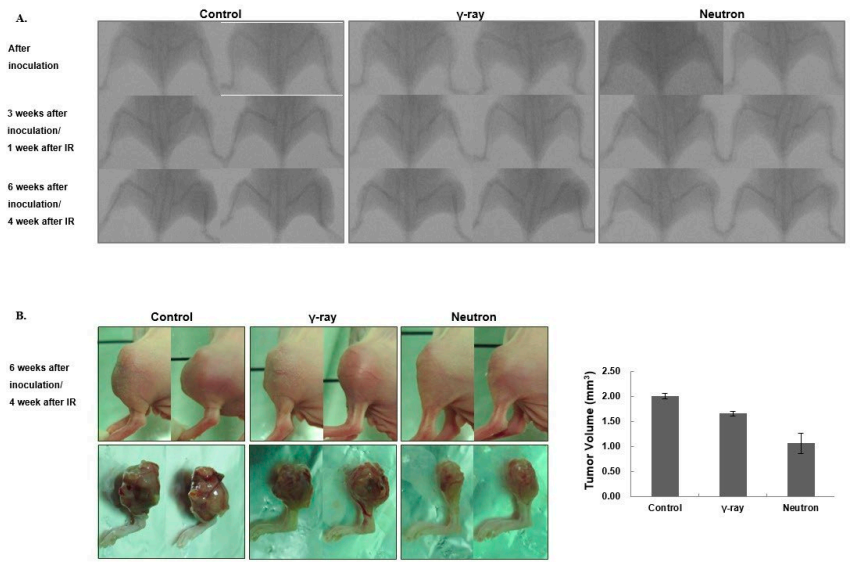
higher relative biological effectiveness (RBE), lower oxygen enhancement ratio (OER), and decreased cell-cycle-dependent radiosensitivity. Carbon ion high-LET radiotherapy is highly efficacious in treating deep-seated malignant OS tumors as compared to conventional approaches. However, the molecular mechanisms of carbon ion- or neutron-induced OS cytotoxicity are largely unknown. As such, this study investigated the therapeutic effects of high-LET neutron radiation on OS in vitro and in vivo.

Methods: The human OS cell lines U2O2 and KHOS/NP were examined in vitro or in vivo with an orthotopic mouse xenograft model after treatment with low-LET (γ-ray) and high-LET (neutron) radiation. Irradiations were performed with a ^{137}Cs γ-ray source (Atomic Energy of Canada, Ltd., Ontario, Canada) at a dose rate of 3.81 Gy/min. Fast neutrons (9.8MeV, 30-40keV/μm) were produced by the bombardment of beryllium by proton $^{9}Be(p,n)^{10}B$ as a nuclear reaction in the cyclotron (MC-50; Scanditronix, Uppsala, Sweden). Paired ionization chambers were used to measure the absorbed dose and dose distribution of fast neutron beams or -rays. Dosimetry data was measured before in vitro study to calculate neutron dose using RBE, 2.2, which has been used for neutron therapy in our institute and represents an equivalent cell killing efficacy as γ -ray as determined by clonogenic assay.

Results: OS cells were significantly more sensitive to high-LET radiation in vitro and in an orthotopic xenograft tumor model. Specifically, neutron radiation-treated cells increased the relative percentage of apoptotic, sub-G1 phase cells via caspase-3/9 activation, increased intracellular ROS, and DNA damage. Correspondingly, the mean size of -irradiated (8 Gy) orthotopic KHOS/NP OS tumors was 195 mm^3 6 weeks after -irradiation (8 Gy), but only 150 mm^3 in mice treated with high-LET neutron radiotherapy.

Conclusion: Our study supports that high-LET neutron radiotherapy provided a stronger therapeutic benefit as compared to low-LET γ-ray radiation by increasing OS cell apoptosis and DNA damage in vitro and orthotopicin vivo, and thus provides further preclinical rationale for high-LET radiotherapy.





Poster 117 #2796123

POSTOPERATIVE CHEMOTHERAPY FOR PELVIC SARCOMAS: ALWAYS "AS PLANNED"?

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Objective: Primary bone sarcomas of the pelvis are rare, surgically challenging, and often have a dreadful prognosis. Two of the most frequent bone sarcomas, the osteosarcomas and the Ewing sarcomas, are chemosensitive and thus their management is realized in multimodal protocols including neo-adjuvant chemotherapy, surgery, and adjuvant chemotherapy (adjCX). It seems logical to initiate the adjuvant chemotherapy as soon as possible after the surgery, but no study ever determined the optimal delay to do so. In our experience we noticed that the frequent complications in the postoperative period often led to a postponement of the adjuvant treatment. We realized a study in order to describe and quantify this problem.

Methods: We realized a retrospective cohort study about all patients operated at the CHU Cochin, Paris, France, for a primary bone sarcoma of the pelvis between 2000 and 2016. We identified and included the patients who had an indication for adjCX after surgery, and the data were collected in the medical files. Our primary outcome was the delay in days between the surgical resection of the tumor and the first day of the first cycle of adjCX, with a delay of less than 6 weeks considered as "on time". Secondary outcomes were: completion rate of the adjuvant treatment, risk factors for delaying or interrupting the treatment. Optional outcome was the impact of a delay on the overall survival or event-free survival.

Results: We identified 117 patients operated on for a pelvic sarcoma between 2000 and 2016. Among those, 32 patients met the inclusion criteria. The overall median delay between surgery and adjCX was 3.88 weeks. Of the 32 patients, 69% began their adjCX on time, and 31% had a median delay of 10 weeks. 25% of all patients interrupted the adjCX. Overall 47% of the patients had an inadequate adjuvant treatment. The delay was strongly associated to postoperative complications. The only significative risk factors were the increasing age and the use of 2 surgical approaches versus one. We could not identify a difference of local recurrence or EFS between patients that had the adjCX on time versus those not on time.

Conclusion: More frequently than previously thought, postoperative chemotherapy for pelvic sarcomas may not be optimally performed due to the numerous complications patients will develop. Larger studies are needed to determine the optimal delay for starting the adjuvant chemotherapy and the real impact of a delayed treatment on prognosis.

Poster 118 #2798046

PATTERNS OF EXTRAPULMONARY METASTATIC DISEASE IN PEDIATRIC OSTEOSARCOMA

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Objective: Osteosarcoma is the most common bone malignancy in pediatric populations. Survival has improved in the last 30 years; however, changing patterns of metastasis have been reported. The purpose of this study is to review the incidence, clinical characteristics, patterns of metastasis, and outcomes of patients with extrapulmonary metastasis at our institution, and to compare outcomes of patients with and without extrapulmonary metastases.

Methods: A retrospective analysis for all patients with osteosarcoma at our institution from 1980-2015 was performed. Patients were divided into two major groups: those with extrapulmonary metastasis and those without. Statistical analysis was performed on both groups to define an association of various factors with outcomes.

Results: In 35 years, 91 patients developed extrapulmonary metastasis while 293 patients did not develop extrapulmonary metastasis. Sites of extrapulmonary metastasis were highly variable and are detailed in Table 1. Four major patterns of metastasis were noted among patients who developed extrapulmonary disease (Table 2). Of patients with extrapulmonary disease, patients who had synchronous pulmonary and extrapulmonary metastasis (n=19) had the worst five-year overall survival (OS=0) ($P<0.0003$). However, patients with extrapulmonary metastasis who never developed pulmonary metastasis (n=6) had the best five-year OS, 0.667 +/- 0.222. For patients who had extrapulmonary metastasis, 57% presented with metastatic disease at diagnosis, versus 15% in patients without extrapulmonary metastasis. Forty-three percent of patients with extrapulmonary metastasis presented with localized disease versus 85% of patients without extrapulmonary metastasis. Patients who had extrapulmonary metastasis had significantly worse overall survival, regardless of stage at diagnosis (localized or metastatic), than patients who did not develop extrapulmonary disease ($P<0.0001$).

Conclusion: Patients with extrapulmonary metastasis at any point in their disease course had worse OS compared with patients without, regardless of stage at diagnosis. Patterns of metastasis in patients with extrapulmonary metastasis greatly influenced OS in this population. No survivors were found among patients with synchronous pulmonary and extrapulmonary metastasis. In contrast, patients with extrapulmonary metastasis who never developed pulmonary metastasis had the highest OS.

Table 1. Sites of Extrapulmonary Metastasis

SITE	NUMBER OF PATIENTS
Bone	49
Pleura	41
Soft tissue	23
Spine	23
Mediastinum	15
Brain	11
Lymph nodes	11
Chest wall	9
Diaphragm	7
Liver	6
Pericardium	5
Kidney	5
Heart	3
Esophagus	1
Retroperitoneum	1
Skin	1
Pancreas	1
Small intestine	1
Spleen	1
Inferior Vena Cava	1

Table 2. Patterns of Extrapulmonary Metastasis

GROUP NUMBER	NUMBER OF PATIENTS	METASTATIS PATTERN	5-YEAR OVERALL SURVIVAL
1	6	Extrapulmonary metastasis only	0.667 +/- 0.222
2	10	Extrapulmonary metastasis prior to pulmonary metastasis	0.500 +/- 0.144
3	19	Synchronous pulmonary and extrapulmonary metastasis	0
4	56	Pulmonary metastasis developed prior to extrapulmonary metastasis	0.244 +/- 0.057

Poster 119 #2800236

JUXTACORTICAL OSTEOSARCOMA: CLINICO-PATHOLOGICAL CHARACTERISTICS AND PROGNOSTIC FACTORS OF SURVIVAL

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Objective: The present study examines the influence of clinical and pathological tumor characteristics on recurrence and survival in patients with primary surface OS. An additional goal was to evaluate treatment selection by treating physicians.

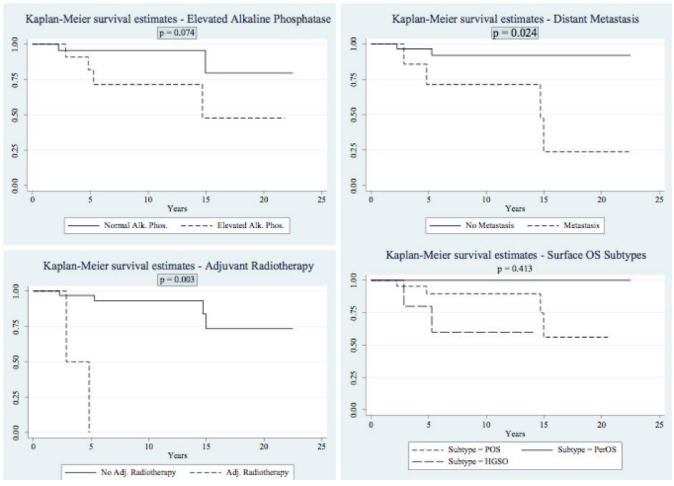
Methods: We performed a retrospective study evaluating all patients that underwent surgical treatment of primary surface OS. We included patients between the years 1992 and 2016 who were treated at one of our affiliated hospitals. We included 40 patients that met these criteria with a mean follow-up period of 9.1 years (range: 1-23 years). There were 26 POS (10.4%), 9 PerOS (3.6%) and 5 HGSO (2%). Medical records of these patients were reviewed for demographics, oncologic outcomes, tumor characteristics, treatment variables and complications. Bivariate analysis was performed to identify potential predictors for oncologic outcomes. As a survival analysis we used a Cox regression.

Results: All but 2 patients were surgically treated with limb-salvage resection. Six patients (15%) died from their disease after a mean survival of 7 years (range: 2–14 years); 4 had a POS and 2 had a HGSO. Compared to prior reports our overall survival was similar or higher. PerOS and HGSO were treated with chemotherapy (neo-adjuvant and/or adjuvant) more commonly than POS. The local recurrence rate was 5% in our cohort (avg. time to recurrence = 35 ± 15.6 months) and no PerOS recurred. Older patients (>30 years of age) were more likely (p = 0.0159) to have a local recurrence, as were those who developed a distant metastasis (p = 0.027). In addition, distant metastasis and the use of adjuvant radiotherapy were significantly associated with decreased overall survival.

Table 1: Bivariate analysis

	Tumor recurrence		*P*-value
	Yes (n=2)	*No (n=38)*	
Tumor type, n (%)			0.283[1]
POS	1 (3.8)	25 (96.2)	
PerOS	0	9 (100)	
HGSO	1 (20)	4 (80)	
Age, years, n (%)	-	-	**0.0159**[1]
<20	0	11 (100)	
20-30	0	16 (100)	
>30	2 (15.4)	11 (84.6)	
Metastasis, n (%)	2 (28.6)	5 (71.4)	**0.027**[1]

[1] Using Fisher's exact test



Kaplan-Meier Survival Curves for Surface Osteosarcoma

Conclusion: Surface osteosarcoma have relatively good overall survival rates. Older patients and distant metastasis were associated with local recurrence of primary surface OS. Distant metastasis and the adjuvant radiotherapy were associated with decreased overall survival. Nevertheless, it is important to highlight that the use of radiation is a reflection of more aggressive tumors, not responding to traditional treatments such as chemotherapy and surgery. Our recurrence and survival outcomes are comparable to those reported in the literature; however, our PerOS patients have higher long-term survival rates compared to previously published figures which reported 10-year survival rates as high as 83%. We believe our results may be crucial to facilitating realistic expectations of treatment success and identifying potential mechanisms to optimize patient care.

Poster 120 #2800408

A QUINOLINE-BASED DNA METHYLTRANSFERASE INHIBITOR AS A POSSIBLE ADJUVANT IN THE THERAPY OF OSTEOSARCOMA

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Objective: Osteosarcoma (OS) derives from transformation of osteoblastic progenitors in any phases of their differentiation. Malignant cells maintain the capability to differentiate. Here we analyze the effects of the novel non-nucleoside DNMT inhibitors (DNMTi) MC3343, as a possible drug candidate for differentiative therapy. OS cells showed, in general, more genes with hyper-methylation than hypo-methylation, thus sustaining the use of DNMTi

Methods: MC3343 was prepared as previously reported (Valente S, J Med Chem 2014). Dnmt1/3a enzyme inhibition assays evaluate specificity of the compound. Efficacy was tested in 10 patient-derived cell lines and 2 patients-derived xenografts. For a more general view on osteogenic differentiation of the OS model, the Human Osteogenesis RT2 Profiler PCR Array was used together with conventional tests measuring enzymes and matrix mineralization. MC 3343 alone (control) or combined in fixed ratio with doxorubicin (DXR, Pfeizer), cisplatin (CDDP, Sandoz) and methotrexate (MTX, Sigma).

Results: In cell-free assays, MC3343 displayed increased potency compared to other DNMTi against DNMT1 and DNMT3b. C50 values ranged from 5-15 μM for MC3343 and from 0.5->100 μM for 5azadC. Sensitivity to MC3343 inversely correlated with expression of DNMT1 or DNMT3a (r= - 0.640 or -0.637, p<0.05, Pearson correlation test). MC3343 determines effects on proliferation, blocking OS cells in G1 or G2/M phases of cell cycle together with induction of differentiation. No effects were observed on cell death. Compared to5azadC, MC3343 has similar anti-proliferative effects but it is more potent in promoting differentiation. Analysis of genes involved on osteoblastogenesis after treatments indeed sustains the specificity of action for MC3343, which was not observed for 5azadC, an agent capable to induce a generalized release of gene expression without regaining the cascade of regulatory genes associated with osteoblastic differentiation that is possibly silenced during OS development. The blockade of DNMTs with MC3343 effectively suppresses the growth of OS PDX and increases the chemosensitivity of OS cells towards doxorubicin and cisplatin, two major drugs in the treatment of OS patients.

Conclusion: MC3343, which restores the dichotomy between proliferation and differentiation, leads OS cells toward mature osteoblasts with concomitant minimization of malignancy. Sinergistic effects with doxorubicin has been documented at preclinical level.

Poster 121 #2804228

LONGER TIME TO TREATMENT IN BONE SARCOMA IS NOT ASSOCIATED WITH WORSE SURVIVAL: AN ANALYSIS OF THE NATIONAL CANCER DATABASE

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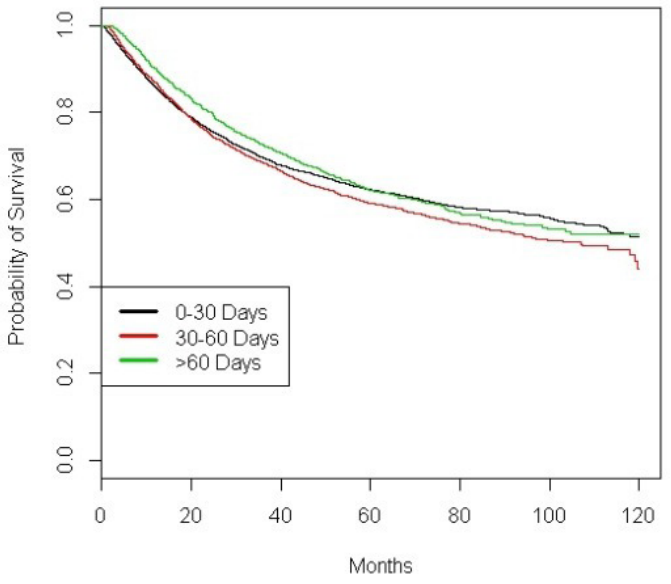
Objective: To determine if time to treatment interval (TTI), defined as the period from diagnosis to first definitive treatment, influences the survival of patients diagnosed with primary bone sarcoma.

Methods: A retrospective analysis of the National Cancer Database identified 15,083 patients with primary bone sarcoma diagnosed between 2004-2013. Patient exclusions included pediatric patients <18 years old (not available from this database), patients that did not receive definitive treatment (n = 1,720) in the form of surgery, systemic therapy or radiotherapy, patients without follow-up data (n = 1,434), and outliers with a TTI > 365 days (n = 34). Final analysis included 11,895 patients. Patients were separated into 3 groups based on TTI. Groups included TTI < 31 days (Group 1), 31-60 days (Group 2), and > 60 days (Group 3). $\chi 2$ -tests identified differences among covariates. Survival was estimated with Kaplan-Meier models and compared with log-rank tests. A Cox proportional hazards model adjusted for all covariates.

Results: Median TTI was 21 days. Approximately 62% of patients had a TTI ≤ 30 days (Group 1), 23% of patients had a TTI = 31-60 (Group 2), and 15% of patients had a TTI > 60 days (Group 3). At five years, survival for

Groups 1, 2 and 3 was 62%, 59%, and 62%, respectively. At 10 years, survival for Group 1, 2 and 3 was 52%, 44%, and 52 %, respectively. Longer TTI did not worsen survival. In fact, Group 2 (HR=0.90; P=0.007) and Group 3 (HR=0.83; P<0.001) had increased adjusted survival compared to Group 1. Shorter survival was significantly associated (P<0.05) with grade 2, 3 and 4 tumors (HR= 1.71, 3.65, and 3.97), stage III and IV disease (HR=1.27 and 3.47), age 51-70 years or >71 years (HR=1.68 and 2.99), radiation or systemic therapy as index treatment (HR=2.26 and 1.40), Charlson score of 1 or ≥2 (HR= 1.16; HR=1.80), and a pelvic tumor site (HR=1.54). Longer survival was significantly associated (P<0.05) with chordoma or chondrosarcoma (HR=0.32 and 0.71), treatment at an academic center (HR=0.72), private insurer (HR=0.74), and female gender (HR=0.89).

Figure 1. Kaplan-Meier Survival Curve; log-rank test P = 0.016



Conclusion: Longer TTI is not associated with a survival disadvantage. This is important in counseling patients, who may delay treatment to receive a second opinion or seek care at a tertiary sarcoma center.

Table 2. Cox proportional hazard model

	Hazard Ratio (95% CI)	P-Value
Total Number of Patients		
Time to Treatment Initiation		
Group 1, (0-30 days)	Reference	
Group 2, (31-60 days)	0.90 (0.83-0.97)	0.007
Group 3, (>60 days)	0.83 (0.76-0.91)	<0.001
Age		
18-30	Reference	
31-50	1.14 (1.00-1.30)	0.055
51-70	1.68 (1.42-1.98)	<0.001
71+	2.99 (2.48-3.61)	<0.001
Sex		
Male	Reference	
Female	0.89 (0.83-0.95)	<0.001
Race		
White	Reference	
Black	0.99 (0.88-1.1)	0.816
Other/Unknown	1.00 (0.87-1.14)	0.944
Charlson/Deyo Score		
0	Reference	
1	1.16 (1.06-1.28)	0.002
≥ 2	1.80 (1.55-2.09)	<0.001
Histology		
Osteosarcoma	Reference	
Chondrosarcoma	0.71 (0.65-0.78)	<0.001
Ewing's Sarcoma	1.02 (0.91-1.14)	0.749
Chordoma	0.32 (0.27-0.37)	<0.001
Other	0.71 (0.63-0.8)	<0.001
Facility Type		
Community Cancer Program	Reference	
Comprehensive Community Cancer Program	0.89 (0.75-1.06)	0.188
Academic Center	0.72 (0.61-0.86)	<0.001
Integrated Network Cancer Program	0.94 (0.76-1.17)	0.595
Other/Unknown	0.54 (0.44-0.67)	<0.001
Insurance		
Uninsured	Reference	
Private Insurance	0.74 (0.64-0.86)	<0.001
Medicaid	1.10 (0.94-1.3)	0.242
Medicare	1.01 (0.85-1.19)	0.910
Other/Unknown	0.87 (0.72-1.05)	0.151
Income		
< $38,000	Reference	
$38,000 - $47,999	1.02 (0.92-1.12)	0.751
$48,000 - $62,999	0.95 (0.86-1.05)	0.302
$63,000+	0.94 (0.85-1.03)	0.197
Unknown	1.33 (0.6-2.91)	0.481
Distance from Facility		
< 21 miles	Reference	
21-50 miles	0.99 (0.91-1.07)	0.748
51-100 miles	1.03 (0.94-1.14)	0.506
>100 miles	0.98 (0.89-1.08)	0.674
Unknown	1.82 (0.82-4.05)	0.141
Transition in Care		
Yes	0.97 (0.91-1.04)	0.390
No	Reference	
Year of Diagnosis	0.99 (0.98-1.01)	0.264
Primary Tumor Site		
Upper Extremity	Reference	
Lower Extremity	1.06 (0.95-1.18)	0.319
Pelvis	1.54 (1.38-1.73)	<0.001
Other	1.23 (1.1-1.37)	<0.001
Tumor Size		
≤ 8.0 cm	Reference	
> 8.0 cm	1.06 (0.94-1.19)	0.324
Grade		
1, Well Differentiated	Reference	
2, Moderately Differentiated	1.71 (1.47-1.99)	<0.001
3, Poorly Differentiated	3.65 (3.14-4.24)	<0.001
4, Undifferentiated	3.97 (3.44-4.65)	<0.001
Unknown	2.95 (2.55-3.41)	<0.001
Clinical Staging		
Stage I	Reference	
Stage II	1.06 (0.94-1.19)	0.324
Stage III	1.27 (1.01-1.59)	0.039
Stage IV	3.47 (3.08-3.9)	<0.001
Unknown	1.26 (1.14-1.39)	<0.001
First-Line Treatment Modality		
Surgery	Reference	
Radiation	2.26 (2.02-2.52)	<0.001
Systemic	1.40 (1.29-1.53)	<0.001
Other	0.97 (0.48-1.94)	0.922
Multi-modal	1.35 (0.97-1.87)	0.074

Poster 122 #2804708

SAFETY & EFFICACY OF HIGH-DOSE METHOTREXATE FOR OSTEOSARCOMA IN ADOLESCENTS VERSUS YOUNG ADULTS

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Objective: Osteosarcoma is a rare cancer of the bone that has a peak incidence in adolescence. The standard of care chemotherapy regimen includes Methotrexate, doxorubicin (Adriamycin) and cisPlatin ("MAP"). The MAP regimen was developed and evaluated in the cooperative group setting and has been widely used by pediatric oncologists for over 15 years. Adults with osteosarcoma often do not receive methotrexate as part of their chemotherapy regimen. At OHSU, it is standard practice to prescribe HDMTX (high-dose methotrexate, defined as 12 mg/m2 or a flat dose of 20 grams) for all patients with osteosarcoma under the age of 40 years.

We sought to evaluate the differences in rate of methotrexate clearance by age. In addition, we assessed the differences in dose intensity (number of doses planned versus administered) according to location of chemotherapy administration, and also assessed differences in toxicities by age.

Methods: We conducted a retrospective review of the electronic medical records of all individuals treated with high-dose methotrexate (HDMTX) at OHSU between 2011-2016. Data collected included from first chemotherapy time point: age; location (adult or pediatric hospital); sex; race & ethnicity; body surface area (BSA); methotrexate dose (12 mg/m2 or 20 grams); serum creatinine; calculated eGFR. For each cycle of HDMTX, we also collected all methotrexate levels and serum creatinine values from MTX infusion start until MTX level ≤0.1 μM. Finally, we also tracked methotrexate-associated toxicities (change in eGFR, readmissions), rate of recurrence, and survival.

Results: Thirty-three patients met eligibility criteria for inclusion. Median age 20 years [range 7-38]. Patients treated at the adult hospital ranged in age from 18-38y versus 7-19y at the pediatric hospital. At the pediatric hospital, the median number of HDMTX cycles received was 12 [range 4-12] while at the adult hospital the median was 5.5 [range 1-12]. Overall, the average dose of MTX administered was 10.4 mg/m2 [range 6.3-12.3]. The average time to clearance of serum methotrexate levels to ≤0.1 μM for patients age 18y or less was 81.2 hours ± 14.4 hrs; the average time for patients over the age of 18y was 142.3 hours ± 67.7 hrs.
Toxicity and survival analyses are ongoing and will be reported at the time of the meeting.

Conclusion: High-dose methotrexate can be safely administered to young adult patients. However, caution must be employed as clearance can sometimes be profoundly delayed despite adequate supportive care. In patients over the age of 18, an individualized plan may be necessary to account for potential methotrexate-associate toxicity.

Poster 123 #2787351

MARKERS OF GONADAL FUNCTION IN PEDIATRIC PATIENTS WITH OSTEOSARCOMA RECEIVING STANDARD CHEMOTHERAPY IN COMBINATION WITH BEVACIZUMAB

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Objective: To determine the impact of standard chemotherapy in combination with the anti-VEGF monoclonal antibody bevacizumab on gonadal function and pubertal development in patients with osteosarcoma.

Methods: Subjects with newly diagnosed osteosarcoma enrolled on a multi-institutional phase II clinical trial (OS2008) from 2008 to 2012 received chemotherapy (cisplatin, doxorubicin, methotrexate ± ifosfamide, etoposide) and surgery. Markers of gonadal function including Tanner stage, testicular volume (males), and serum measurements of luteinizing hormone, follicular stimulating hormone (FSH), estradiol, and free/total testosterone were assessed at baseline, mid-therapy, end of treatment, and yearly up to 5 years after treatment. Gonadal status and risk of dysfunction were determined at each time point. Wilcoxon signed rank test was used to compare markers at different time points for patients with late pubertal status.

Results: Median age at diagnosis of 34 evaluable patients was 12.2 years (range 6.9-19.1 years); 17 were male. Pubertal status at diagnosis was pre-pubertal (Tanner stage 1) in 7 (M:F 4:3), early-to-mid puberty (Tanner 2-3) in 15 (M:F 7:8), and late pubertal (Tanner 4-5) in 12 (M:F 6:6). Central hypogonadism was present at baseline in 12 patients (35%; M:F 7:5) but decreased to 5 patients (16.7%; M:F 4:1) mid-therapy, 4 (14.3%; M:F 3:1) at end of therapy, and none by 1 year off therapy. Testosterone/LH levels were suggestive of compensated Leydig cell insufficiency in 14% of males at the end of therapy and 29.4% at last evaluation. Germ cell injury (GCI) was suspected in 14% of males at the end of therapy; mean (SD) FSH pre-therapy was 1.43 (1.52), and at end of therapy 6.43 (5.12). GCI was suspected in 17.6% at last evaluation and confirmed by semen analysis in 2 males. Laboratory values were suggestive of primary ovarian insufficiency in 8 females (53.3%) mid-therapy, and 5 (35.7%) at end of therapy; mean (SD) FSH pre-therapy was 2.95 (1.74) and at end

of therapy 51.46 (46.88). All resolved on subsequent follow-up [mean (SD) FSH at 1 year follow-up 6.12 (1.61)]; all developed menarche or resumed normal menses.

Conclusion: Central hypogonadism occurred in one third of patients before therapy. Patients exposed to bevacizumab and chemotherapy experienced gonadal dysfunction that was transient in females but persistent in a subset of males. Further study is needed to assess the contribution of bevacizumab and the lasting impact of this therapy on fertility and gonadal function.

Poster 124 #2796860

INDUCTION OF ADAPTIVE IMMUNITY AGAINST OSTEOSARCOMA USING ONCOLYTIC VIROTHERAPY

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Objective: Osteosarcoma (OSA) is a devastating bone cancer that disproportionately affects children and adolescents. Despite advances in cancer therapy, the prognosis with OSA has remained stagnant for over thirty years, highlighting an unmet need for novel treatment strategies. Oncolytic viruses, such as vesicular stomatitis virus (VSV), selectively replicate in and destroy tumor cells, exposing viral antigens and tumor-associated antigens, activating an anti-tumor immune response to potentially delay or prevent metastases. OSA occurs commonly in dogs, and its comparable clinical presentation creates opportunities to accelerate translational OSA research.

Methods: We are investigating the potential of oncolytic virotherapy with VSV to initiate anti-tumor immunity in canine OSA, with the intent to inform future clinical trials for human patients. We are using RNA sequencing to determine the number of immune-cell transcripts in the tumor environment, and peripheral blood mononuclear cells (PBMCs) to determine lymphocyte effector functions against autologous tumors, autologous normal fibroblasts (non-malignant control), and allogeneic tumors using flow cytometry and ELISpot assays. We are using massive parallel sequencing of amplified, rearranged lymphocyte antigen receptors to identify clonal frequency in tumor-infiltrating lymphocytes and draining lymph nodes, and to assess the effect of immunotherapy on peripheral clonal expansion and attrition throughout the remission period. For each immune assay, pre-treatment samples provide an intrinsic control for each case, allowing determination of the anti-tumor immune response induced by VSV. Safety and efficacy of VSV treatment are being monitored using conventional criteria. Correlating the induced immunity with clinical endpoints will elucidate characteristics associated with survival and prognosis in response to treatment.

Results: Eight dogs have been enrolled in the study, and we have established autologous OSA cell lines and fibroblast cultures, as well as serial cryopreserved samples of PBMCs, from each one. Experimental methods have been optimized, including characterization of anti-tumor reactivity against allogeneic tumor cells from control (unaffected) dogs. RNA sequencing and massive parallel sequencing of rearranged antigen receptors from these eight dogs is in progress, and results will be discussed.

Conclusion: Our results will provide valuable information regarding the mechanisms of immune activation by VSV and its potential translation to humans with OSA and other connective tissue sarcomas. Determining prognostic factors will help guide treatment decisions, targeting VSV therapy primarily toward patients expected to respond favorably.

Poster 125 #2804243

PATIENT/PARENT OSTEOSARCOMA GENOME-WIDE REGISTRY (POWR) PROVIDES THE SARCOMA COMMUNITY WITH AN UNDERUTILIZED RESOURCE FOR GENOMIC AND MEDICAL HISTORY DATA

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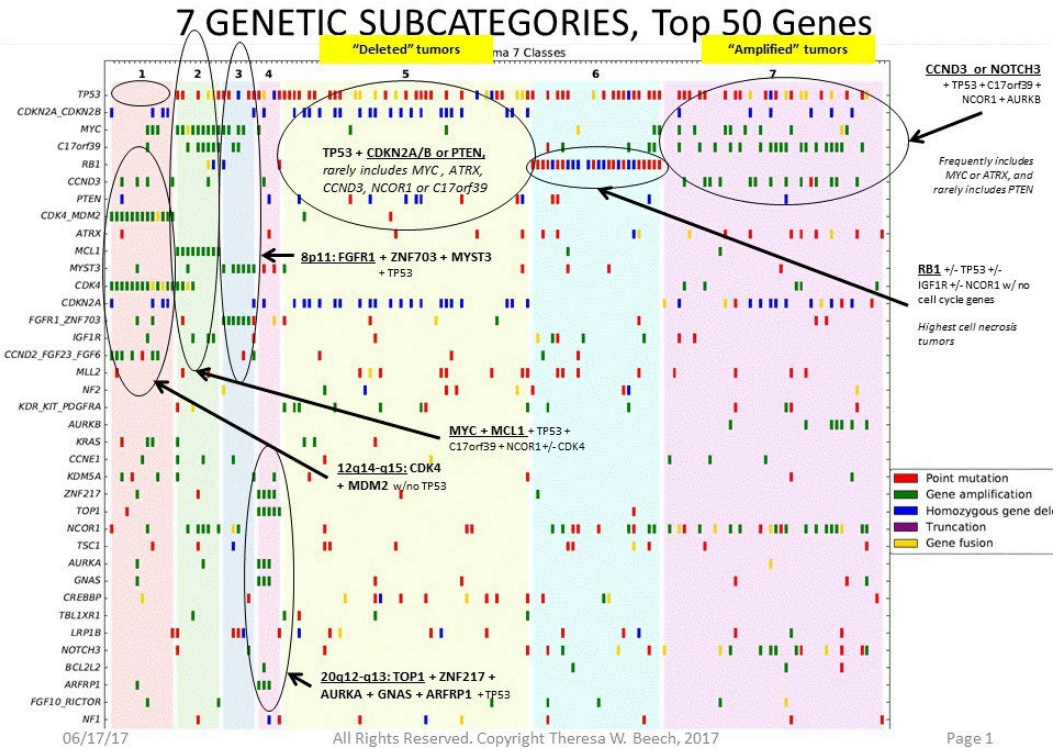
Objective: Patient derived data is an underutilized resource for obtaining data on poor prognosis sarcomas such as relapsed/refractory osteosarcoma. In less than a year, communicating primarily on-line, the global patient/parent osteosarcoma community created the first-ever Patient/Parent Osteosarcoma Genome-Wide Registry (POWR) containing genomic and medical history information on >110 tumors. We will share insights from this on-going patient derived registry.

Methods: Genomic reports (primarily Foundation One or MSKCC IMPACT) and medical history information of >50 tumors were provided by patients/parents. Genetic sequencing data on 63 pediatric tumors was downloaded from the Foundation One data portal. IRB approval for data capture and analysis was granted by Hummingbird IRB, Cambridge, MA. Genomic reports identified Genomic Alterations (GA: base substitutions, indels, copy number alterations, fusions/rearrangements) and Variants of Unknown Significance (VUS). Medical history data includes: disease presentation; % necrosis; surgeries; time to relapse; number/location of relapses; treatments; time to death.



Regression Analysis of Top 50 Genes with GA Yields 7 Distinct Genetic Sub-Types which are Statistically Significant and Biologically Relevant

Results: Mean number of GA (with VUS) is 13.8, range 1 - 46; mean age is 16, range 5 - 52; sex ratio is 63%/37% male/female. Table 1 shows the % occurrence of genes with GA and VUS. Co-amplification loci occur at 8q21-8q24 (MYC, RAD21, RUNX1T1) and 17p11-17p12 (C17orf39, NCOR1, FLCN). ATRX and MYC are mutually exclusive. Alternative Lengthening of Telomeres appears in 40-50% of tumors. Regression analysis of top 50 genes (GA only) yields 7 genomic sub-types (see image 1).

MYC amplified tumors have a trend to poor outcomes. Of 13 MYC tumors with medical history data, 10 are dead/ on hospice, 2 have heavy turmor burdens, and 1 is NED. 5/13 were never NED, and 6/13 progressed on chemo. Mean time to death is 18 months (range 7-33 months), and mean time to initial relapse is 4 months (range 0-18 months). Initial disease presentation is not significant, nor is % tumor necrosis (mean 54%, range 5-95%). Overall mean % tumor necrosis is 51%, range 0-97%. RB1 tumors have a significantly higher mean % necrosis (86%) compared to others (43%).

Conclusion: Statistical analysis of patient derived relapsed/refractory osteosarcoma tumor data yields new insights into the genomics, as well as identifying a potential biomarker for poor outcome patients. POWR provides a model of patient/parent provided genomic and medical history data, gathered quickly and globally, which can be a resource for the sarcoma community.

% OCCURENCE OF GENES WITH GA & VUS

GENE	% OCCURENCE	GA or VUS
TP53	50.9%	GA
CCND3	25.0%	GA
MYC	25.0%	GA
C17orf39	24.1%	GA
RAD21	23.2%	VUS
FLCN	22.3%	VUS
CDKN2A	19.6%	GA
RB1	19.6%	GA
NCOR1	17.9%	VUS
ATRX	17.0%	GA
CDKN2B	15.2%	GA
RUNX1T1	15.2%	VUS
PRKDC	14.3%	VUS
CDK4	13.4%	GA
MCL1	13.4%	GA
PCLO	13.4%	VUS
BRCA2	11.6%	BOTH
CCNE1	11.6%	GA
SMARCA4	11.6%	GA
BLM	9.8%	BOTH
MLL3	9.8%	BOTH
PTEN	8.9%	GA
ZNF217	8.9%	BOTH
ATM	8.0%	BOTH
DDR2	8.0%	VUS
GNAS	8.0%	BOTH
IGFR1	8.0%	GA
NTRK1	8.0%	BOTH

Gene occurences may be either GA or VUS or a combination of both.
Amplifications only: CCND3, MYC, C17orf39, RAD21, NCOR1, RUNX1T1, CDK4, MCL1, and CCNE1.
Mutations/deletions/truncations/rearrangements only: TP53, CDKN2A/B, RB1, ATRX, BRCA2, PTEN, and ATM.
All other genes include both.

Poster 126 #2791477

PROGNOSTIC EFFECT OF DELAY OF PREOPERATIVE CHEMOTHERAPY IN OSTEOSARCOMA PATIENTS: A RETROSPECTIVE COHORT STUDY

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Objective: Chemotherapy for treatment of osteosarcoma was demonstrated to be effective in eradicating primary tumor and pulmonary metastases in the 1970s. The effective agents have been utilized in various combination regimens and have escalated the survival rate from <10 to 75 %. Unfortunately, however, despite these impressive advances no change in survival expectancy of patients with osteosarcoma during the past 40 years has occurred. Preoperative chemotherapy would initiate immediate treatment against micrometastases, which may lead to survival benefit. However, little is known about the prognostic effect of delay of preoperative chemotherapy. The aim of this study was to determine the appropriate time interval from initial visit to initiation of neoadjuvant chemotherapy in the treatment of osteosarcoma.

Methods: A retrospective study was performed on 142 osteosarcoma patients under 40 years, who had been surgically and medically treated in Seoul National University Hospital from January 2000 to December 2013. Sixty-nine patients were given preoperative chemotherapeutic agents within 15 days and 73 patients delayed chemotherapy more than 15 days from the initial visit. Mean duration of follow-up was 76.2 months. The Kaplan-Meier method and the log-rank test were used to calculate survival rates and survival rate difference between two cohorts.

Results: There were no statistically significant differences between the two cohorts in terms of age, gender, AJCC stage and surgical margin. The overall 10-year survival rate of the 142 patients was 73.9%. The 10-year survival estimates of 69 patients who were included in within-15-day cohort and 73 patients in the beyond-15-day cohort were 81.8% and 64.5% respectively (p=0.025).

Conclusion: Minimizing time for staging work-up and early introduction of preoperative chemotherapy may lead to improvement in oncologic outcome of osteosarcoma patients.

Poster 127 #2781017

EXTRAPULMONARY SEEDING OF OSTEOSARCOMA AFTER THORACIC PROCEDURES: A LITERATURE REVIEW AND TWO CASE REPORTS

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Objective: Orthopedic surgeons are well aware of the risk of biopsy-site tumor seeding; however we wish to highlight the rare risk of tumor seeding associated with thoracic instrumentation in patients with osteosarcoma (OST).

Methods: We conducted a literature search on Scopus, Google Scholar, and Pubmed with keywords: “entry-site” “contamination” “osteosarcoma” “migration.”

Results: We identified 2 reports of OST with extrapulmonary tumor seeding associated with thoracic instrumentation in our review in addition to our 2 cases (Table1).

Patient 1: A 21-year-old man with 5 time recurrent OST presented with a new soft tissue mass just underneath a one-year-old chest tube surgical scar. The patient was initially diagnosed with OST of the left femur 3 years prior and a pelvic/lung relapse a year off therapy. He underwent a hemipelvectomy and 6 cycles of chemotherapy followed by a right lung metastasectomy with negative margins. Intraoperatively a chest tube was inserted through a trocar incision in the right lateral chest wall and left in place for 3 days. One year later he presented with a new superficial unresectable soft tissue mass in the chest wall at the chest tube scar which subsequently broke through the skin (Figures 1,2). He received palliative radiation and died within a month of treatment.

Patient 2: A 12-year-old male originally with localized right distal femur OST relapsed 5 years later with malignant pleural effusion. A pleural catheter drainage system (PleurX ©) was inserted until the effusion resolved (3 months) (figure 5). Two months following catheter removal, the patient suffered a multi-site relapse including disease encasing the extra-pulmonary cavity (figure 3,4). He died 5 months later.

Conclusion: Orthopedic surgeons are well aware of the risk of biopsy-site tumor seeding. However, extrapulmonary seeding associated with thoracic procedures is rare. Only 4 cases, including ours, have been reported, most commonly involving the skin. These cases suggest this phenomenon represents aggressive, often incurable OST, and imminent death; the median recurrence time from instrumentation was 5 months.

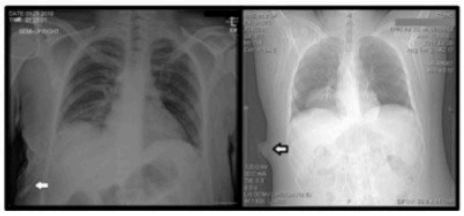
Our hope is that by drawing attention to tumor contami-

nation associated with thoracic instrumentation, doctors will be mindful of the risks involved. More research and education into this phenomenon is required to minimize such risks.

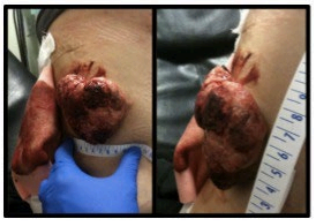
Table 1: Characteristics of Cases of OST Seeding Following Thoracic Instrumentation

Initial Diagnosis	Localized (right hip)	Localized (distal femur)	Localized (proximal tibia) [West J Med 166:65]	Right leg [J of Pediatr Surg 31: 1443]
Gender	*Male	*Male	Male	Female
Age	21	18	20	18
Location of relapses	Lungs, left hip, upper right lateral chest wall, pelvis, toe	Paraspinal, vertebral, lungs, epidural space, pleural cavity	Thorax, lung	Left lung, diaphragm, ribs
Number of relapses	5	5	2	3
Type of Invasive procedure	Chest tube	Pleural catheter	VATS	VATS
Site of contamination	Skin	Pleural Cavity	Skin	Skin
Time between invasive procedure and onset	12 months	5 months	5 months	4 months
Outcome	Deceased 13 months following instrumentation	Deceased 10 months following instrumentation	Deceased 7 months following instrumentation	Not specified

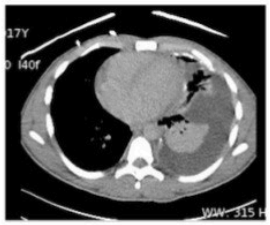
VATS = Video Assisted Thoracoscopic Surgery. *Indicates patients presented at Rush Hospital



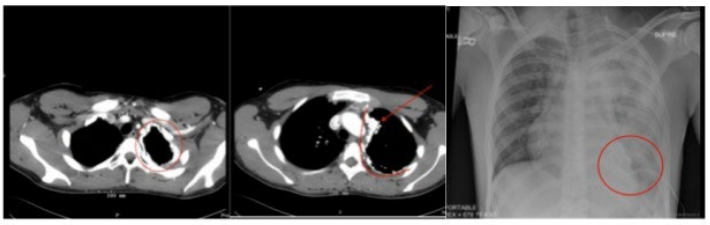
(Figure 1)
Left Chest tube placement (arrow) status post wedge resection. Right soft tissue mass (arrow) six months later.



(Figure 2)
Gross image of the fungating soft tissue mass broken through the skin.



(Figure 3)
CT of chest displaying malignant pleural effusion.



(Figure 4)
CT of Chest displaying cancer coating pleural space.

(Figure 5)
CT of chest displaying pleural catheter

Poster 128 #2796075

MALIGNANT TRANSFORMATION OF A RECURRENT GIANT CELL TUMOR OF BONE UNDER TREATMENT BY DENOSUMAB

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Objective: Spontaneous malignant transformation of conventional Giant Cell Tumor of Bone (GCT) is extremely rare. Malignant transformations have been described as a long term complication following radiotherapy, or in connection with pre-existing p53 or H-ras genes abnormalities.

Denosumab is considered to be a very useful drug in the management of GCT. It is prescribed either as a life-long therapy for non-operable cases, or as an adjuvant treatment before resection of a surgically challenging GCT. However the safety of high doses of Denosumab in the treatment of GCT may be a new subject of concern.

Methods: We report a case of a 44 years-old male patient who developed a malignant transformation of a recurrent GCT 6 months after initiation of treatment with Denosumab.

Results: The patient was diagnosed in 2011 with a GCT of the right proximal tibia which was treated by curettage. A first recurrence in 2013 was also treated by curettage. Both times histological analyses confirmed a conventional GCT and an a posteriori genetic analysis confirmed the presence of the H3F3A gene mutation. A second recurrence occurred in 2014 which motivated the introduction of a treatment by Denosumab. Six months after the start of the medication the main lesion was stable in size but the imaging showed a growing nodular ossification on the posterior aspect of the tibia associated to painful symptoms. Due to the extent of the GCT a wide resection of the tumor and a total knee replacement with tumor prosthesis were planned.

The histological analysis of this second recurrence re-

vealed a high grade conventional osteoblastic osteosarcoma. The resection margins were considered focally marginal and thus the patient underwent an above-knee amputation. Surgery was followed by adjuvant chemotherapy for conventional osteosarcoma. The patient is currently disease-free.

Conclusion: Denosumab is an efficient and useful drug in the management of difficult cases of GCT. However it has been shown to induce morphologic changes in the histology of treated GCT, which can exhibit pseudosarcomatous features. Since 2015, in addition to our case report, three other cases have been published concerning a malignant transformation of a conventional GCT under treatment of Denosumab. The paucity of cases makes it impossible to draw any conclusion about the role of Denosumab in malignant transformation of GCT. Nevertheless, we recommend that physicians prescribing this medication be vigilant to morphologic tumor changes during the treatment.

Poster 129 #2797066

BISPHOSPHONATE AS MAINTENANCE IN VERY HIGH RISK OSTEOSARCOMA

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Objective: To report our experience using bisphosphonates as maintenance in patients with poor prognosis osteosarcoma (OST).

Methods: We defined "High Risk OST (HRO)" as: Poor Responder (Group A), First Relapse Resected (Group B) - excluding late isolated resected lung nodule which has a relatively good progrnosis, and Primary Metastatic, Multiple Relapses or Unresectable Disease (Group C). We searched for all HRO patients from 04/01/2005 to 06/15/2017 who were less than 50 years of age who had received a bisphosphonate after completion of chemotherapy.

Results: During this period 16 of the 23 patients with HRO received at least 4 bisphophonate doses (15-ZA, 1-Aldronate), 7 were female and 9 were male. The median age was 17 (7-29). The monthly Zolendronic Acid (ZA) dose was 2.3mg/m2 (4mg max) as in the COG safety study. The aldronate dose was 70mg weekly. Group A (n=6) received a median of 6.5 doses of ZA (4-26), Group B (n=5) a median of 12 (4-24), and Group C (n=5) median 23 (7-32). Four of 5 Group C patients also got bevacizumab median 9 doses (1-20).

Conclusion: Our single institution, retrospective preliminary study suggests that bisphosphonates may benefit some high risk patients with osteosarcoma. We are planning on opening a prospective pilot study to explore this hypothesis.

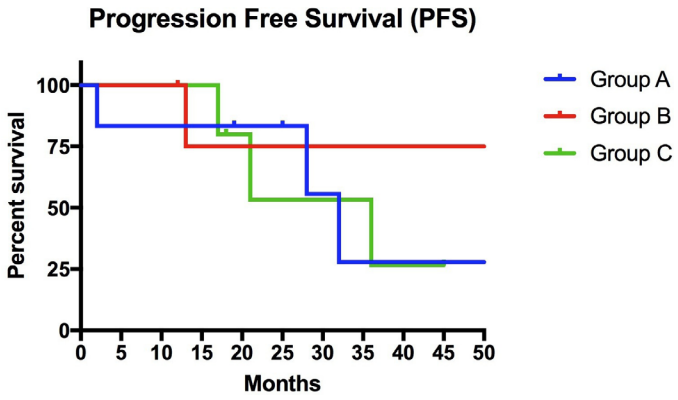

Figure 1: Progression Free Survival (PFS): Group A- PFS median 32 months, Group B- PFS median was undefined and Group C- PFS median was 36 months.

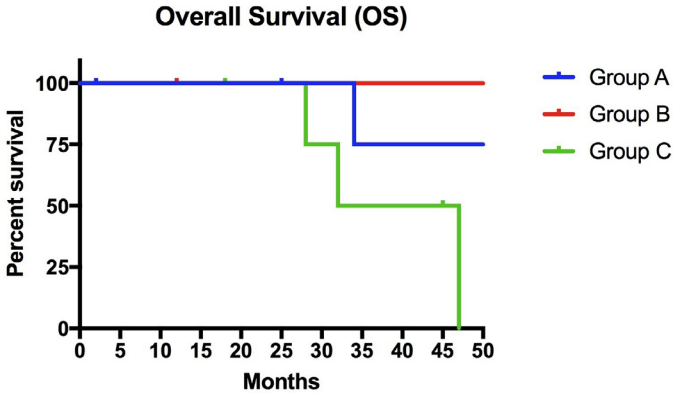

Figure 2: Overall Survival (OS): Groups A&B had an undefined median OS and Group C had a median OS of 39.5 months.

Poster 130 #2804241

OSTEOSARCOMA OF THE FEMUR WITH COLONIC AND MESENTERIC METASTASIS: A CASE REPORT AND REVIEW OF THE LITERATURE

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Objective: Osteosarcoma is a rare diagnosis with approximately 2000 new cases per year in the United States. Up to a third of all patients are diagnosed with metastatic disease at presentation, which drastically decreased their chance for cure. The most often location for metastasis is lung, followed by bone. Very rarely does sarcoma spread intra-abdominally. This entity has been described as sarcomatosis and is most often diagnosed in cases of soft tissue sarcomas.

Methods: We document a case report on a single patient who experienced metastatic osteosarcoma to the colon and omentum. The patient was nearly two years removed

from his initial resection of a distal femoral osteoblastic and fibroblastic osteosarcoma treated with chemotherapy and wide resection. He had been doing quite well until he developed abdominal symptoms which rapidly progressed.

Results: Imaging and pathology were obtained and were consistent with intra-abdominal metastatic osteosarcoma resulting in bowel obstruction with a rapid decompensating and death of the patient. This report documents an exceedingly rare patient presentation and diagnosis as well as a review of the pertinent literature regarding intra-abdominal metastasis of osteosarcoma. Our presentation will provide a review of the very limited literature on metastatic osteosarcoma to the abdomen and will discuss unifying symptoms, imaging and patient characteristics which are common in all cases.

Conclusion: Although lung and bone are the most common metastatic presentations, OS is a can develop the ability to metastasize to many anatomic locations including intra-abdominal. This poster presentation will provide information on previous case reports, which are very few, and will discuss unifying characteristics of this group of patients including physical symptoms, imaging workup, pathology evaluation and treatment options for these patients. Based on our experience with this entity, we recommend performing a thorough physical exam and obtaining appropriate imaging in OS patients with significant abdominal complaints.

Poster 131 #2804306

CLINICAL OUTCOME OF OSTEOSARCOMA IN PATIENTS OLDER THAN 40 YEARS OF AGE

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Objective: Osteosarcoma is the most commonly diagnosed primary malignant bone tumor and has a predilection for adolescents and young adults. Lttle is known about the clinical outcome of elderly patients with osteosarcoma. The aim of this study is to investigate the clinical features and prognostic factors in elderly patients with osteosarcoma.

Methods: We retrospectively reviewed the records of 50 patients with high-grade osteosarcoma who were admitted to our hospitals between 2000 and 2016. Information on tumor-related and treatment-related factors, local and distant relapse, follow-up period, and outcome were collected from the patients' medical charts. The mean follow-up period was 40.0 months for all patients.

Results: The 30 males and 20 females had a mean age of 60.9 years. The sites of primary lesions were appendicular bones in 32 patients, axial bones in 12, and craniofacial bones in 6. Forty-one patients had a primary osteosarcoma, and 9 patients had a secondary osteosarcoma. Forty-three patients had localized disease and 7 had distant metastatic disease at diagnosis. Forty patients received definitive surgery for a primary tumor. Chemotherapy was given to 39 patients. Among these patients, neoadjuvant and/or adjuvant chemotherapy was conducted in 32 patients. Five-year overall survival (OS) for all 50 patients was 48.7%. Multivariate analysis revealed that metastasis at diagnosis and no chemotherapy were significantly correlated with poor OS. Five-year OS was 55.2% for 43 patients without distant metastasis at diagnosis. Among the patients who had no metastasis at diagnosis, definitive surgery and chemotherapy were significant prognostic factors for OS. Five-year OS and event-free survival (EFS) for 36 patients who received definitive surgery without metastasis at diagnosis was 63.1% and 51.4%, respectively. There was no prognostic factor for OS but neoadjuvant and/or adjuvant chemotherapy significantly affected EFS in these patients.

Conclusion: In general, the prognosis in older patients with osteosarcoma is still poorer compared with children and adolescents. In this study, presence of distant metastasis at diagnosis, without definitive surgery, and without chemotherapy were significantly correlated with poorer OS. The role of chemotherapy in elderly patients with osteosarcoma has remained controversial but those without metastasis who have undergone definitive surgery should be regarded as good candidates for neoadjuvant and adjuvant chemotherapy.

Poster 132 #2783918

INSTITUTIONAL EXPERIENCE WITH FOUNDATION ONE TESTING IN SARCOMA: MOLECULAR ALTERATIONS AND CLINCIAL OUTCOMES

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Objective: 1) Determine the frequency of potentially actionable alterations in adults with soft tissue sarcoma via FoundationOne testing.
2) Determine response and duration to targeted therapy predicted by genetic testing.

Methods: We identified adult patients with diagnosis of sarcoma treated at University of Rochester who had FoundationOne testing sent between 2014-2017. FoundationOne is a next generation sequencing service (NGS) covering a panel of over 400 genes via DNA sequencing and over 250 genes via RNA sequencing as well as introns of 31 genes. With IRB approval, we developed a REDCap database to capture demographic information, genomic profiling, tumor characteristics, systemic therapies and response. We compared therapeutic targets suggested by FoundationOne report with treatment responses and clinical outcomes.

Results: From 2014-2017, 24 patients with a diagnosis of sarcoma had FoundationOne testing. Of these, 1 patient was found to have a mutation for which there is an FDA-approved therapy for sarcoma. 11 patients (45.8%) had alterations associated with sensitivity to FDA-approved targeted therapies in other cancer types, and 16 patients (66.7%) had alterations for which clinical trials may be available. 7 patients were treated with targeted therapy, with 4 patients demonstrating partial response or stabilization of disease. Overall disease control rate was 16.7%.

Additional alterations were detected of unclear clinical utility. 8 patients had fusions, 2 of which have not been previously described in the literature. A TPM4-NTRK3 fusion was found in a patient with malignant peripheral nerve sheath tumor and a PML-JAK1 fusion was found in a patient with undifferentiated pleomorphic sarcoma. Tumor mutational burden was reported in testing conducted after 2016 (7 patients) with an average of 3.9 mutations per megabase (range 1-7).

Conclusion: Soft tissue sarcomas may harbor actionable mutations for which there are targeted therapies available. Genomic testing was associated with clinical benefit for a subset of patients. Additional alterations were identified of unclear clinical significance and may warrant further study. Given the rarity of these tumors and molecular alterations, a multi-institutional collaboration may be required to establish the efficacy of matched targeted therapies.

Alterations and Responses

ID	Histology	Total Number of Alterations [1]	Genomic Alterations [2]	Targeted Therapy and Response
1	Pleomorphic sarcoma w/ myofibroblastic differentiation	5	PML-JAK1 fusion	
2	Leiomyosarcoma	18	ATRX I1049fs*4 CCNE1 amplification RB1 loss exons 3-27 TP53 deletion exons 5-6	
3	Undifferentiated pleomorphic sarcoma	9	NF1 rearrangement intron 32	
4	Angiosarcoma, epithelioid variant	2	MYST3 amplification NCOR2 T948fs*24	
5	Pleomorphic malignant fibrous histiocytoma	13	TP53 C141fs*28 B2M R65Fs*2 LEF1 G113R	
6	Metastatic pleomorphic sarcoma	17	MET amplification CDK6 amplification C17orf39 amplification TP53 loss	Crizotinib - ongoing PR since 1/2015
7	Favor alk-negative inflammatory myofibroblastic tumor	7	RET E511K	Sunitinib - PD Sorafinib - PD

8	Metastatic solitary fibrous tumor	20	NF1 W1662fs*18 CDKN2A/B loss p14ARF exon 1 and CDKN2B NAB2-STAT6 fusion	Everolimus - PD
9	Inflammatory monomorphic undifferentiated sarcoma	8	none	
10	Malignant solitary fibrous tumor	11	NAB2-STAT6 fusion ZNF703 amplification	Sunitinib - PD
11	Malignant peripheral nerve sheath tumor	17	TPM4-NTRK3 fusion AURKA amplification - equivocal MAP3K6 K1024*	Larotrectinib (on study) - ongoing PR since 11/2015
12	Malignant peripheral nerve sheath tumor	11	SS18-SSX2 fusion TOP1 R449W PBRM1 V215fs*9 - subclonal	
13	Leiomyosarcoma	6	TP53 S241Y	
14	Angiomyolipoma	6	TET2 S792*	
15	Osteosarcoma	12	MAP3K6 L1107fs*11	
16	Atypical fibroxanthoma/ fibrous histiocytoma	49	NF2 R57* ATM F1445fs*5 and P2699S EZH2 Y646N CDKN2A p16INK4a R80* and p14ARF P94L MLL2 Q3575* NOTCH1 L2067fs*44 and P1770S NOTCH2 R1838* PTPRO splice site 662-1G>A RAD50 Q298*, SMARCA4 Q115* TET2 Q1664* TP53 splice site 920-2A>T	
17	Undifferentiated pleomorphic sarcoma	14	PTEN loss FAS loss exons 3-7 RB1 loss exons 6-27 TP53 N239D	
18	Inflammatory myofibroblastic tumor	10	DCTN1-ALK fusion	Crizotinib - PR x 3 mo then PD Ceritinib - Intolerant Alectinib - PD
19	Intimal sarcoma	19	MDM2 amplification CCND3 amplification CDKN2A p16INK4a loss and p14ARF loss exons 2-3 FRS2 amplification	
20	Myxofibrosarcoma	17	CD274 (PD-L1) amplification - equivocal PDCD1LG2 (PD-L2) amplification - equivocal CRKL amplification JAK2 amplification - equivocal[3] KDM4C amplification - equivocal TNFRSF14 loss	
21	Monophasic synovial sarcoma	11	SS18-SSX2 fusion[4] TNFRSF11A amplification - equivocal BCL2 amplification - equivocal[5]	
22	Soft tissue sarcoma (NOS)	10	APC S2497L CDKN2A/B loss	
23	Dermatofibrosarcoma	11	COL1A1-PDGFB fusion CDKN2A/B loss	Imatinib - ongoing PR since 4/2017
24	Embryonal rhabdomyosarcoma	5	ATM S381fs*27	

1. Total number of alterations detected including variants of uncertain significance
2. Highlighted alterations per FoundationOne report
3. PD-L1 expression 20% IHC
4. Refines diagnosis to Synovial Sarcoma (FISH at URMC and MSKCC negative)
5. BCL2 positive by IHC

Poster 133 #2804834

PREVALENCE OF MISMATCH REPAIR DEFICIENCY IN UNDIFFERENTIATED PLEOMORPHIC SARCOMAS

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Objective: Pembrolizumab has recently been approved by the Food and Drug Administration (FDA) for the treatment of unresectable or metastatic solid tumors, which are microsatellite instability-high (MSI) or mismatch repair deficient (MMRD), including sarcomas. Previous studies on MMRD in sarcomas have been small. Since a subset of undifferentiated pleomorphic sarcomas (UPS) have been shown to respond to PD-1 inhibition (SARC028), we sought to better understand the prevalence of MMRD in a large series of UPS.

Methods: A tissue microarray comprised of tissue cores from 107 UPS cases was constructed and stained with immunohistochemical studies for MLH1, MSH2, PMS2 and MSH6. Expression of these markers was scored for each core as either lost (no expression in tumor nuclei) or retained (any expression in tumor nuclei).

Results: Two of 107 cases showed loss of expression of MLH1 with concordant loss of PMS2, while 2 of 105 cases (2 cases were not evaluable) showed loss of expression of MSH2, with concordant loss of MSH6. Approximately 4 % of this cohort showed MMRD.

Conclusion: Although uncommon overall, some cases of UPS have MMRD and these patients could qualify for pembrolizumab treatment under FDA guidelines. Efficient screening will be important to identify appropriate patients for either trial and/or approved treatment as only ~ 1 in 25 cases of UPS show MMRD. Only isolated MMRD/MSI sarcoma cases have been treated with PD-1 inhibition to date. Additional investigation on large microarrays of different sarcoma subtypes is on-going. In addition, correlation of MMRD with MSI by molecular testing, and immunohistochemistry for CD8-positive infiltrates and PD-L1 expression is underway. Further research is needed to further determine the efficacy of pembrolizumab in the treatment of MMRD sarcomas.

Poster 134 #2787471

DETECTION OF NOVEL FUSION GENES IN SARCOMA BY ANCHORED MULTIPLEX PCR AND NEXT-GENERATION SEQUENCING

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Objective: An estimated 20-30% of sarcomas are driven by expressed gene fusions, with specific sarcoma subtypes associated with unique gene fusions. Thus gene fusions represent important biomarkers for sarcoma subtype classification and minimal residual disease (MRD) detection. Targeted next-generation sequencing (NGS) provides a valuable tool to detect fusion genes in low-input clinical samples, however conventional target-enrichment methods require prior knowledge of partner genes and do not detect novel fusions. We developed a targeted NGS assay based on Anchored Multiplex PCR (AMP™) that permits amplification of fusion transcripts from a single end, enabling identification of novel fusion partners. Here, we present a compilation of novel fusions recently identified in sarcoma with this assay, providing an updated view of the molecular landscape of translocation-associated (TA) sarcomas.

Methods: We developed the Archer® FusionPlex® Sarcoma NGS assay to simultaneously detect and identify fusions of 26 genes associated with soft tissue cancers. This assay is based on AMP, which utilizes molecular barcoded adapters and unidirectional gene-specific primers for open-ended amplification of fusion transcripts.

Results: Here, we synthesize both reported and unpublished descriptions of the novel fusions detected by the Archer FusionPlex Sarcoma assay. These results were obtained from FFPE specimens that were of variable input RNA quality, yet were highly concordant with conventional assays, including fluorescence in situ hybridization (FISH), immunohistochemistry (IHC), RT-PCR and Sanger sequencing. Over 25% of the 26 genes targeted in this assay were shown to fuse to novel partners, and several well-known fusion genes, particularly ALK, NTRK3 and USP6, formed multiple unique chimeric transcripts. Instances of notable cases include an early and unexpected documentation of EWSR1-CREB3L1 fusion in sclerosing epithelioid fibrosarcoma, and two novel USP6 fusions that were not identified by FISH in aneurysmal bone cyst as well as novel USP6 partners in nodular fasciitis.

Conclusion: The Archer Sarcoma Assay is a valuable tool to investigate TA sarcomas, identifying both expressed known and novel fusion transcripts across varying types of soft-tissue tumors via NGS. Results obtained with this

assay support the demand for NGS-based methods of novel fusion detection to further enhance our understanding of molecular drivers in connective tissue oncology.

Poster 135 #2788006

FREQUENCY OF CDK PATHWAY GENE ALTERATIONS IN BONE SARCOMAS

***J. Charlson**, Medical College of Wisconsin, Wauwatosa, Wisconsin, USA; S. Trabucco, S. Ali, P. Stephens, Foundation Medicine, Inc, Cambridge, Massachusetts, USA*

Objective: Recently, inhibitors of CDK4 and CDK6 have been approved for treatment of advanced breast cancer. CDK pathway mutations have been noted in osteosarcoma tissue samples, suggesting possible additional applications of these inhibitors. This study is undertaken to evaluate the prevalence of CDK pathway mutations in bone sarcomas. In addition, the author will present a case of metastatic conventional chondrosarcoma, with equivocal CDK4 amplification, that responded to palbociclib.

Methods: Foundation Medicine databases were queried for cases of osteosarcoma, Ewings sarcoma/PNET, chondrosarcoma, and chordoma. Mutations in CDK pathway genes (including CCND1, CCND2, CCND3, CCNE1, CDK4, CDK6, CDKN2A, CDKN2B) were tabulated for each of the bone sarcoma subtypes, including chordoma. With Medical College of Wisconsin IRB approval, a relevant, de-identified case with will be briefly reviewed along with CT scan images.

Results: 851 cases of bone sarcoma were identified in the Foundation Medicine database. The most common bone sarcoma in the database was osteosarcoma, with 347 cases (including 7 cases of extraskeletal osteosarcoma). Among osteosarcomas, 45.0 % of cases had CDK pathway mutations; Ewings sarcoma/PNET 17.3 %, chondrosarcoma (not including soft tissue chondrosarcoma, suspected to represent extraskeletal myxoid chondrosarcoma) 42.3 %, and chordoma 41.9 %. In each tumor type, the majority of alterations were noted in CDKN2A and CDKN2B.

Conclusion: Genomic alterations in the CDK pathway are common in several bone sarcoma subtypes. The therapeutic relevance of these mutations remains to be determined, but these findings suggest a potential area for clinical investigation.

Poster 136 #2804534

PREDICTIVE ROLE OF APOPTOTIC FACTOR FAS FOR RESPONSE TO TRABECTEDIN IN SECOND LINES OF ADVANCED SOFT TISSUE SARCOMA. A SPANISH GROUP FOR RESEARCH ON SARCOMA (GEIS) STUDY

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Objective: There are several second-line options for the treatment of advanced soft-tissue sarcomas (ASTS) such as gemcitabine combinations, trabectedin, pazopanib, eribulin or olaratumab plus doxorubicin in cases where anthracyclins are still possible. There is an unmet need for predictive biomarkers which hinders the rational selection of the best sequence in second line therapy. In line with this, we published the prognostic value of apoptotic factor FAS in first line of ASTS. This study analyses FAS predictive role in different second line schemes.

Methods: Most relevant selection criteria for this study were having received trabectedin in 2nd line or beyond for ASTS between January 2007 and June 2016, progressive disease after at least one previous line for ASTS and signed CI. Demographic, clinical, therapy and outcome data were collected in an on-line registry. A TMA was set up for FAS staining (Cell Signaling) with Formalin-fixed paraffin-embedded (FFPE) blocks from diagnostic time. Two expert blinded pathologists reviewed and classified FAS expression as negative, weak or strong. Kaplan–Meier estimations were used for time-to-event variables and the log-rank test was used to compare groups.

Frequency of Genetic Alterations in CDK Pathway in Bone Sarcomas (Percent)

	CDKN2A	CDKN2B	CCND1	CCND2	CCND3	CCNE1	CDK4	CDK6
Osteosarcoma	25.0	19.7	0.9	2.9	9.8	9.2	10.7	0.3
Ewings/PNET	13.7	11.0	0.8	1.2	0	1.2	1.2	0
Chondrosarcoma	30.6	22.5	0	0.9	2.7	0.9	7.2	0.9
Chordoma	36.3	31.5	0.8	0	0	2.4	3.2	0

Results: A series of 198 patients accomplished selection criteria, and tissue was available in 129 of them. Forty-six pts (24%) had metastases at diagnosis and median time to metastases was 18.8 months (CI 16,3-21.3). Previous line to trabectedin consisted of gemcitabine combinations 83 (42%), Doxorubicin-based 65 (33%) and others 50 (25%). Median PFS for previous and trabectedin lines were 3.5 (2.8-4.2) and 3.4 (2.8-4) months respectively. FAS positive entailed significantly better PFS for the previous trabectedin line: 4.1 (1.5-6.7) vs 3.0 (2.5-3.5) months, p=0.01 whereas FAS positive was related with worse PFS for the trabectedin line 2.5 (2.2-2.8) vs 3.7 (2.7-4.8) months, p= 0.028. These results were more notorious for L-sarcoma cases: 7.0 (3.6-10.5) vs 4.3 (1.9-6.6) months, p=0.017 in previous line and 2.4 (2.2-2.6) vs 6.5 (3.8-9.3) months, p < 0.001 in trabectedin. From trabectedin administration, FAS positive cases had significantly worse OS especially in L-sarcomas: 11.9 (5.2-18.7) vs 21.7 (12.7-30.8) months, p= 0.002.

Conclusion: FAS showed to be a predictive biomarker for PFS and OS, for trabectedin administration in ASTS. The different prognostic role of FAS across distinct lines and its relevance in L-sarcomas deserve further attention. Analysis of prognostic role of other biomarkers is ongoing.

Poster 137 #2804678

CELL CYCLE DYSREGULATION IN EPITHELIOID HEMANGIOENDOTHELIOMA

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Objective: Epithelioid hemangioendothelioma is a rare, primitive sarcoma with endothelial differentiation. It is characterized by WWTR1(TAZ)-CAMTA1 gene fusion, which is found in over 95% of cases and is thought to be the initial oncogenic event in these tumors. However, little is known about mutations that collaborate with WWTR1-(TAZ)-CAMTA1 gene fusion to drive tumor progression. The major objective of this study was to determine other mutations that collaborate with WWTR1(TAZ)-CAMTA1 to contribute to EHE tumor progression.

Methods: Genomic alterations were identified using Foundation Medicine's FoundationOne genomic platform, which uses DNA capture-based next generation sequencing to determine the entire coding sequence of 315 cancer related genes and the introns of 28 genes that are often rearranged or altered in cancer. Mutations are scored as known somatic, likely somatic, or variant of unknown significance. Only mutations scored as known somatic or likely somatic were retained for analysis. 30 cases were tested in total using a representative formalin-fixed paraffin embedded tumor block in each case.

Results: All EHE tumors harbored WWTR1(TAZ)-CAMTA1 fusions, which was the only genetic finding in 14 cases. The other 16 cases had from 1 to 4 additional mutations each (1 mutation = 8 cases; 2 mutations = 6 cases; 3 mutations = 1 case; 4 mutations = 1 case). Recurrent mutations were found in CDKN2A (4 cases), CDKN2B (2 cases), RB1 (2 cases), and APC (2 cases). CDKN2A and CDKN2A were both deleted in two cases. Mutations identified only once were: MSH3, PIK3CA, FANCA, LRRK2, ATRX, CCT6B, KDM5C, POT1, SMARCA4, MUTYH, EPHB1, BRCA1, MLH1, DDX3X, KEAP1, NOD1, and MAP3K1.

Conclusion: EHE has a quiet genome with relatively few genetic alterations in addition to WWTR1(TAZ)-CAMTA1. The finding of 14 (of 30) cases with only WWTR1(TAZ)-CAMTA1 fusion emphasizes that this gene fusion is the initial genetic event in EHE tumorigenesis. Secondary mutations are enriched for cell cycle genes encoding tumor suppressors (CDKN2A/B, RB1, APC, ATRX), suggesting that loss of cell cycle checkpoints is involved in tumor progression in EHE. Further studies are underway to correlate loss of tumor suppressor/cell cycle checkpoint genes with clinical behavior in EHE.

Poster 138 #2759227

COMPLEX REARRANGEMENT OF PDGFRB ASSOCIATED WITH MULTI-FOCAL INFANTILE MYOFIBROMATOSIS

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Objective: Infantile myofibromatosis (IM) is a rare condition in which there is growth of uni- or multi-focal myofibromas in the skin, muscle, soft tissue, bone, and viscera of infants. Children with visceral involvement have a poor prognosis. Germline activating point mutations of PDGFRB have been described in familial IM. Here we describe a novel complex rearrangement of PDGFRB that disrupts the juxtamembrane domain and is associated with IM.

Methods: A newborn girl presented with innumerable subcutaneous nodules, confirmed to be IM by biopsy. Staging MRI of the abdomen demonstrated innumerable enhancing masses throughout the osseous and muscular tissues of the abdomen and pelvis with additional foci involving the pancreatic head and adjacent to the superior mesenteric artery. A clinical next generation sequencing test (FoundationOne Heme®) of tumor DNA and RNA ex-

tracted from FFPE tissue revealed a novel PDGFRB rearrangement. Sanger sequencing of tumor DNA and RNA confirmed this alteration. Functional studies in PDGFRB null mouse embryonic fibroblasts (MEFs) expressing this mutation, WT PDGFRB, and an empty vector control, and response to PDGFRB inhibitors are ongoing and will be presented.

Results: A clinical next generation tumor sequencing test demonstrated a complex insertion/deletion within PDGFRB (Figure 1). RNA sequencing confirmed high expression of PDGFRB in tumor. Further characterization of this alteration by Sanger sequencing revealed a complex rearrangement in which 73 nucleotides of exon 12 of the PDGFRB transcript are replaced by 136 nucleotides of PDGFRB exon 15. This results in a PDGFRB protein in which 25 amino acids of the auto-inhibitory juxtamembrane domain are replaced by 46 amino acids generated by reading exon 15 of PDGFRB out of frame (Figure 1). Subsequently, the sequence reverts to the wild type reading frame of PDGFRB, including the kinase domain. Notably, this alteration eliminates the juxtamembrane arginine residue at position 561 which has been reported to form a salt bridge that tethers the auto-inhibitory juxtamembrane domain to the kinase domain of PDGFRB. Functional characterization of this alteration is ongoing and will be presented.

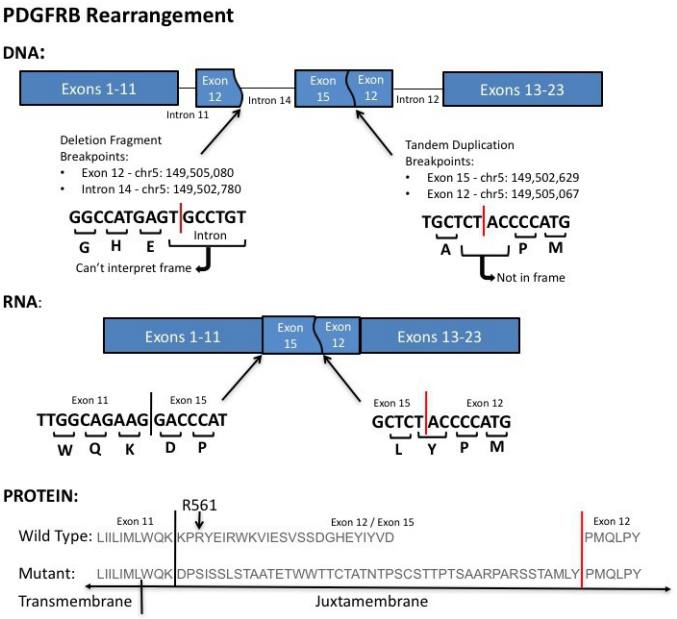

Figure 1: Complex rearrangement of PDGFRB identified in an infant with multi-focal infantile myofibromatosis.

Conclusion: A novel internal tandem duplication in PDGFRB is associated with IM. Rearrangement of the juxtamembrane domain may be a novel mechanism of activation of PDGFRB.

Poster 139 #2791162

A 22-YEAR EVALUATION OF MUSCULOSKELETAL ONCOLOGY IN-OFFICE CORE NEEDLE BIOPSY ERROR RATES FOLLOWING CONSULTATION WITH MUSCULOSKELETAL TRAINED PATHOLOGISTS VERSUS COMMUNITY PATHOLOGISTS

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Objective: In-office core needle biopsies are a time and cost-effective method for diagnosing a musculoskeletal tumor. The diagnostic accuracy of a biopsy is multifactorial. This study investigates if there is a difference in the diagnostic accuracy of a core needle biopsy based on a pathologist's sub-specialization. We hypothesize that biopsies read by a non-musculoskeletal trained pathologist will generate more errors than those specimens that are read by a fellowship trained musculoskeletal pathologist.

Methods: IRB approval was obtained for a prospective study evaluating musculoskeletal tumor in-office biopsies performed by a fellowship trained orthopedic oncologist. Between November 1995-April 2015 (Group 1) biopsies were performed at an academic institution with musculoskeletal pathologists as consultants. From May 2015-April 2017 (Group 2) biopsies were performed at a community hospital with non-musculoskeletal pathologists as the consultants. In Group 2 a musculoskeletal pathologist was consulted as a second reader of the pathology in some cases, as deemed necessary by the primary surgeon or primary pathologist. The collected data was then retrospectively reviewed.

Results: 1203 in-office core needle biopsies were performed. 161 patients were excluded. 907 patients were in Group 1 and 134 in Group 2. There were a total of 66 errors (6%) made in the initial diagnosis, 46 (5%) in Group 1 and 26 (19%) in Group 2. Biopsies were deemed nondiagnostic in 2.8% of patients.

Number of Errors and Classification Change

Error Made	Group 1	Group 2
Malignant to Benign	0	1
Benign to Benign	19	11
Benign to Malignant	19	7
Malignant to Malignant	2	7

Conclusion: In-office core needle biopsies provide diagnostic results with a low rate of error. This is the first study, to our knowledge, to look at the diagnostic accuracy of a core needle biopsy specimen based on the sub-specialization of the reading pathologist. Adequate tissue sampling was achieved in 97% of biopsies over 22-years with an error rate of only 6%. Despite this, a clear difference in error rates is evident based on the consultation of a musculoskeletal trained versus community trained pathol-

ogist, nearly quadrupling from 5% to 19% when a specimen was initially read by a community trained pathologist alone. The results indicate that there is less error when specimens are reviewed at a specialized institution by musculoskeletal trained pathologists.

Poster 140 #2804352

DIAGNOSTIC VALUE OF THE DETECTION OF USP6 GENE REARRANGEMENT BY FISH IN CYSTIC GIANT CELL LESIONS OF BONE IN DAILY PRACTICE. THE EXPERIENCE OF A SINGLE INSTITUTION OF THE FRENCH BONE TUMOR NETWORK RESOS

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Objective: Cystic Giant Cell Lesions of Bone (CGCLB) encompassed several benign and malignant tumors with specific treatment. Among them Aneurysmal Cyst (AC) is a benign but destructive expansile neoplasm due to recurrent translocations involving the USP6 gene. We wanted to evaluate the diagnostic value of the detection of USP6 gene rearrangement by FISH in daily practice.

Methods: We searched for USP6 rearrangement by FISH with a break apart probe in 70 paraffin-embedded consecutive biopsies (54 surgical and 16 microbiopsies) of CGCLB from 2010 to 2016.

Results: FISH was interpretable in 90% of cases. 88% of AC showed a USP6 rearrangement. None of the 15 Giant cell tumors with secondary aneurysmal changes has a USP6 rearrangement. For 4 lesions USP6 rearrangement was essential for the diagnosis. They encompassed : one bone cyst initially thought to be a unicameral bone cyst with aneurysmal changes, a giant cell lesion of small bone, a soft tissue tumor and a bone tumor for which the first diagnosis was Giant Cell Tumor on microbiopsy.

Conclusion: The search for USP6 gene rearrangement by FISH is an ancillary technique which can be used to enhance accurancy of the diagnosis of Cystic Giant Cell Lesions of Bone especially in small biopsy.

Poster 141 #2804718

CSF1 OVER-EXPRESSION AND CSF1 SPLIT DO NOT PREDICT CLINICAL OUTCOME IN TENOSYNOVIAL GIANT CELL TUMOURS

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Objective: Both localized- and diffuse- Tenosynovial Giant Cell Tumours (TGCT) are considered neoplastic. Genetic changes leading to over-expression of Colony Stimulating Factor1 (CSF1) are thought to be the driver mechanisms resulting in an admixture of neoplastic and reactive cells coined as landscape effect. Both localized- and diffuse-TGCT have identical CSF1 alterations in approximately 60-70% of the cases. The influence of these CSF1 alterations on clinical presentation and surgical outcome is unknown. In this study, we correlated CSF1 expression patterns with TGCT tumour characteristics and clinical outcome (recurrence).

Methods: 25 Carefully selected therapy naïve knee TGCT patients, >2 years follow-up, were included (median age 44 (IQR 26-61) years, 56% female) and 5 TGCT-look alike patients (synovitis of other cause) as a negative control. TGCT-type was defined, according to WHO-standard, on clinical and radiological imaging, and blinded for researchers. HE stained slides were used to establish histological diagnosis and slide selection. Using digital correlative microscopy, CSF1 RNA In Situ Hybridization, CSF1 split-apart Fluorescence In Situ Hybridization (FISH) probes were evaluated on selected slides. For CSF1 split-apart FISH scoring, 3 regions expressing CSF1 mRNA were selected from each sample. A cutoff of >2/100 cells was defined as CSF1 split positive. Results were correlated with TGCT-type and recurrence after median follow-up of 51 (IQR 40-60) months. Recurrent disease was detected in 2/9 and 9/16 in localized and diffuse cases, respectively.

Results: CSF1-gene rearrangement was detected in 76% of TGCT cases (78% localized and 75% diffuse). Irrespective of the clinical type, all TGCT cases (both types) showed CSF1 upregulation with the presence of characteristic landscape effect (Table, Figure). 3/5 negative control cases also showed CSF1 upregulation, but without the typical CSF1 gene rearrangement. There was no difference observed between clinical subtypes of the samples. CSF1 expression was located interstitial in both localized- and diffuse-type.

Table Proportion of cases with CSF1 mRNA expression of CSF1 split signal

	N	CSF1 mRNA in situ	CSF1 split
Localized	9	Interstitial (9/9) (100%)	7/9 (78%)
Diffuse no recurrence	7	Interstitial (7/7) (100%)	6/7 (86%)
Diffuse recurrence	9	Interstitial (9/9) (100%)	6/9 (67%)
Negative control	5	Interstitial and synovial lining (3/5) (60%)	0/5 (0%)

Figure Overview of Haematoxylin & Eosin, CSF1 RNA ISH and CSF1 split-apart FISH results of two TGCT cases.

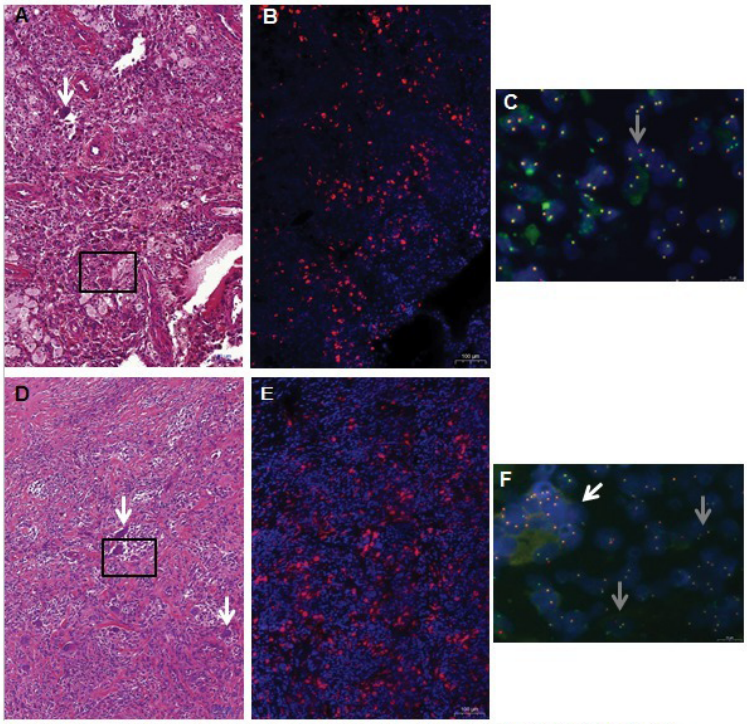

Figure A-C: A 43 year-old male patient with localized-TGCT, treated with open synovectomy, without recurrence, after 4.5 years follow-up.
Figure D-F: A 43 year old female patient suffering diffuse-TGCT, with MRI proven recurrent disease and progressive clinical complaints, after almost 5 years follow-up. Currently, wait and see treatment for recurrent disease.

Using correlative digital microscopy, different slides were aligned between the different experiments. (*A*,*D*) HE staining showing the presence of synovial-like cells, a variable number of giant cells (white arrow), foam macrophages and siderophages. (*B*,*E*) CSF1 mRNA ISH of the same region showing cells with CSF1 expression in red and outnumbering proportion of negative cells indicated by the blue nuclei after DAPI staining. The intermingled pattern of CSF1 high expressing cells with several non-CSF1 expressing cells represents the landscape effect. The regions correspond to the region in panel *A* or *D*, respectively. (*C*,*F*) CSF1 split-apart FISH; red = centromeric to CSF1, green = telomeric probe. Yellow signal represent co-localisation of the signal meaning no rearrangement, upon chromosomal rearrangements of the CSF1 region the red and green signal separate (grey arrow heads). A giant cell is indicated by white arrow head. The squared boxes in panel *A* and *D* represent the area used for the FISH in panel *C* or *F*, respectively.

No difference was observed between the absolute number of CSF1 mRNA expressing cells nor in their distribution pattern. Both show a similar landscape effect, that makes a relative estimation of a percentage of upregulated cells unreliable. Finally, CSF1 split was detected in majority of cases in both localized- and diffuse-TGCT. No predominant enrichments for translocation negative cases in any of these subtypes was detected.

Conclusion: Analysis of CSF1 expression pattern using mRNA ISH and locus specific FISH to identify tumor cells in localized- and diffuse-TGCT could not clarify the difference in clinical presentation nor predict disease progression. Since over-expression of CSF1 was also observed in non-TGCT lesions, only the combination of CSF1 RNA ISH and CSF1 split-apart probe, to identify CSF1-gene rearrangement, may support diagnosis.

Poster 142 #2804895

THE EVOLUTION OF THE TRANSCRIPTIONAL PROFILES IN PRIMARY AND METASTATIC OSTEOSARCOMA AS COMPARED TO THEIR NORMAL SURROUNDING TISSUES

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Objective: Osteosarcoma is the most common primary bone tumor in adolescents. The molecular tumorigenesis is unknown. Metastasis is associated with poor outcome in patients with osteosarcoma. The underlying mechanism of disease progress is a focus of research.

Methods: We collected fresh-frozen specimens in triplet from 13 osteosarcoma patients treated at Memorial Sloan-Kettering Cancer Center, including their primary tumors, metastatic lesions, and respective surrounding normal tissues. The transcriptional profile was measured using Affymetrix microarrays with the Transcriptome Analysis Console Software. The evolution of transcriptional pattern was established using k-mean algorithms.

Results: Enough messenger RNA for Microarray assay was obtained from 29 specimens including 6 normal tissues, 13 primary tumors, and 10 metastatic lesions. Their gene expression value followed a normal distribution as expected except one sample. The hierarchical cluster analysis showed most of the primary osteosarcoma specimens stayed in one branch and most of the metastatic tumor were in another branch. K-mean clustering identified 5 evolution patterns of the transcriptional profiles in normal, primary, and metastatic osteosarcoma specimens. More than 1500 genes were found to be significantly differentially expressed among them as showed in the heatmap.

Conclusion: The evolution of transcriptional profile revealed in this unique cohort of osteosarcoma specimen may shed light on genes and pathways involved in tumorigenesis and progression of this disease.

Poster 143 #2783036

INCIDENCE OF SUICIDE IN PATIENTS WITH CHONDROSARCOMA, OSTEOSARCOMA, AND EWING SARCOMA

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Objective: Recent studies have demonstrated increased suicide rates among patients with cancer. To our knowledge, large cohort studies examining suicide rates among patients diagnosed with primary malignancies of the bone such as chondrosarcoma, osteosarcoma, and Ewing sarcoma have not been performed. Several factors, including but not limited to the psychosocial and psychosomatic effects of advanced pain, illness, organic mental syndromes, and preexisting psychopathological abnormalities have been identified to confer a vulnerability to suicide. Using the SEER databas, the objectives of this study are to identify incidence rate, trends, and risk factors of suicide in patients with these malignant cancers.

Methods: The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database was used to search for patients diagnosed with chondrosarcoma, osteosarcoma, and Ewing sarcoma between 1973 and 2014. In total, 15,401 cases of patients with chondrosarcoma (6032), osteosarcoma (6365), and Ewing sarcoma (3004) were identified. Patient demographics, tumor characteristics, incidence, and survival trends were all analyzed to determine which variables increased the risk of suicide.

Results: Among the 15,401 SEER registry patients diagnosed with chondrosarcoma, osteosarcoma, and Ewing sarcoma observed for 704,490 person years, 37 suicides were identified with a rate of 257 per 100,000 person-years. In contrast, the US general population suicide rate was 11.8 per 100,000 person-years. Suicide rates were higher in those who were single widowed Caucasian males ($p<0.05$). Chondrosarcoma had the highest rate of suicide patients with 0.28% and Ewing sarcoma had the lowest rate with 0.10%. Cox regression analysis demonstrated that patients with chondrosarcoma were more likely to commit suicide and had shorter survival times when compared to patients with Ewing sarcoma ($p<0.05$).

Conclusion: Patients diagnosed with chondrosarcoma, osteosarcoma, and Ewing sarcoma have more than 20 times the incidence of suicide compared with the general US population. This study demonstrated single and widowed white males were highest among those with these tumors to commit suicide, similar to the general population. In addition, patients with chondrosarcoma have the highest rate of suicide. Additional research and effort should also be devoted to the psychological toll that the cancer, treatments, and resulting morbidity have on patient. Indication for early course involvement of palliative and supportive care.

Table 1: Demographic, clinical and tumor data.

Variable		Chondrosarcoma (N=6032)	Osteosarcoma (N=6365)	Ewing Sarcoma (N=3004)
Clinical Variables				
Median Age (years)		62.4	34.1	24.2
Gender				
	Males	3364 (55.8 %)	3460 (54.4 %)	1808 (60.2 %)
	Females	2668 (44.2 %)	2905 (45.6 %)	1196 (39.8 %)
	M:F	1.26:1	1.19:1	
Race				
	Caucasian	5226 (86.6 %)	4867 (91.0 %)	2688 (89.5 %)
	African American	433 (7.2 %)	911 (3.6 %)	102 (3.4 %)
	Asian	316 (5.2 %)	548 (5.0 %)	202 (6.7 %)
	Other	57 (1.0 %)	39 (0.5 %)	12 (0.4 %)
Anatomical Site				
	Bone	4868 (80.7 %)	5945 (93.4 %)	2325 (77.4 %)
	Soft Tissue	744 (12.3 %)	252 (4.0 %)	522 (17.4 %)
	Skull	121 (2.0 %)	39 (0.6 %)	30 (1.0 %)
	Other	299 (5.0 %)	129 (2.0 %)	127 (4.2 %)
Tumor Data				
	Average Size (cm)	8.5	9.7	8.9
Background Tumor Grade				
	Grade I	1819 (30.2 %)	240 (3.8 %)	9 (0.3 %)
	Grade II	1966 (32.6 %)	350 (5.5 %)	15 (0.5 %)
	Grade III	946 (15.6 %)	3343 (52.5 %)	683 (22.7 %)
	N/A	1301 (21.6 %)	2432 (38.20 %)	2297 (76.5 %)
Metastasis (at presentation)		250 (4.1 %)	572 (9.0 %)	448 (14.9 %)

Table 1: Demographic, clinical and tumor data.

Table 2: Overall survival, median survival, and incidence.

Variable	Sample Size (N)	Overall Survival (Months)	Median Survival (Months)	Incidence (per 100,000)
Chondrosarcoma	6032	96.5	66	0.31
Osteosarcoma	6365	81.8	37	0.32
Ewing sarcoma	3004	79.2	39	0.17

Table 2: Overall survival, median survival and incidence.

Poster 144 #2762131

DEMOGRAPHICS, STAGE DISTRIBUTION AND SURVIVAL OF PRIMARY PROSTATE SARCOMAS

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Objective: To evaluate demographic info, stage distribution, and disease-specific (DSS) and overall survival (OS) for children (age 0-25 years) versus adults (>25 years) diagnosed with prostate sarcoma (PPS)

Methods: The SEER database was queried for subjects diagnosed with a PPS between the years 1973 to 2014. DSS and OS was estimated by Kaplan-Meier analysis. Survival comparisons for surgically managed versus surgery + radiation therapy (RT) subjects were compared with a log-rank test.

Results: Of 1,165,297 persons diagnosed with primary prostate cancer in the United States over this study period, 288 were identified as having sarcoma (incidence 0.025%). 29% of subjects were under age 26 at diagnosis, and 33% of PPS' are rhabdomysarcoma histology.

Rhabdo histologies: The mean age at diagnosis is 12.7 years. Between age 0-25 years rhabdo accounted for

98% of PPS diagnoses (76% embryonal, 13% alveolar, 9% not otherwise specified); after age 25 rhabdo was only 7% of new diagnoses. Localized, regional, or distant disease occurred in 19%, 26% and 55% of cases. The 10-year DSS and OS for rhabdo was 79% and 44%.

Non-Rhabdo histologies: The mean age at diagnosis is 68.3 years. The most common diagnoses were leiomyosarcoma (32%) and carcinosarcoma (27%), with no other sarcoma histology exceeding 10% of cases. Localized, regional, or distant disease occurred in 40%, 34%, and 25% of cases. The 10-year DSS and OS was 36% and 12%. For localized cases, adding RT to surgery did not result in improvement in DSS or OS. For regional cases, RT added to surgery appears to improve DSS (median survival not reached vs 23 months for surgery) and OS (median survival 39 months for the combination vs 22 months for surgery), but was not statistically significant.

Conclusion: Rhabdo is the almost exclusive diagnosis in persons age 0-25, and non-rhabdo histologies are most prevalent in those over age 25. The addition of RT to surgical resection may improve DSS and OS in regional non-rhabdo, but there is not enough power in this study to detect statistical differences. DSS and OS for non-rhabdo histologies is inferior to those of rhabdo. Limitations include inability to control for known-prognostic variables such as IRS surgical-pathologic grouping of rhabdo cases, use of chemotherapy, and doses of RT used. Despite these limitations, this is the largest reported series of the incidence, stage distribution, and survival for this extremely rare urologic malignancy, and is useful to inform patients about prognosis.

Poster 145 #2785489

THE BIOLOGY OF OSTEOSARCOMA (BOOST) REGISTRY AND BIOBANK

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Objective: Osteosarcoma (OS) affects approximately 800 people per year in the United States, with about half under 20 years of age, thus it is difficult to aggregate patients for epidemiologic research. For instance, the Children's Oncology Group registers only about half of pediatric OS patients in a given year. In order to expand the opportunity for OS patients to take part in etiologic research we established the online Biology of Osteosarcoma (BOOST) Registry and Biobank, hosted at osteosarcoma.umn.edu, in February, 2017, which is open to patients diagnosed at any age; first-degree relatives may also register deceased patients. Here we describe the initial experience of recruitment and data collection.

Methods: The BOOST study website went live on 1/3/2017, was advertised on patient-oriented social media starting 1/14/2017 and presented at an osteosarcoma patient meeting on 2/24/2017. Participants are sent a DNA collection kit, answer an online questionnaire, and may release medical records.

Results: Through 5/11/17 there were 127 probands who completed enrollment online. 112 registered themselves while 15 deceased probands were registered by a first-degree relative. 110 reside in the United States, 7 in Canada, 4 in the England/United Kingdom, 2 in Australia, and 1 in each of the following Brazil, South Africa, Bermuda and Italy. Mean age at diagnosis was 19.6 years [standard deviation (SD) = 15.9] and the median year of diagnosis was 2013. Females comprised 72 (59.5%) of probands. Tumors were located in the long bones of the lower legs in 91 (77.8%), arms in 9 (7.7%), trunk in 9 (7.7%), and elsewhere in 8 (6.8%). 25 (20.8%) of probands reported the presence of metastatic disease at diagnosis. Of 112 living probands who were sent DNA collection kits, 66 (58.4%) have already returned them with a mean time to return of 27 days (SD = 37.2).

Conclusion: We have demonstrated that a substantial number of osteosarcoma patients will participate in an online registry and biobank. Patients' clinical characteristics reflect that in unselected populations, with about 3/4 tumors located in the long bones of the lower legs and with 20% having presented with distant disease. However, whereas a slight majority of osteosarcoma patients are male, nearly 60% of our participants are female. In order to improve accrual, and to recruit males in proportion to disease occurrence, we will initiate advertising on social media, internet search results, and to physicians specializing in the treatment of osteosarcoma. Updated accrual numbers and patient characteristics in BOOST will be presented at the CTOS meeting.

Poster 146 #2804803

VENOUS THROMBOEMBOLIC EVENTS (VTE) IN SARCOMA PATIENTS: RETROSPECTIVE ANALYSIS OF AN INSTITUTIONAL DATABASE

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Objective: Venous thromboembolic events (VTE) are a well-known complication of cancers, most notably adenocarcinomas and hematological malignancies. Sarcomas are usually not considered thrombophilic, but little has been published on the incidence and risk factors of VTE in sarcoma patients. The purpose of this study was to report the prevalence of clinically detected, symptomatic VTE in bone and soft tissue sarcoma (STS) patients and to identify risk factors associated with VTE.

Methods: A total of 995 consecutive sarcoma patients from an institutional database (2002 to 2015) were reviewed. A matched case-control study (1:4) was created:

76 VTE cases were matched with 304 controls based on age and tumour type. The following information was gathered: demographics; diagnosis of thromboembolism by Doppler ultrasound or dedicated computed tomography; sarcoma subtype; disease stage; presence of vessel compression, existence of predisposing factors (postoperative setting, central venous catheter placement). Chi-squared and student's t-test were used to compare groups while risk factor identification was done using uni and multivariable logistic regression models.

Results: 76 patients (62 M, 24 F), aged 16-88 years, had at least one VTE, resulting in a prevalence of 7.9% in sarcoma patients and an overall event rate was 9.5%. The most common subtypes of sarcomas associated with VTE were: liposarcoma (15), undifferentiated pleomorphic sarcoma (13), osteosarcoma (11), leiomyosarcoma (11), synovial sarcoma (8), Ewing sarcoma (5). We found that patients with metastatic disease (OR=6.43; 2.55-16.21, p<0.001) had higher odds of developing a VTE while tumor grade and anatomic location were not apparent risk factors. When looking at treatment modalities, patients who had either chemotherapy (OR=9.15; 5.02-16.67, p<0.001) or surgery (OR=2.35; 1.24-4.47; p=0.01) had increase odds of developing a VTE.

Conclusion: This study is the largest series of VTE in bone and soft tissue sarcoma and it demonstrated that thromboembolic events are infrequent in sarcoma patients and are associated with aggressive disease behavior as well as medical interventions. Future analysis will include timing of events to better understand the at-risk period.

Poster 147 #2799422

VOLUME-OUTCOME RELATIONSHIP IN SARCOMA TREATMENT

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Objective: Multidisciplinary treatment is desirable in the care of sarcomas because sarcomas comprise of many kinds of histology and can occur in connective tissue of all parts of the body. However, there are no strict guidelines for referrals of sarcoma patients in Japan, and sarcoma care is not centralized to high-volume centers. The objective of this study is to examine a relationship between patient survival and the number of patients who received treatment in that hospital per year.

Methods: We used hospital-based cancer registry data of sarcoma patients diagnosed in Japan in 2007. We analyzed a relationship between survival time and the volume of the hospital using cox proportional hazard regression model. Survival time was defined as the time from the diagnosis to the death. The hospitals were categorized into 3 groups; high-volume: more than 20 new sarcoma patients per year; middle-volume: 10 to 20 patients per year; and low-volume: less than 10 patients per year.

Results: We identified 2522 sarcoma patients who were newly diagnosed in 2007. Median age was 58 yr and Less than half (47.4%) was male. Cox proportional hazard regression analysis adjusting for age and sex revealed that survival rate was statistically higher among patients treated at middle- and high-volume hospitals than at low-volume hospital (hazard ratio (HR) of death was 0.74 (95%CI 0.62-0.88) for middle and 0.72 (95%CI 0.63-0.82) for high-volume hospitals). Analysis adjusted for age, sex and stage also revealed that survival rate in the middle- and high-volume hospitals was higher than low-volume hospitals (HR 0.76, 95%CI 0.63-0.90 for middle-volume; HR 0.70, 95%CI 0.61-0.80 for high-volume).

Conclusion: Survival rate of sarcoma patients who received treatment in middle- or high-volume hospitals was higher than patients who received treatment in low-volume hospitals. Our data suggest that volume-outcome effects likely exist in sarcoma treatment. Further analyses that adjust for other potential confounders, such as comorbidity, is necessary.

Poster 148 #2803774

ASSOCIATION BETWEEN SARCOMA DEVELOPMENT AND RADON EXPOSURE IN CONNECTICUT

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Objective: Radon is a radioactive gas found naturally in the environment with known carcinogenic effects including a well-documented association with lung cancer and proposed association with pediatric leukemia. Radon is readily tested and is often included in routine home inspections as part of the home buying process. An association with pediatric sarcoma has not been evaluated. The objectives of the study include: 1) to establish if there is an increased incidence of pediatric sarcomas in regions of Connecticut and 2) to determine whether there is an association between domestic radon levels and the presence of sarcoma in pediatric patients living in Connecticut.

Methods: A retrospective case review was performed to identify all cases of pediatric sarcomas in patients between 1-19 years of age diagnosed at Connecticut Children's Medical Center (CCMC) between 2005 and 2015. The incidence in CT was compared to the national incidence using a two proportions z-test. The geographic dis-

tribution of cases was used to identify target townships in Connecticut for radon testing. An activated charcoal radon detector was placed in the homes of the study group and a control group between Jan 2017-Feb 2017 and radon levels were measured. Radon levels were compared between sarcoma and non-sarcoma households using a T-test.

Results: Seventy-three patients meeting the inclusion criteria were diagnosed with bone and soft tissue sarcoma at CCMC during the study assessment timeframe. This represents about 1/3 of pediatric sarcoma cases in CT during that time. There were 37 pediatric sarcoma cases in Hartford county, yielding an incidence of 1.65 per 100,000. There were10 pediatric sarcoma cases in towns of the Farmington Valley, yielding an incidence of 4.03 per 100,000, which is elevated compared to the overall incidence in CT of 2.51 per 100,000. This is significant with a z score of 2.12 (p[=-.033). This is also elevated when compared to the national incidence of 2.08 per 100,000 according to SEER stat data. Radon levels were tested in 13 study homes and 15 control homes. The average radon level was 1.08 pCi/L in sarcoma households and 1.88 pCi/L in non-sarcoma households, which was not clinically significant (P=.062).

Conclusion: While there does appear to be an increased incidence of pediatric sarcomas in the Farmington Valley compared to other regions of CT and the nation, there does not appear to be an association between domestic radon levels and the presence of sarcoma in pediatric patients.

Poster 149 #2804741

OCCUPATIONAL INJURIES AMONG ORTHOPEDIC ONCOLOGY SURGEONS

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Objective: Orthopaedic oncology is a surgical subspecialty that is physically and mentally demanding as it can involve prolonged and complex surgical procedures, as well as a significant rate of surgical complications and poor oncologic outcomes related to the patient population. These physical and psychological stressors may place the surgeons at a higher risk for work-related "occupational" injuries that can impact their practice and the delivery of care. The purpose of this study was to assess the prevalence and characteristics of occupational injuries among orthopaedic oncology surgeons.

Methods: A modified version of the physical discomfort web-based survey was developed to assess occupational injury among orthopaedic oncology surgeon members of the Musculoskeletal Tumor Society (MSTS), the Canadian (CANOOS) and European Musculoskeletal Oncology Societies (EMSOS). The cross-sectional survey queried musculoskeletal complaints by region, psychological disturbances, as well as treatment and required time off work. Sixty-seven surgeons responded.

Results: The overall prevalence of occupational injury among orthopedic oncologists was 84% (musculoskeletal 76%; psychological 50%; and both 43%). The most prevalent musculoskeletal diagnoses were low back pain (39%), lumbar disk herniation (16%), tendinitis (15%), lateral epicondylitis (13%) osteoarthritis and varicose vein (10% each). Overall, 46% required surgery and 31% required time off work. Psychological disorders were reported by 33 respondents overall; the most prevalent were burnout (27%), anxiety and insomnia (20% each) and depression (11%). Factors associated with time off work were age, and years in practice and factors associated with psychological were subspecialty in spine and percentage in research however, none were significant in logistic regression models.

Proportion of Orthopaedic Oncologists Surgeons with diagnosed musculoskeletal disorders per region requiring treatment and time off work

Region	Proportion of injured respondents (%)	Proportion of injured respondents requiring treatment (%)	Proportion of injured respondents requiring surgery (%)	Proportion of treated respondents requiring time off work (%)
Neck	24	56	6	13
Shoulder	27	72	22	22
Elbow	13	67	0	0
Forearm, wrist, and hand	39	62	23	23
Hip and thigh	7	80	20	17
Knee and lower leg	13	56	56	40
Ankle / foot	7	100	20	40
Lower back	55	51	8	24

Conclusion: Orthopaedic oncologists report a high prevalence of occupational injury, both musculoskeletal and psychological. Low back injury and burnout are the most commonly reported work-related disorders. Strategies optimizing the operative environment and preventative measures for work-related stress should be the focus of future initiatives.

Poster 150 #2804652

FACTORS ASSOCIATED WITH RECURRENT GIANT CELL TUMORS OF THE UPPER EXTREMITY

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Objective: The purpose of this investigation was to establish the recurrence rate of giant cell tumors of bone of the upper extremity and compare it to the rates published in literature in the same and different locations. The second objective, was to identify potential modifiable and non-modifiable predictors of recurrence specifically for giant cell tumors of bone of the upper extremity.

Methods: We retrospectively reviewed 92 patients with a primary giant cell tumor (GCT) of the upper extremity above the age of 18 years treated at one of our five urban hospitals from 1971 to 2015. All GCT's were histologically confirmed. Factors evaluated included demographics, tumor location, tumor size, clinical presentation, treatment modality, recurrence rate, metastasis rate and the radiographic classification according to the Enneking and Campanacci classification systems among other variables. A bivariate analysis was performed to identify factors associated with recurrence. Variables with a p-value <0.10 were then include in a multivariable logistic regression models to identify factors independently associated with recurrent GCT.

Results: The local recurrence rate of GCT's was 39.3%, over a mean follow-up of 68.7±51.1 months. Three quarters of the recurrences occurred within 37 months after initial diagnosis. This was similar when compared to the recurrence rate in the reported literature, up to 58%. The most common location for a GCT was the radius (48.8%), followed by the humerus (18.6%), the ulna (18.6%), metacarpal bone (9.3%) and phalangeal bone (4.7%). Giant cell tumors of the radius showed a significantly higher recurrence of 57.1% compared to all other locations combined 25.0% (p= 0.031) (Table 1). Intralesional curettage was performed most frequently (74.4%), followed by resection (23.3%) and amputation (2.3%). In bivariate analysis, resection or amputation had a significantly lower recurrence than in patients treated with intralesional curettage (9.1% v. 50.0%, p= 0.029) (Table 2). However, tumor location and surgery type were not independent predictors of recurrence in multivariable logistic regression analysis. There was a positive correlation between treatment with intralesional curettage and recurrence of GCT of the distal radius (r=0.25). (Table 3)

Conclusion: We found a more aggressive biological behavior in GCT of bone of the distal radius when compared to other locations. This is characterized by higher recurrences rates. Our findings emphasize the importance of tumor resection with negative margins in the radius when possible in primary or recurrent disease. Resection with negative margins maybe more attainable with the use of combined preoperative therapy with pharmacologic agents such as Denosumab followed by reconstruction techniques with hemicortical or hemiosteoarticular allografts.

Table 1: Bivariate analysis

Variable	All patients (n=43)	Recurrence No (n=26)	Recurrence Yes (n=17)	P-value
Location, n (%)				**0.031**[1]
Radius	21 (48.8)	9 (42.9)	12 (57.1)	
Other locations	22 (51.2)	17 (77.3)	5 (22.7)	
Surgery, n (%)				**0.029**[1]
Intralesional curretage	32 (74.4)	16 (50.0)	16 (50.0)	
Resection or amputation	11 (25.6)	10 (90.9)	1 (9.1)	

[1] Logistic regression showed no independent significance

Table 2: Logistic regression Including Tumor Location and Surgery Type

Characteristic	Odds Ratio	Standard error	95% Confidence Interval	*P* Value
Location (reference: radius)	3.65	0.27	[0.91, 14.6]	0.0068
Surgery (reference: intralesional curettage)	0.13	0.14	[0.01, 1.2]	0.0068

Area under the receiver operating characteristic curve = 0.77
Pseudo R2, 0.18
P-value for Hosmer-Lemeshow test, 0.47

Poster 151 #2804239

WHAT FACTORS INFLUENCE PATIENT EXPERIENCE IN ORTHOPEDIC ONCOLOGY OUTPATIENT CLINIC VISITS? A PROSPECTIVE COLLECTION OF 162 PATIENT ENCOUNTERS

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Objective: Patient satisfaction and patient reported outcomes (PROs) are becoming increasingly important in determining the efficacy of clinical care. Press Ganey® Medical Practice Survey ("Press Ganey® survey") is a questionnaire used to evaluate patient satisfaction in the outpatient clinic setting. In this study, our group evaluated prospectively collected survey information to determine what factors contributed to patients' likelihood to recommend our practice as well as our providers.

Methods: Basic demographic data along with survey category responses were prospectively collected. Data was recorded electronically and obtained in accordance with the medical center's preexisting protocol. Frequency and percent were presented for all categorical variables as well as for outcome variables "MD Likelihood To Recommend" and "Likelihood Recommend Practice". Analysis of variance was applied continuous variables and Chi-square/Fisher's exact test was applied to assess between categorical variables. Firth logistic regression analyses were performed using Least Absolute Shrinkage and Selection Operator (LASSO) to identify predictive factors for each outcome of interest.

Results: 162 patient surveys were collected over a 2-year period of time and were included in the study. Response rate was 17%. Bivariate analysis identified out-of-state

residents were more likely to recommend the MD as well as the practice than in-state residents. Regression analysis identified that "likelihood to recommend practice" was positively associated with MD Confidence (OR=11.6), Sensitivity To Needs (OR=5.8), and Staff Work Together (OR=36). Regression analysis identified that "MD likelihood to recommend" was positively associated with MD Friendliness/Courtesy (OR=14.4), MD Confidence (OR=48.2), MD Instructions Follow up Care (OR=2.5), Sensitivity To Needs (OR=16.1).

Variable		odds ratio	95% confidence interval
Modeling MD Likelihood To Recommend			
MD Friendliness/Courtesy	Not completely satisfied vs	14.4	(2.5, 84.3)
MD Confidence	Completely satisfied	48.2	(6.2, 376.5)
MD Instructions Followup Care		2.5	(0.4, 17.4)
Sensitivity To Needs		16.6	(1, 262.5)
Modeling Likelihood Recommend Practice			
MD Confidence	Not completely satisfied vs	11.6	(2.1, 63.4)
Sensitivity To Needs	Completely satisfied	5.8	(1.3, 26.7)
Staff Work Together		36.1	(7.9, 165.1)

Variables with significant odds ratios associated with patient likelihood to recommend the practice and the physician.

Conclusion: In this study, evaluating patient responses to Press Ganey surveys identified that on bivariate analysis, out-of-state residents were more likely to be pleased with their care and recommend the doctor and practice. Regression analysis identified that doctor confidence, sensitivity to needs, staff working together, friendliness/courtesy and instructions for follow up care were all associated with the likelihood of the patient to recommend the doctor as well as the practice. Future studies may be directed at how to improve these areas of care which are most valued by the patient while still optimizing clinical care.

Poster 152 #2804273

SETTING UP AN IN-HOSPITAL CLINICAL CARE NETWORK FOR PATIENTS WITH NEUROFIBROMATOSIS TYPE-1

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Objective: Malignant peripheral nerve sheath tumors (MPNST) is commonly a high-grade sarcoma, which has chemo-resistant property, resulting in dismal prognosis despite a radical resection with or without radiotherapy. Given that not a few MPNST patients with neurofibromatosis type-1 (NF1) were not recognized until it's too late for adequate treatment. We, musculoskeletal oncologists, hypothesized that multidisciplinary approach to all of the NF1 patients and their relatives could improve the understanding of many faces of symptoms. Moreover, both patients and physicians could share the knowledge for possible clinical signs of MPNST development, leading to the early diagnosis of MPNST, and improvement of the prognosis. The aim of this study is to set up a multidisciplinary in-hospital clinical care network, and report the short-term outcome of this system.

Methods: At the beginning, an orthopaedic oncologist, a neurosurgeon, and a pediatrician agreed strongly on the need of NF1 care network, and tried to make an arrangement of other specialties including dermatology, plastic surgery, ophthalmology, genetic counseling, psychiatry and so on. Finally, in-hospital NF1 clinical care network was established, and a multidisciplinary care started from January, 2014. Age-dependent preventive medical care checklist was prepared according to the "Preventive Management of Children with Congenital Anomalies and Symptoms, Cambridge University Press, 2000".

Results: Pediatrics, Ophthalmology, Neurosurgery, Orthopaedic surgery, Psychiatry, Dermatology, Plastic surgery, and Genetic counseling essentially participated in the network. For a patient less than 15 years old, a pediatrician plays key roles of this network, and clinical examination by neurosurgeon, orthopaedic surgeon, and ophthalmologist is mandatory. Physicians of other specialty were consulted in case of the occurrence of related symptoms, such as mammalian cancer and thyroid tumor. Since January, 2014, total eight-two NF1 patients were enrolled in this care network. Mean age was 24 years ranging from 0 to 70. Forty-eight were female. Forty-three patients were with NF1 family history (52%). There were 8 patients (9.8%) with MPNST, and 23 patients (28%) with scoliosis. Although questionnaire surveillance was not performed, general reputation of this NF1 care network is favorable, particularly for parents of young NF1 patients.

Conclusion: Multidisciplinary NF1 care network has been established in our institution. Considering that NF1 patients have various symptoms in various organs including malignant neoplasms, this multidisciplinary approach may improve the patients' ADL and QOL in addition to the parents' feeling of relief.

Poster 153 #2776597

DESCRIPTIVE EPIDEMIOLOGY AND CLINICAL OUTCOMES OF BONE SARCOMAS IN ADOLESCENT AND YOUNG ADULT PATIENTS IN JAPAN

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Objective: There have been far fewer improvements in the clinical outcomes of adolescent and young adult (AYA) patients with cancer compared to children and older adults, possibly because fewer studies focus on patients in this age group. Sarcomas represent one of the most common types of cancer in AYA. However, there have been a few studies that focused on the clinical outcomes of AYAs with bone sarcoma or on nationwide statistics that included a sufficient number of patients. The aims of this study were to determine the nationwide incidence of bone sarcoma in AYA patients compared to other age groups and to establish whether a correlation exists between the AYA age group and poor disease-specific survival (DSS) in Japan.

Methods: A total of 3,457 patients with bone sarcoma (1,930 male and 1,527 female) were identified from among 63,931 records in the Bone and Soft Tissue Tumor (BSTT) registry, a nationwide Japanese database, during 2006–2013. Of these, 521 were patients aged ≤14 years (children), 1,123 were aged 15–39 years (AYAs), 982 were aged 40–64 years (adults), and 831 were aged ≥65 years (elderly). We analyzed the epidemiological features of AYAs compared to other age groups.

Results: AYA patients did not exhibit any extreme patterns in any of the investigated parameters compared to other age groups. On multivariate analysis, AYA patients with bone sarcomas overall did not exhibit worse DSS rates; however, the DSS correlated inversely with age. The same tendencies were observed for each of osteosarcoma, chondrosarcoma, and Ewing's sarcoma. Overall, the poor prognostic factors in patients with overall bone sarcoma were age >65 years (HR: 3.74; 95% confidence interval [CI]: 2.66–5.28; P < 0.001), high tumor grade (HR: 3.77; 95% CI: 1.93–7.37; P < 0.001), tumor size >16 cm (HR: 2.20; 95% CI: 1.52–3.19; P < 0.001), and positive surgical margins (HR: 1.78; 95% CI: 1.21–2.62; P = 0.004)

Conclusion: This study is the first to provide data on the descriptive epidemiology and clinical outcomes in AYA patients with bone sarcomas using a nationwide large-scale database. Our data demonstrated that DSS rates of AYA patients with bone sarcomas were not inferior to those of other age groups.

Poster 154 #2791848

PAIN AND NUMBNESS ARE RISK FACTOR FOR NONDETECTION OF SOFT TISSUE SARCOMA AT THE FIRST VISIT MEDICAL FACILITY

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Objective: The first step in the treatment of soft tissue sarcoma (STS) is detection of the tumor. But, some patients' lump was not found at 1st visit medical facility and it may be a cause of diagnostic and treatment delay. The aim of this study was to assess nondetection rate of STS at 1st visit medical facility and identify associated risk factors.

Methods: Prospectively collected data in our department were sourced to identify patients diagnosed with STS between 1 January 2008 and 30 November 2016. Patient and tumor factors were analyzed by using Chi-square test and t-test to assess the impacts of nondetection of STS at 1st visit medical facility for STS treatment, and using multinomial logistic regression to identify independent risk factors for nondetection of STS at 1st visit medical facility.

Results: This study included 108 patients (71 male and 37 female). The mean patient age was 58.7 years (range, 1-89). The mean tumor size was 8.2 cm (range, 2.0-30). Twenty-five sarcomas (23%) were low-grade, and 83 (77%) were high-grade. Forty-two (39%) were superficial, and 66 (61%) were deep.
Fourteen tumors (13%) were not detected at 1st visit medical facility. Their mean time to present to our institute from 1st medical facility visit was significantly longer than that of the patient whom tumors were detected at 1st visit medical facility (14 months vs. 2.8 months, p<0.01).
The risk factors for nondetection were awareness of pain and/or numbness (OR 6.67 [95%CI: 1.85-24], p<0.05), age: younger than 65 years old (OR 3.34 [95%CI: 0.89-12.5], p=0.07), and gender: male (OR 3.56 [95%CI: 0.806-15.7], p=0.09).

Conclusion: Pain and numbness are quite common symptom of orthopedic patients. On the other hand, STSs are a very rare disease, and most of them are painless mass. So, if STS patient has pain or numbness, we tend to pay too much attention to their pain or numbness and it may result in nondetection of STS.
Moreover, age: younger than 65 years old and gender: male can also lead to nondetection of STS. Enlargement is a very important finding for STS. If patients are not aware of enlargement of their lump and don't have enough time to attend regularly, it would be difficult to suspect STS.
In conclusion, nondetection rate of STS at 1st visit medical facility was 13% in our cohort. Awareness of pain and/or numbness, age < 65 years old, and gender: male is associated with nondetection of STS at 1st visit medical facility.

Poster 155 #2738046

CORRELATION AND COMPARISON BETWEEN THE PATIENT REPORTED OUTCOMES MEASUREMENT INFORMATION SYSTEM (PROMIS) AND THE TORONTO EXTREMITY SALVAGE SCORE (TESS) IN ORTHOPAEDIC ONCOLOGY

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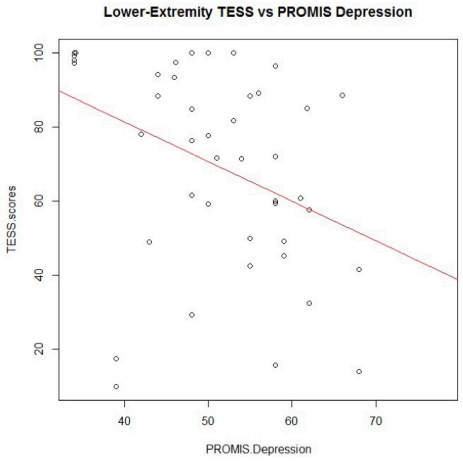
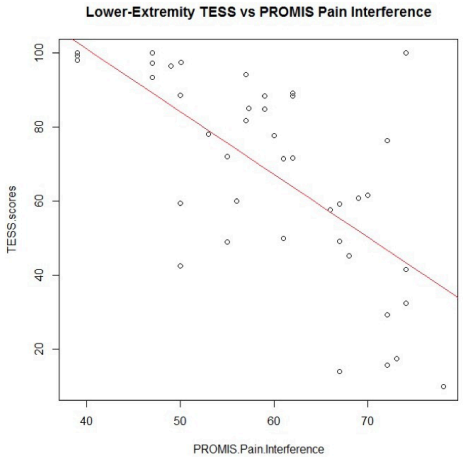
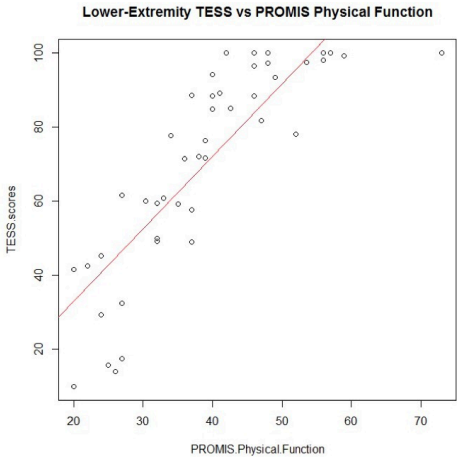
Objective: The Patient Reported Outcomes Measurement Information System (PROMIS), a computer-adaptive scoring system recently developed by the National Institute of Health, represents a potential common measurement tool with the advantage of reduced burden on patients. It has been studied in several orthopedic populations, but its role in orthopedic oncology has not yet been established. The purpose of this study was 1) to assess the correlation of PROMIS scores (Physical Function, Depression, and Pain Interference) with Upper Extremity (UE) and Lower Extremity (LE) TESS; and 2) to calculate the floor and ceiling effects of each outcome measure.

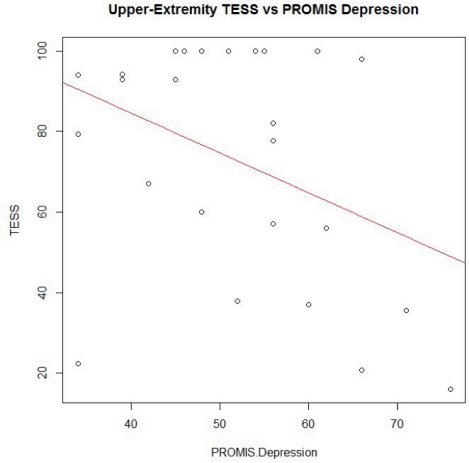
Methods: This prospective cohort study included all patients over 18 years of age that underwent surgical treatment of a bone or soft tissue tumor by one of three orthopedic oncologists at a single institution over a one-year period. Pre-operative TESS and PROMIS (Depression, Pain Interference, and Physical Function) scores were administered to all patients. Correlation between each PROMIS measure and the LE and UE TESS was assessed using the Pearson coefficient, and the floor and ceiling effect of each PROMIS measure was calculated and compared to that of the LE and UE TESS.

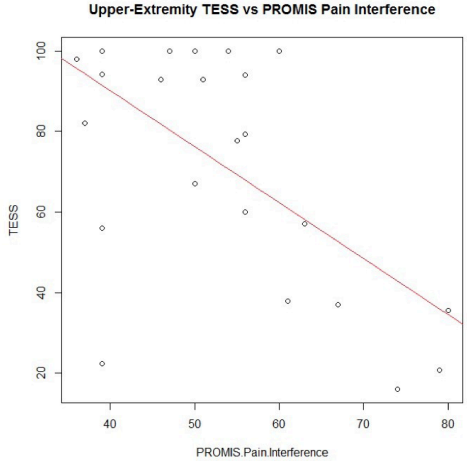
Results: The PROMIS Physical Function score demonstrated strong positive correlation with the LE TESS ($r=0.84$, $p<0.001$) and weak positive correlation with the UE TESS ($r=0.16$, $p=0.055$). The PROMIS Depression scores demonstrated moderate negative correlation with the LE TESS ($r=-0.38$, $p=0.010$) and weak correlation with the UE TESS ($r=-0.20$, $p=0.055$). The PROMIS Pain Interference scores demonstrated a strong negative correlation with LE TESS ($r=-0.71$, $p<0.001$) and minimal correlation with the UE TESS ($r=-0.09$, $p=0.001$). The UE TESS had a range of scores from 16-100 with a 27% ceiling effect and no floor effect, and the LE TESS had a range from 10-98 with no floor or ceiling effect. PROMIS Depression, Pain Interference, and Physical Function scores ranged from 34-78, 39-78, and 20-73, for LE patients, and from 34-76, 37-80, and 24-70 for UE patients, respectively. There was no floor or ceiling effect for any PROMIS measures.

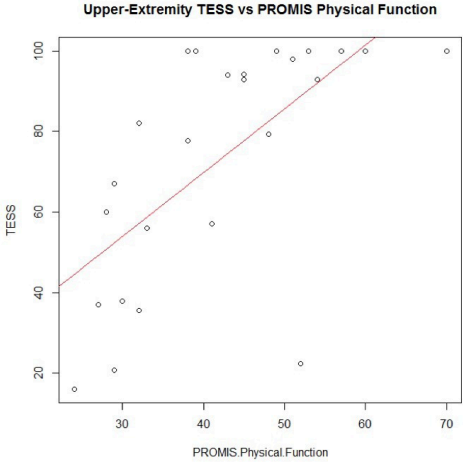












Conclusion: The PROMIS survey is an accurate and precise alternative to the TESS in an orthopedic oncology clinic, with the additional benefit of reduced ceiling effect.

Poster 156 #2803572

SYSTEMATIC REVIEW OF PATIENT REPORTED OUTCOMES FOLLOWING SURGERY FOR RETROPERITONEAL SARCOMA

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Objective: Management of retroperitoneal sarcoma (RPS) often requires extensive surgery including multivisceral resection. The potential for treatment morbidity to significantly impact survivors' quality of life (QOL) is significant. Capturing patient-reported outcomes (PROs) can aid in the clinical decision-making prior to and following radical surgical procedures for RPS. This systematic review synthesizes the current literature describing outcomes involving QOL, including PROs, in the management of abdominal/retroperitoneal sarcoma.

Methods: We performed a systematic review of the literature to identify studies of retroperitoneal/abdominal sarcoma that included outcomes related to QOL. Medline, PubMed and Cochrane databases were searched for publications between 1965-2016. The age group was limited to ≥18 and the language to English. Grey literature was screened, including abstracts from academic meetings of the American Society of Clinical Oncology and Connective Tissue Oncology Society. References of the included studies were also reviewed. PRISMA and Cochrane Review guidelines were followed. Two reviewers independently screened citations and extracted data. A narrative synthesis of outcomes related QOL is presented.

Results: Of 2408 articles, we identified 772 that included abdominal/retroperitoneal sarcoma, 26 of which contained at least one QOL related outcome. 11 of the selected studies included PROs, of which only 1 compared pre- vs. post-operative outcomes, albeit in a cross-sectional fashion. Measures distributed were general and varied widely, with over 20 types. Reports that omitted measures used descriptive techniques and invalidated surveys to report the patient experience, of which the majority were retrospective (n=8). Only 2 were found to be prospective and the remainder consisted of case reports (n=5). Patients with resected RPS were found to experience a wide range of symptoms including unresolved pain, sleep disturbances, lack of energy, bowel/bladder issues, neuropathy, infertility and sexual dysfunction. Psychological concerns included irritability, anxiety, depression, loneliness and delirium. Statistical results varied due to the abundance of studies merging patients with other disease sites and non-sarcoma histologies (n=21).

Conclusion: The vast majority of abdominal/retroperitoneal sarcoma studies do not outline QOL outcomes, and even fewer include those reported by patients. If conveyed, descriptive classifications are commonly used, and measures, when included, are not specific to RPS patients. Studies must include QOL measures and a disease-specific RPS QOL tool is advocated.

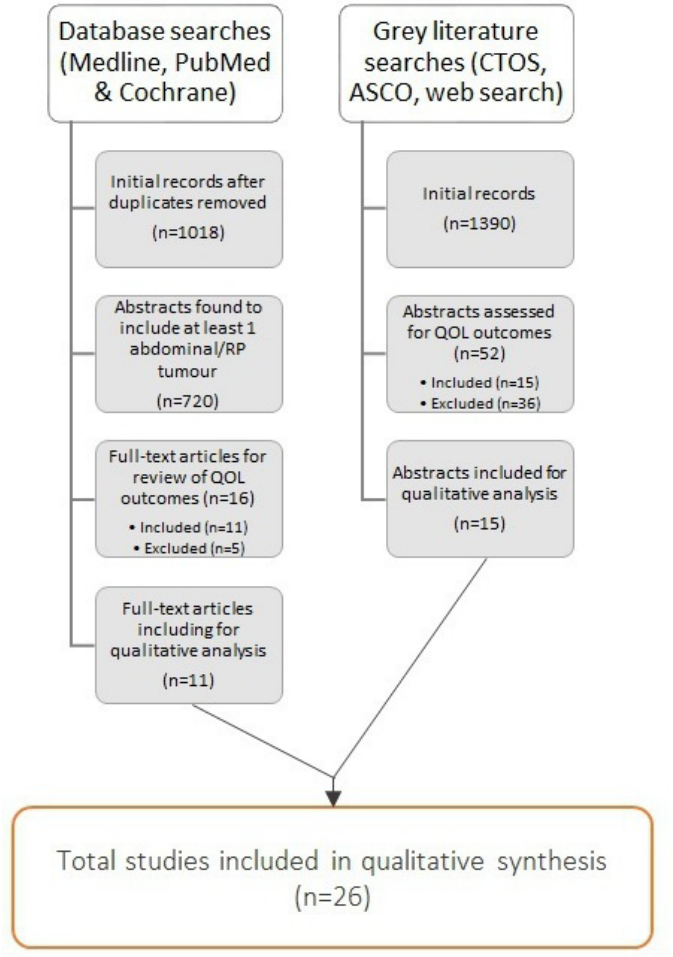

Figure 1. Flow Chart of Systematic Review

Poster 157 #2804647

THE EFFECT OF TENOSYNOVIAL GIANT CELL TUMOURS ON DAILY LIVING; AN ONLINE CROSS-SECTIONAL ANALYSIS OF FUNCTIONALITY AND QUALITY OF LIFE IN 337 PATIENTS

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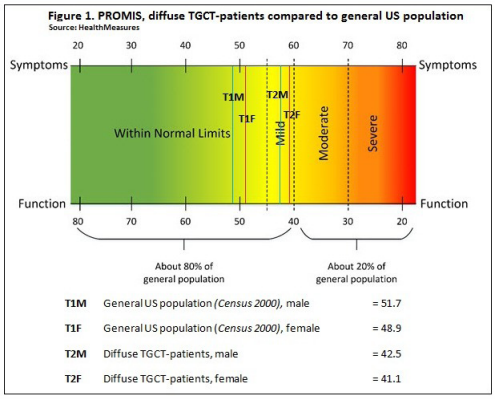
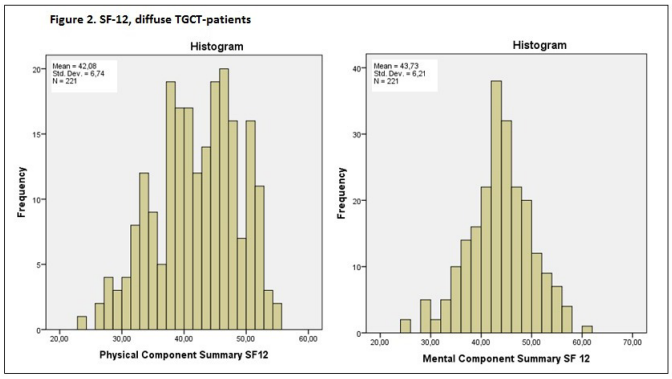
Objective: Tenosynovial Giant Cell Tumour (TGCT) is a rare, benign lesion. A distinction is made between localized- and diffuse-type. The impact of TGCT on daily life is currently ill described. We used crowdsourcing to obtain big data and to evaluate impact on daily living.

Methods: An online questionnaire, partially validated, was composed together with TGCT patients. Members

of the largest known TGCT Facebook community 'PVNS is pants' [2744 members,12-05-2017] were encouraged to complete this questionnaire within a timeframe of six months. To confirm disease presence and TGCT-type, patients were requested to share histological or radiological confirmation, after completing the questionnaire.

Results: 337 Questionnaires (80% female, mean age 41 (range 11-76) years), originated from 30 different countries (USA 43%, UK 20%, The Netherlands 13%) were ultimately completed. 22% of questionnaires was confirmed, via secure email.
TGCT was typically located in lower extremities: knee (71%), hip (10%). Mean age at diagnosis was 35 (range 7-75) years. Diffuse-TGCT was diagnosed in 68%. Most performed first surgery was arthroscopy (57% localized, 57% diffuse), followed by open synovectomy, one or two-staged, (35% localized, 42% diffuse). Adjuvant therapies, mainly radiotherapy and 90-Yttrium, were given in 10% localized-type and 29% diffuse- type. Recurrence rate was 36% and 66% in localized- and diffuse-type, respectively.
Effect of TGCT on daily living in diffuse-TGCT of lower extremities: 9% of working population was not able to (fully) perform working activities, 62% could not perform sport-activities. Validated questionnaires' results are shown in table.
In EQ5D5L, female patients scored worse for anxiety/depression (p=0.03). Patients with recurrence of TGCT experienced more pain/discomfort (p>0.000) and anxiety/depression (p=0.03). When ≥1 surgery was performed, mobility results were declined (p=0.03). General health state (EQ-VAS) was higher for arthroscopy, compared to synovectomy (p=0.03).
In PROMIS, patients with ≥1 recurrence(s) and ≥1 sugery(s) show deteriorated outcome (p=0.02, p=0.04). Figure 1 & 2 compare results of diffuse-TGCT patients to general US population, for PROMIS and SF12.





Conclusion: According to crowdsourcing, diffuse-TGCT of lower extremities shows significant impact on daily living, especially in patients with recurrent disease. TGCT patients show declined quality of life and are limited in daily activities, sports and work.

Table Results of EQ5D5L[$] general health state, PROMIS, SF-12 questionnaires in 219 diffuse-TGCT patients, lower extremities.

Groups[$$]	EQ5D5L-VAS 0 = worst score 100 = best score		PROMIS T-score (mean=50)		SF-12 PCS[†] score (mean=50)		SF-12 MCS[††] score (mean=50)	
	Mean score	**p***	**Mean score**	**p***	**Mean score**	**p***	**Mean score**	**p***
Gender Male | Female	72.3 | 66.6	0.123	42.6 | 41.1	0.205	42.9 | 41.8	0.340	45.0 | 43.3	0.089
Current age <40 years | ≥40 years	68.6 | 67.2	0.639	41.4 | 41.5	0.885	42.6 | 41.7	0.323	44.1 | 43.4	0.330
TGCT localisation Knee | hip, ankle, foot	68.5 | 66.1	0.507	41.0 | 42.6	0.158	42.1 | 42.0	0.880	43.5 | 44.5	0.310
Initial surgery Arthroscopy | open synovectomy**	70.6 | 63.6	**0.034**	41.5 | 41.6	0.939	42.2 | 41.9	0.769	43.9 | 43.5	0.640
Recurrence No | yes	69.3 | 67.1	0.495	43.0 | 40.7	**0.019**	42.9 | 41.6	0.169	44.0 |43.6	0.607
Total amount of surgeries (n=202) 1 surgery | >1 surgeries	68.0 | 66.9	0.734	42.6 | 40.6	**0.044**	42.0 | 41.9	0.863	44.0 | 43.5	0.571

[$]EQ5D5L-VAS, table shows general health state, results of domains of EQ5D5L are only described in abstract
[$$]First mentioned group is also first mentioned mean score
[†]PCS, Physical Component Summary, [††]MCS, Mental Component Summary
*p, P-value, **Open synovectomy, One- or two-staged.

Poster 158 #2790263

INTEGRATIVE SARCOMA CARE: MAXIMIZING OPPORTUNITIES & OVERCOMING OBSTACLES DEVELOPING STANDARDS OF CARE

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Objective: Studies indicate that one third of patient have distress associated with their cancer diagnosis. Sarcoma patients are a particularly debilitated group and vulnerable to the development of significant psychosocial difficulties. This may be in part due to the fact that surgery up to and including amputation can be the primary treatment modality. Despite high levels of pain and psychosocial / emotional distress, few sarcoma patients are referred to psychosocial oncology. Sarcoma is a multi-system disorder that influences all aspects of the life of affected individuals including social interactions, family relations, peer interaction, intimate relationships, employment, spiritual attitudes.

Methods: During 2016, 141 patients were identified as Sarcoma patients in the on-line data management system at our Comprehensive Cancer Center. Our multidiscipliary tumor board (MDT) discusses newly diagnosed Sarcoma patients weekly. Our integrative multidisciplinary team of professionals consisting of Surgical, Medical, Radiation Oncology specialists, in addition to Clinical Psychology specialists with advanced training and expertise in Psychosocial Oncology, deliver comprehensive care for people affected by Sarcoma. The addition of a psychologist as a staple part of the Sarcoma MDT enables an assessment of psychosocial coping and adaptation to the Sarcoma population, providing a critical component to the team.

Results: A decision triage algorithm for assignment of patients to appropriate service delivery domains is reviewed at the MDT. Incorporating guidelines, as required by the Comission on Cancer and the National Comprehensive Cancer Network, allow for systematic evaluation, referral and treatment. These guidelines have distinct advantage - their performance is integrated into the overall referral system of the department of Medicine and the Comprehensive Cancer Center. This translates into a powerful resource for upgrading the cost/quality balance in medical care.

Conclusion: Further promising areas for future research include the evaluation of psychological interventions to improve patients' styles and strategies for coping with pain, physiologic function/dysfunction and body image issues. This integrative team is in the position to provide an avenue and vehicle for future research.

– RADIATION ONCOLOGY / DIAGNOSTIC RADIOLOGY ADVANCES IN DIAGNOSIS & BIOMARKER DISCOVERY RADIOMICS –

Poster 159 #2804839

OUTCOMES OF RADIATION ASSOCIATED SARCOMAS: A LARGE INSTITUTIONAL SERIES

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Objective: Radiation associated sarcoma (RAS) is a rare complication from radiation therapy for neoplastic process. We investigated the clinicopathological characteristics, treatment strategies and oncologic outcomes of these patients.

Methods: An IRB approved institutional database of 13,321 primary bone or soft tissue sarcomas (1960-2017) was queried to find sarcomas arising within prior RT field of distinct prior malignancies at least 1 year after completion. Cases meeting criteria were further analyzed.

Results: 235 RAS were identified, representing 1.76% of sarcomas seen at our institution. Features of prior malignancies included: breast cancer (22.6%), Hodgkin lymphoma (14.5%), prostate (6.8%), non-Hodgkin lymphoma (4.7%), cervical SCC (4.3%), retinoblastoma (3.8%), colorectal (3.0%), NSCLC (2.6%), testicular (2.6%), ALL (1.7%), neuroblastoma (1.7%), embryonal rhabdomyosarcoma (1.7%), Chordoma (1.7%), Ewing sarcoma (1.7%), and medulloblastoma (0.9%); 2 had Li Fraumeni's syndrome. Prior malignancies were treated with RT with median dose of 54 Gy (range 8-152.2 Gy); 44% had chemotherapy. Median age at prior malignancy was 47 years (2 mo-87 years) and for RAS was 60 years (10-93 years). Median interval from prior malignancy to RAS was 11 years (1-50 years). Features of RAS included: female (57.4%), male (42.6%), soft tissue (67.2%), bone (32.8%), trunk (62.6%), head/neck (19.6%), extremity (17.9%), abdomen (10.6%), spine/bony pelvis (14.9%), and others; histologies osteosarcoma (26.4%), angiosarcoma (15.7%), UPS/MFH (11.9%), fibrosarcoma (11.1%), MPNST (8.5%), leiomyosarcoma (5.5%), and others (20.9%); median size 6.6 cm (0.5-27 cm), grades 1 (3%), 2 (38.7%), and 3 (48.9%). 81.7% were M0. Treatment of RAS consisted of surgery only (50.2%), surgery+RT (34.9%), RT only (8.5%), or neither (6.4%); 40.9% had chemotherapy. On Cox multivariate analysis, age (p=0.002) and size >5 cm (p=0.01) predicted worse OS whereas surgery predicted better OS (HR 0.480, p= 0.001). Radiation associated MPNST has worse survival

(HR 2.62) than other radiation associated sarcoma histologies.

Conclusion: RAS have worse outcomes than spontaneous bone and soft tissue sarcomas with variability across histologies, size, age, and sites. Further understanding of clinical and biological differences/similarities across and between RAS vs. spontaneous sarcomas may improve treatment strategies. Given the rarity of this disease, multi-institutional collaboration on this rare complication of treatment is needed and an international registry of Radiation Associated Sarcomas (INT-RAS) will be launched to study and characterize these rare sarcomas.

Poster 160 #2740067

SURVEILLANCE FOR LUNG METASTASIS FROM GIANT CELL TUMOR OF BONE

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Objective: Early detection of lung metastasis from giant cell tumor of bone (GCTB) may lead to better outcomes. However, literature on effective surveillance strategy for lung metastasis from GCTB is scarce. This study aimed to develop an effective surveillance strategy for lung metastasis by determining 1) the optimal surveillance schedule by analyzing time-to-event data taking into account the risk factors of lung metastasis, and 2) the effective diagnostic modality for lung metastasis by comparing the diagnostic performance of chest radiography and chest CT.

Methods: 333 patients who underwent surgery for GCTB with FU > 2 years were reviewed. For surveillance, all patients underwent chest radiography and 169 (51%) had additional CT. Time to lung metastasis were calculated and cumulative incidence was estimated. Risk factors for lung metastasis were identified by multivariate analysis using the Cox proportional hazards model. Diagnostic performance of chest radiography and chest CT was compared by sensitivity, specificity, positive predictive value (PPV), negative predictive value, and diagnostic accuracy.

Results: Twenty-five (7.5%) of the 333 patients developed lung metastasis. Mean interval from surgery to metastasis was 47 months (range, 0 to 167). Twenty-three (92%) of the 25 metastases were diagnosed within 4 years of surgery. Cumulative incidence at 1, 3, and 5 years were 1.2%, 5.6%, and 6.5%, respectively. Among the possible risk factors for lung metastasis, local recurrence (LR) of the primary tumor was the only independent factor associated with development of metastasis (RR = 6.6, $p < 0.001$). Median interval from LR to metastasis was 15 months and 17 metastases (85%) occurred within 3 years of LR. Cumulative post-LR incidence at 1, 3, and 5 years were 15.4%, 21.5%, and 21.5%, respectively. When diagnostic modalities for lung metastasis were compared, chest CT was more sensitive (100% vs. 32%), had higher positive predictive value (81% vs. 57%) and diagnostic accuracy (96% vs. 92%) than chest radiography.

Conclusion: Intensified surveillance for lung metastasis is warranted in GCTB patients with LR, especially for 3 years from the diagnosis of LR. Chest CT is an effective diagnostic modality for detecting lung metastasis from GCTB.

Poster 161 #2782133

THE BIOLOGIC SIGNIFICANCE OF TUMOUR GROWTH DURING PREOPERATIVE RADIOTHERAPY FOR EXTREMITY STS

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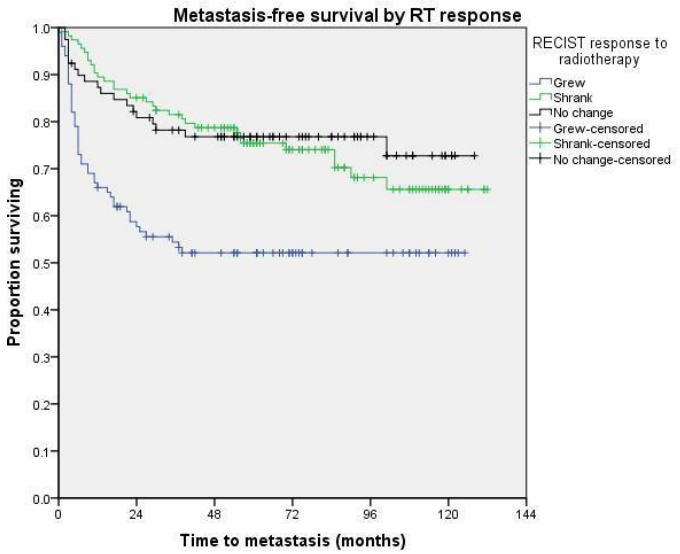
Objective: Tumor volume changes during preoperative radiotherapy (RT) for extremity soft tissue sarcoma (STS) may necessitate adaptive re-planning (for growth) or can lead to less complicated resections and improved functional outcomes (for shrinkage). However, it is unclear what impact tumor volume changes have on oncologic outcome for these patients. The aim of this study was to investigate whether or not local tumor response to preoperative RT has prognostic significance in terms of local or systemic disease control.

Methods: MRI scans performed before and after preoperative RT were available for 309 patients treated for extremity STS from June 2001-December 2012. Preoperative RT was delivered over 5 weeks (2Gy daily, 50 Gy total); most received image-guided intensity modulated RT (IMRT). Tumor volume on pre-RT and post-RT MRI scans was measured to evaluate tumor response, as was percentage change in T2-weighted signal (177 paired images were available). Using RECIST criteria, tumor response to RT was categorized as growth, shrinkage, or no change if tumor volume increased by ≥20%, decreased by ≥20%, or demonstrated <20% change. Local recurrence-free, metastasis-free, and overall survival were estimated by Kaplan Meier and compared with the log rank test.

Results: Of 309 patients examined, 117 tumors shrank, 106 grew, and 86 were unchanged. A high proportion of myxoid liposarcomas shrank (only 1 grew) and a high proportion of the MFH family of tumors (MFH, UPS, myxofibrosarcoma) grew. There was no difference in local recurrence-free survival based on tumor response to preoperative RT (5-year LR-free survival 98.2%, 94.0% and

98.7% for shrinkers, growers and no change, respectively, p= 0.063). However, tumors which demonstrated growth during preoperative RT had significantly worse metastasis-free survival (5-year metastasis-free survival 75.4%, 52.1% and 76.8% respectively, p<0.001) and overall survival (5-year overall survival 82.6%, 54.7% and 78.1%, respectively, p<0.001). For cases where the T2 signal increased, metastasis-free survival was also poorer (no change, 66.0%, decreased 73.5%, increased 46.2%, p=0.035).



Conclusion: Extremity STS that increase in volume on preoperative RT had worse metastasis-free and overall survival, likely attributable to unfavourable tumor biology. These results support the radiosensitive biology of myxoid liposarcoma and radioresistive biology of the MFH family of sarcomas as documented in the literature. Importantly, there was no difference in local recurrence risk based on RT-response reinforcing the importance of a multidisciplinary treatment approach to patients with sarcoma. Tumors which demonstrated growth during preoperative RT underwent radiation replanning in order to provide proper RT coverage of the enlarging “at risk” volume.

Poster 162 #2799219

SECONDARY LEUKEMIA AND MYELODYSPLASTIC SYNDROME IN 483 PATIENTS WITH EWING SARCOMA AND OSTEOSARCOMA

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Objective: Outcomes in patients with Ewing sarcoma (ES) and osteosarcoma have improved over the past 40 years due to refinements in surgical techniques, radiotherapy and chemotherapy. Long-term survivors, however, may be at risk for therapy-related acute leukemia or myelodysplastic syndrome (t-AL/MDS).

Methods: We retrospectively reviewed the clinicopathologic characteristics of 483 patients with osteosarcoma (n=330) and ES (n=153) treated at our institution between 1994 and 2014. A univariate and multivariate competing risk analysis was used to analyze predictors of t-AL/MDS. We also conducted a nested case control study to compare cumulative chemotherapy dose and volume of bone marrow irradiated via the exact two-sided Wilcoxon rank test.

Results: The median follow-up for surviving patients was 75 months (range 0.7-253). Thirteen patients developed t-AL/MDS, all of whom received chemotherapy and 11 of whom were treated with radiotherapy. On univariate analysis, primary disease in the pelvis, thoracic or lumbar spine (HR 5.11, 95% CI 1.51-17.35, p=0.009) and radiotherapy to >55.8 Gy (HR 5.42, 95% CI 1.66-17.68, p=0.005) were associated with development of t-AL/MDS. On multivariate analysis, only receipt of >55.8 Gy of radiotherapy remained statistically significant (HR 3.97 95% CI 1.01-15.59, p=0.05). For osteosarcoma and ES, the 10-year cumulative incidence of t-AL/MDS in patients receiving >55.8 Gy radiotherapy to the pelvis, thoracic and lumbar spine was 9.5% and 11.5%, respectively. In our nested case control study, the median cumulative doses of etoposide (4000 mg/m2 vs. 2850 mg/m2, p=0.007), ifosfamide (72 g/m2 vs. 57 g/m2, p=0.03) and vincristine (13.5 g/m2 vs. 10.5 g/m2, p=0.04) were higher in cases than controls.

Conclusion: Osteosarcoma and ES patients receiving >55.8 Gy of radiotherapy to the pelvis, thoracic or lumbar spine appear to be at increased risk for t-AL/MDS. Treatment with high cumulative doses of chemotherapy may further augment this risk.

Poster 163 #2800328

IMPACT OF LOCAL TREATMENT MODALITIES ON SURVIVAL FOR PATIENTS WITH HIGH-GRADE EXTREMITY SOFT-TISSUE SARCOMAS: AN ANALYSIS OF 2,937 PATIENTS

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Objective: Small randomized trials have not shown a difference in overall survival (OS) based on local treatment modality for patients with extremity soft-tissue sarcomas (ESS) but were underpowered for OS analyses. This study examines the impact of local treatments on OS and sarcoma mortality (SM) using modern data from a large US registry.

Methods: The Surveillance, Epidemiology, and End Results (SEER) Program was analyzed to identify patients with stage II-III, high-grade ESS diagnosed between 2004-2013 and treated definitively with 1) Amputation alone, 2) Limb-sparing surgery (LSS) alone, 3) Preoperative radiotherapy (RT) + LSS, or 4) LSS + post-operative RT. Multivariable analyses (MVAs) utilizing the entire cohort and matched pair analyses utilizing 1:1 matched cohorts examined the effect of local treatment on OS and SM.

Results: From SEER, 2,937 patients were included--168 amputation alone, 775 LSS alone, 484 preoperative RT + LSS, and 1510 LSS + post-operative RT. On MVA (Table), amputation was associated with significantly inferior OS (Hazard Ratio [HR], 1.59; 95% confidence interval [CI], 1.24-2.04) and SM (HR, 1.52; 95% CI, 1.12-2.07) compared to LSS alone. Both preoperative RT + LSS (HR, 0.60; 95% CI, 0.48-0.75) and LSS + post-operative RT (HR, 0.70; 95% CI, 0.60-0.72) had improved OS relative to LSS alone. SM was also improved with pre-operative RT (HR, 0.75; 95% CI, 0.58-0.97) and post-operative RT (HR, 0.82; 95% CI, 0.67-0.99) compared to LSS alone. Estimated 5-year OS from matched pair analysis was 53.3% (95% CI, 46.2-59.9%) with LSS alone compared to 65.4% (95% CI, 58.9-71.1%) with preoperative RT + LSS. Matched pair analysis also resulted in an estimated 5-year survival of 60.9% (95% CI, 56.5-65.0%) for LSS alone versus 69.2% (95% CI, 65.1-73.0%) for LSS + post-operative RT. Matched pair analysis also showed significantly reduced SM when preoperative RT was added to LSS; however, there was no statistically significant difference in SM between LSS alone and LSS + post-operative RT.

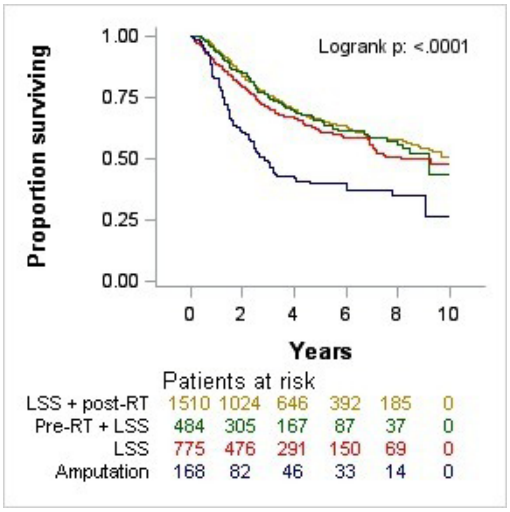

Figure 1. Overall survival by treatment in entire cohort--Kaplan Meier estimates

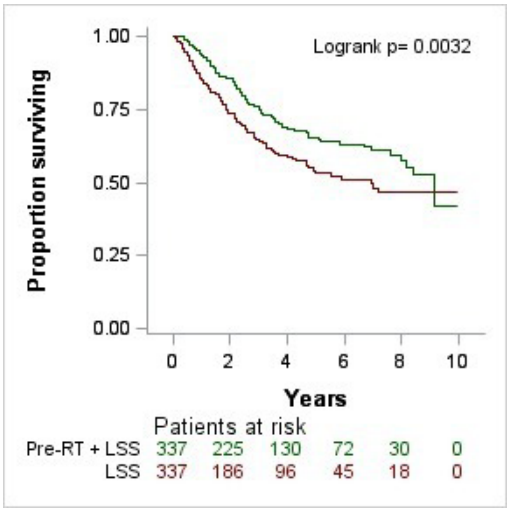

Figure 2. Overall survival from matched pair analysis comparing pre-operative RT + LSS to LSS alone--Kaplan-Meier estimates

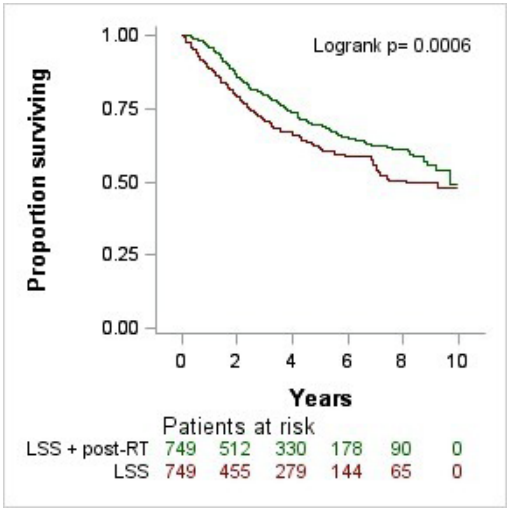

Figure 3. Overall survival from matched pair analysis comparing LSS + post-operative RT to LSS alone--Kaplan-Meier estimates

Multivariable Cox regression of overall survival and multivariable competing risk analysis of sarcoma mortality in entire cohort

	Overall Survival		Sarcoma Mortality	
Treatment	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value
LSS	Reference		Reference	
Amputation	1.59 (1.24, 2.04)	<.001	1.52 (1.12, 2.07)	.007
Preoperative RT + LSS	0.60 (0.48, 0.75)	<.001	0.75 (0.58, 0.97)	.031
LSS + post-operative RT	0.70 (0.60, 0.82)	<.001	0.82 (0.67, 0.99)	.046

Death from other causes considered a competing risk in sarcoma mortality analysis. All analyses adjusted for baseline patient demographic, reporting cancer center, and patient prognostic characteristics.

Conclusion: For patients with high-grade ESS, LSS combined with preoperative RT or post-operative RT resulted in the best OS outcomes. SM also seemed to be improved with the addition of either preoperative or post-operative RT in MVA of the entire cohort. However, after performing matched pair analysis, the benefit of post-operative RT was no longer significant on MVA of SM. Overall, these results reinforce the effectiveness of LSS and emphasize the importance of RT as a component of limb-sparing treatment for high-grade ESS.

Poster 164 #2782443

A PILOT STUDY TO ASSESS THE ROLE OF RESECTION AND RADIOLOGICAL SURVEILLANCE OF RETROPERITONEAL, ABDOMINAL AND PELVIC SCHWANOMMAS

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Objective: The surgical management of intra-abdominal schwannomas is complex due to their rarity, heterogenous presentations, and relative morbidity. Due to relative rarity , their natural history, such as malingant potential and rate of growth, has not been firmly elucidated. Consequently, there is great variation in the resection policies amongst different centres; ranging from a default resectional policy to only intervening for signficantly symptomatic patients or if the schwannoma demonstrates concerning behaviour. The role of radiological surveillance in post operative patients is also an unknown quantity.
From past experiences at the Midlands Abdominal & Retroperitoneal Sarcoma Unit, much of the centre's current management is based upon the following empiric hypotheses:
1) Most intra-abdominal schwannomas can be kept under observation unless there is a clear indication for surgery, or there is significant growth in size over a short period
2) Clinically significant recurrence after R0/R1 resection or progression after function preserving R2 resection is rare and radiological surveillance is of little value
The aim of this pilot was to assess if the above hypotheses were tentatively valid, and thus could be tested more rigourously by incorporated them into an international multi-centre study. If these hypotheses hold true, then a predictive tool or nomogram to guide management (observation or resection) can be created and promulgated.

Methods: A retrospective analysis was performed of consecutive patients between 2007 and 2016 inclusive presenting with intra-abdominal schwanommas. They were identified from the patients discussed at the weekly sarcoma multidiscplinary team meeting between the above dates. The following data was extracted from the electronically stored hospital notes: demographics, radiological investigations, histopathological results and functional status of the patient at the last consultation. For patients with a schwannoma in situ, the volume (V) of the schwannoma was calculated for every scan using V=pi*a*b*c/6 by approximating them as ellipsoids. Rates of growth were calculated by comparing the volume changes of individual schwannomas over time. Scans after resections were assessed for recurrence or any residual disease.

Results: The early results so far are: 45 patients presented between 2007 and 2016 inclusive with 27 females (60%) and 18 males (40%), with a median age of 61 years old. 25 patients (56%) presented with incidentally found schwannomas. 9 patients had 3 or more scans with schwannomas in situ, with varying rates of growth 25.3% - 12.5% per annum. 1 schwannoma increased in size by 82% over 210 days from the date of the initial CT, and thus required resecting. 21/45 (47%) patients had a resection of their schwannoma. 20/21 patients did not have residual disease or recurrence with a follow-up time range of 10-1176 days. 1/21 had recurrence following a planned R2 resection.

Conclusion: The pilot study's limited data tentatively suggests that schwannomas of low risk can be followed with observation and there is little scope for post-resection radiological surveillance. Incorporation of greater number of patients from a multi-centred study is required to provide the required evidence for a guide to managing intra-abdominal schwannomas.

Poster 165 #2804657

IONIZING RADIATION ENHANCES THE SENSITIVITY OF DESMOID TUMOR CTNNB1 S45F MUTANT TO SORAFENIB

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Objective: To test whether sorafenib or radiotherapy (RT) are effective agents for DT with S45F mutation, and whether the combination of RT with Sorafenib is additive or synergistic treatment.

Methods: We treated the desmoid cell strains isolated from patient tumors with various doses of sorafenib, radiation or both and examined the cell survival with soft agar assays.

Results: Both the wild type and S45F mutant DT cell lines responded well to radiation in a dose-dependent manner. Sorafenib significantly inhibited capacity of colony formation and cell proliferation of mutant DT cells, but had no notable effect on the wide type cells. The CTNNB1 S45F mutant cells also showed the sensitivity to Sorafenib in a dose-dependent manner. Combination treatment of Sorafenib and radiation resulted in additive effects on cellular anchorage-independent growth.

Conclusion: A combination treatment of Sorafenib and radiation could be good strategy for the treatment of desmoid tumor patients and clinical trials should be explored.

Poster 166 #2804789

REDUCTION IN MIR-19B EXPRESSION AFTER PRE-OPERATIVE RADIOTHERAPY PREDICTS IMPROVED DISEASE FREE SURVIVAL IN SOFT-TISSUE SARCOMA

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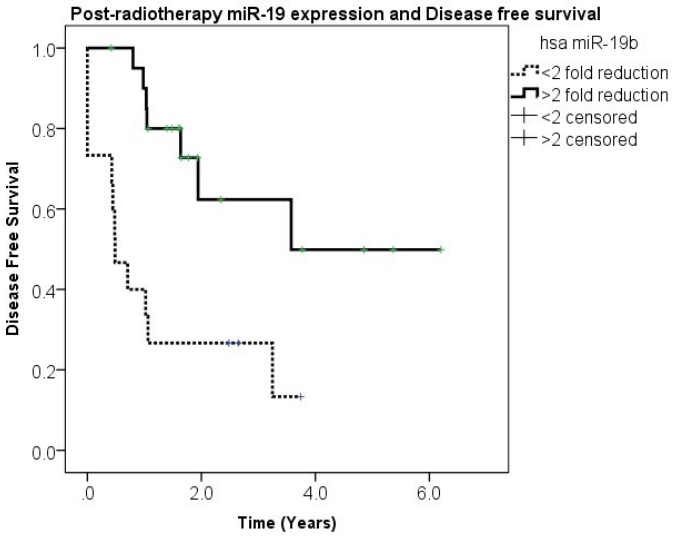
Objective: Preoperative radiotherapy is commonly prescribed in the curative management of soft-tissue sarcomas (STS). MicroRNAs (MiR) are 19-23 nucleotide RNAs that post-transcriptionally regulate the translation of target mRNAs. We aimed to identify candidate miR biomarkers of pre-operative radiotherapy response.

Methods: Seventy-two matching pre-treatment and post-radiotherapy STS formalin fixed paraffin embedded (FFPE) specimen were obtained from 36 patients of which 27 had high grade undifferentiated pleomorphic sarcomas, liposarcomas and leiomyosarcomas. On a hematoxylin and eosin slide, the study pathologist identified the location and presence of live STS cells within these FFPE specimens. Total RNA was extracted and miRNA profiling was done using the Fluidigm 96.96 microfluidic array, a high-throughput qRT-PCR technique utilizing TaqMan probes (ThermoFisher). The expressions of 375 miRs and 2 endogeneous control RNAs (U6 and RNU48) were assessed. Comparisons in miR expressions of STS before vs. after radiotherapy were done using paired Student t-test with a threshold p-value <0.00038 (Bonferroni correction) as an indicator of potential significance. Candidate miRs were then evaluated for their correlation with patient disease free survival (DFS) with a threshold p-value <0.05 considered as significant on log-rank test. Multivariate backward stepwise cox regression analysis was performed using patient age, gender, disease size, grade, depth, stage and resection margins as co-variables.

Results: There were 130 and 128 miRs that were quantifiable (Ct<35) in 80% of the pre-treatment and post-treatment specimens, respectively. The expression of U6 was significantly (p<1E-04) increased following radiotherapy. Normalization of the miRs was thus performed using the expressions of miR-24 and 494 as they were well expressed (Ct range: 13-29) in all samples, did not differ significantly following radiotherapy, and had the least inter-sample variance. A median 2.4-fold down-expression of miR-19b (p=1.4E-4) following radiotherapy was the only miR expression that significantly altered. With a median follow-up of 2 years, there were 19 deaths and recurrences among the 36 patients. A greater than 2 fold reduction in miR-19b expression was associated (p=0.001) with a longer DFS. Clinical disease stage and change in miR-19b expression remained significantly (p<0.05) associated with DFS on multivariate analyses.



Greater reduction in tumor miR-19b expression following pre-operative radiotherapy was signicantly (log-rank p=0.001) associated with shorter disease free survival (DFS).

Conclusion: In this small cohort of matched STS FFPE samples, the expression of miR-19b was found to be significantly reduced following pre-operative radiotherapy. A >2-fold reduction in miR-19b was associated with improved DFS. MiR-19b belongs in the oncogenic miR-17-92 cluster, which is known to target PTEN and BCL2L11, among other tumor suppressors. Greater reduction of miR-19b could lead to increased STS cell death from radiotherapy.

Poster 167 #2785089

RADIOTHERAPY WITHOUT SURGERY FOR SOLITARY FIBROUS TUMORS; THE GLOBAL SFT INITIATIVE

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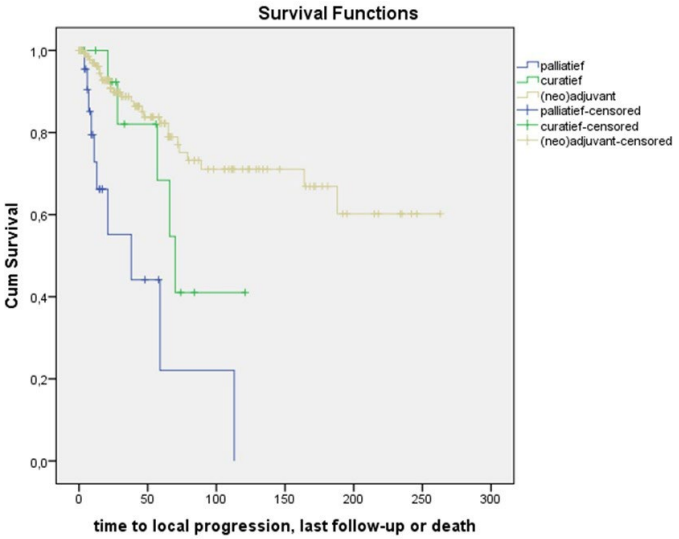
Objective: Solitary Fibrous Tumor (SFT) is very rare, may arise anywhere in the body, and can run an indolent as well as a malignant clinical course. Surgery is potentially curative, but the role of definitive and palliative radiotherapy (RT) is less well described.

Methods: A retrospective study was performed in 6 sarcoma centers, retrieving clinical data on patients receiving definitive or palliative radiotherapy RT without surgery and compared to a subgroup that did receive surgery and RT. Local control (LC) and overall survival (OS) were calculated from start of RT until local progression or death. Differences across subgroups and modalities were tested using Log-Rank and Chi-square tests.

Results: Definitive RT was prescribed to 16 patients, median total dose of 60Gy in 30 fractions, mitotic count >4 in 25%. LC rates after 1, 2 and 5 years were 100%, 93,8% and 81,3% respectively and for overall survival 100%, 93,8% and 87,5% respectively. Remarkably, the median OS after definitive RT was not significantly different than after perioperative RT in 140 patients receiving a median dose of 54Gy (p-value 0.448). Furthermore, OS rates after 1, 2 and 5 years were not statistically significantly different after definitive RT (100%, 93.8%, 87.5%) compared to R2 resections (100%, 100%, 80.8%).
A total of 23 patients were treated with palliative intent (median total dose of 39Gy in 13 fractions, mitotic count >4 in 50%). Local control rates after 1, 2 and 5 years were 78,3%, 69,6% and 60,9% and for overall survival 69,6%, 60,9% and 52,2% respectively.



Conclusion: In unresected patients treated with definitive RT, 81,3 % were locally controlled at 5 years. If an R2 resection is anticipated, RT with curative intent should be considered. More than half of the patients irradiated with palliative intent can expect to be locally controlled and to survive beyond 5 years. Therefore, RT may result in favorable outcome parameters even without surgery. Although prospective studies are warranted, they are hampered by the extremely low incidence rates of SFT.

Poster 168 #2738105

A PROSPECTIVE STUDY OF PROTON REIRRADIATION OF RECURRENT AND SECONDARY SOFT TISSUE SARCOMA

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Objective: Proton reirradiation for recurrent or secondary soft tissue sarcomas in previously-irradiated fields has not been previously described. We hypothesized that this strategy would provide acceptable toxicity and result in favorable survival outcomes.

Methods: Patients with a soft tissue sarcoma in a previously-irradiated field were enrolled on a prospective trial of proton reirradiation. The primary endpoint was provider-reported acute toxicity. Secondary endpoints included late toxicities, local control, and overall survival. Toxicity was scored using CTCAEv4.0. The Kaplan-Meier method was used to estimate overall survival. Local failure was estimated using cumulative incidence with competing risks.

Results: 23 patients were treated with proton reirradiation a median of 40.7 months (range 10-272) following their initial irradiation course. The median recurrent tumor size was 5.0 cm (IQR 4.6). The median doses for the initial and retreatment courses were 5040 cGy 6840 cGy (CGE), respectively. Acute toxicity data were available in all patients; late toxicity data were available in 21/23 patients. There were no grade 4/5 toxicities. One patient (4%) experienced acute grade 3 toxicity (dysphagia). The most common grade 2 acute toxicities were fatigue (26%), anorexia (17%), and urinary incontinence (13%). There were 2 grade 3 late wound infections (10%) and 1 grade 3 late wound complication (5%). Grade 2 late complications included lymphedema (10%), fracture (5%), and fibrosis (5%). At a median follow-up of 36 months following reirradiation, the 3-year cumulative incidence of local failure was 41% (95%CI [20%-63%]). Median overall survival and progression-free survival were 44 and 29 months, respectively, corresponding to 3-year rates of 64% (95%CI [39%-81%]) and 43% (95%CI [21%-62%]). In extremity patients, amputation was spared in 7/10 (70%).

Conclusion: Proton reirradiation of recurrent/secondary soft tissue sarcomas is well tolerated in this first-ever prospective study. Local control and survival outcomes in this high-risk population are encouraging.

Poster 169 #2761278

EFFECTIVENESS AND SAFETY OF TISSUE EXPANDER FOR ADJUVANT HELICAL TOMOTHERAPY IN CURATIVELY RESECTED RETROPERITONEAL SARCOMA

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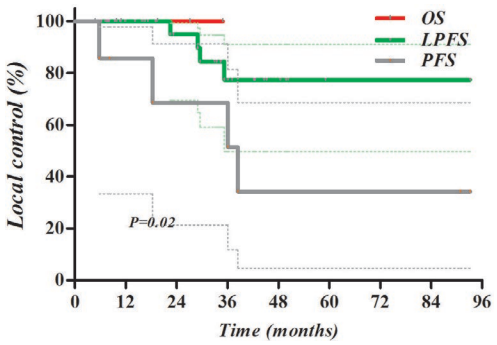
Objective: We investigated the effectiveness and the safety of a tissue expander (TE) for adjuvant helical tomotherapy (HT) in curatively resected retroperitoneal sarcoma (RPS).

Methods: This study was conducted with 60 RPS patients who received curative resection with or without TE insertion followed by HT from June 2009 to December 2016 at Samsung Medical Center. Among the 60 patients, TE was inserted in 37 (61.7%) patients. The quality of TE insertion was evaluated, as reported in the previous study, according to the correlation of clinical target volume and retroperitoneal surface volume covered by TE and was defined as follows (Excellent; ≥85%, good; 70 to 85%, fair; 50 to 70%, and poor; <50%. The median follow-up period after surgery was 19.4 months (range, 4.5 to 93.2 months).

Results: Table 1 displays the differences in baseline clinicopathologic characteristics between the patients with and without TE. TE was inserted more frequently in liposarcoma histology cases (P=0.001), and higher biologically equivalent dose (BED, α/β=10) was used in patients who had TE insertion (median, 72.0 gray [Gy] vs. 67.1 Gy, P=0.02). Depending on TE insertion, a significant difference in tumor size (median, 17.0 cm in TE group vs 10.5 cm in no TE group, P=0.04) and R2 resection (16.2% in TE group vs 0.0% in no TE group, P=0.05) were observed.

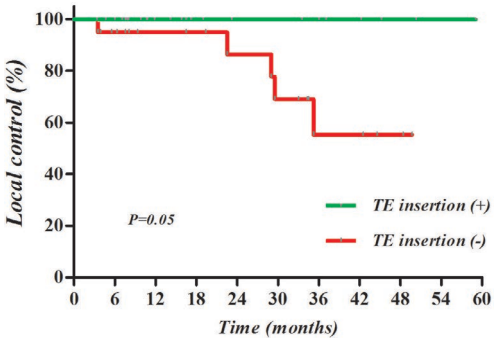
The quality of TE insertion was excellent in 18 (48.6%), good in ten (27.0%), fair in six (16.2%), and poor in three (8.1%) patients. In the aspect of the acute adverse event, there was no significant difference according to TE insertion or not. Local control (LC) of all enrolled patients was 91.4%, and overall survival was 95.6% at 2-years. LC was significantly different according to the completeness of resection (P=0.02, Figure 1). TE insertion was not a significant factor of local control in all enrolled patients (92.3% in no TE vs 91.1% in TE group at 2 years, P=0.62). In the subgroup of patients who had R1 or unknown margin status, however, local control rate was significantly higher in the TE insertion group (90.9% in no TE vs 100.0% in TE group at 2 years, P=0.05, Figure 2). Additionally, there was no local recurrence so far in patients



Baseline clinicopathologic characteristics of 60 enrolled patients

Variables		TE (n=37)	No TE (n=23)	P
Age – year	Median Range	55 34-78	53 33-68	0.49
Sex – n (%)	Male	19 (51.4)	9 (39.1)	0.26
Presentation	Primary Recurrent	26 (70.3) 11 (29.7)	19 (82.6) 4 (17.4)	0.37
Tumor size (cm)	Median Range	17.0 2.0-50.0	10.5 2.0-34.0	0.05
Completeness of resection	R0 R1 R2 Unknown	2 (5.4) 18 (48.6) 6 (16.2) 11 (29.7)	5 (21.7) 9 (39.1) 9 (39.1) 0 (0.0)	0.05
FNCLCC Tumor grade	1 2 3	15 (40.5) 18 (48.6) 4 (10.8)	8 (34.8) 9 (39.1) 6 (26.1)	0.34
Histology	Well differentiated liposarcoma Dedifferentiated liposarcoma Leiomyosarcoma Other	14 (37.8) 20 (54.1) 0 (0.0) 3 (8.1)	4 (17.4) 12 (52.2) 7 (30.4) 0 (0.0)	0.001
BED (α/β=10)	Median (Gy) Range (Gy)	72.0 60.0 – 80.5	67.1 45.6 – 75.0	0.02

who got 72 Gy or higher BED, though follow-up period is not enough to draw a concrete conclusion.



Conclusion: TE for adjuvant HT in RPS is feasible and makes it possible to deliver potential higher RT dose and LC with acceptable toxicity. The extent of resection is the most important prognostic factor for LC.

Poster 170 #2768385

THE ROLE OF STEREOTACTIC BODY RADIOTHERAPY AND RADIOSURGERY IN THE MANAGEMENT OF SOFT TISSUE AND BONE SARCOMAS

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Objective: Contemporary highly conformal radiotherapy techniques, such as stereotactic body radiotherapy (SBRT) or stereotactic radiosurgery (SRS) allow to obtain high local control rate (LC) in many primary and metastatic cancers, however their role in the management of metastatic sarcomas has not been yet established. The aim of the study was to determine the usefulness and efficacy of SBRT/SRS in the management of sarcomas.

Methods: We analyzed consecutive patients with soft tissue and bone sarcomas treated in our cancer center with SBRT/SRS. The following parameters regarding radiotherapy were analyzed: indication for SBRT/SRS, site, number of lesions, number of recurrences before SBRT/SRS, previous irradiation in-field, total dose (TD), dose per fraction (DF), method of dose prescription, treatment technique, volumes of GTVs and PTVs, early and late toxicities, best obtained SBRT/SRS result, in-field and field border progression. Additional parameters included, tumor grade, date of primary diagnosis, primary tumour site, systemic therapy received before and after SBRT/SRS, and date of overall disease progression, if occurred. The Kaplan-Meier estimator was used to calculate progression-free survival (PFS).

Results: Totally n=31 patients who underwent 1-3 SBRT/SRSs on 1-5 target lesions were included. The indications for irradiation were: oligometastatic disease(59.5%), oligoprogression(21.6%), primary definitive treatment(5.4%), recurrence definitive treatment(10.8%), and adjuvant setting(2.7%). The irratiated sites were: lungs(43.2%), head&neck(21.6%), bones(16.2%), central nervous syste(8.1%), liver (5.4%), lymph nodes(2.7%), and soft tissues(2.7%). The dose was delivered by linacs (IMRT: 21.6%, VMAT: 54.1%), CyberKnife (21.6%) and GammaKnife (2.7%). DF varied from 4 to 18 Gy, and TD from 8 to 60 Gy. GTVs and PTVs were between 0.5-110.94 cm3 (mean GTV 17.16 cm3) and 3.29-138.1 cm3 (mean PTV 38.64 cm3), respectively. SBRT/SRS allowed to obtain complete response in 18.9%, partial response in 10.8%, stable disease in 62.1% and progressive disease in 8.1%. No acute or late toxicity grade 3 or above was observed. In-field progression (at any time) was identified in 18.9% of patients. Median PFS was 9.4 months (95% CI: 2.7-16.0).

Conclusion: SBRT/SRS allows to obtain high LC with excellent treatment tolerance in patients with sarcomas. This treatment modality may be considered as an alternative to surgery in selected clinical situations, especially in oligometastatic and oligoprogressive disease.

Poster 171 #2781431

LONG TERM SURVIVAL AFTER HIGH-DOSE-RATE BRACHYTHERAPY FOR HIGH RISK RETROPERITONEAL SARCOMAS

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Objective: The aim of this study is to assess the long-term outcome of patients with retroperitoneal sarcomas (RPS) treated by aggressive surgical resection in combination with high-dose-rate (HDR) brachytherapy. Intraoperative radiotherapy (IORT) delivered with electron beam has been previously studied, however, the role of intraoperative HDR-brachytherapy is less well described. This represents the largest series of intraoperative HDR-brachytherapy in the treatment of RPS.

Methods: Patients with a diagnosis of RPS were selected from a database of all patients receiving IORT at Johns Hopkins Hospital from November 2006 through May 2014. Clinicopathologic features were collected and overall survival (OS), local control (LC) and progression free survival (PFS) were assessed.

Results: Fifty patients with RPS underwent maximal surgical resection in combination with HDR-brachytherapy at a median dose of 12 Gy (IQR:12-10 Gy). 42 patients underwent additional external beam radiotherapy (33 preoperative, 9 postoperative). High risk features were present across this cohort including: [Recurrent RPS (68%), high grade (G2/G3=80%), positive margins (R1= 52%)]. Median tumor size was 10.5 cm (IQR:15-6.75 cm) and a median of 3 organs (IQR:4.5-1.5) were resected. Common histologies included liposarcoma (n=24; 48%), leiomyosarcoma (n=11; 22%) and high grade spindle cell tumor (n=6; 12%). Median follow up was 41.5 months (IQR: 58.5-22.5 months). The 5-year OS, LC, and PFS of all patients were 57.7%, 29.8% and 26.8% respectively. Median LC and PFS were 36 months and 26 months respectively. Those receiving HDR-brachytherapy for recurrent disease had a higher risk of local recurrence compared to IORT for primary RPS [HR 3.00 (95% C.I. 1.21-7.42); p=0.017], although this did not translate to a significant decrease in overall survival [HR 2.1 (95% C.I. 0.69-6.38); p=0.19]. Patients with higher tumor grade (G3) showed higher risk of disease progression [HR 3.25 (95% C.I. 1.11-9.52); p=0.03], and trend towards increase in local recurrence [HR 2.64 (95% CI 0.89-7.80); p=0.08]. Margin status (R0 vs. R1) did not affect local control rates significantly [HR 1.45 (95% CI 0.71-2.97); p=0.31].

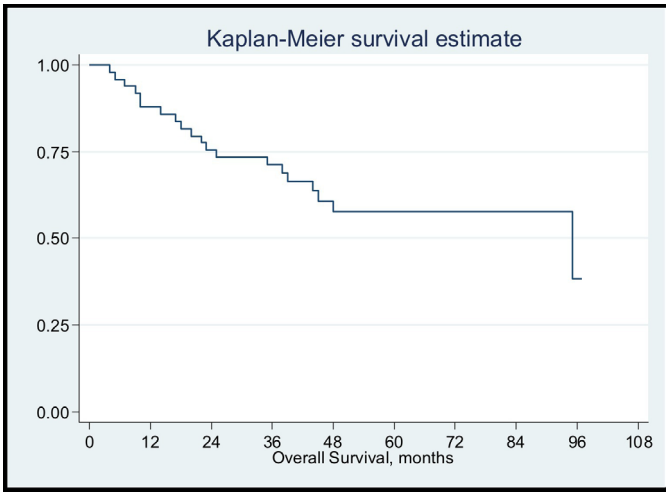

Figure 1: Overall survival of patients with resected retroperitoneal sarcoma receiving HDR-IORT

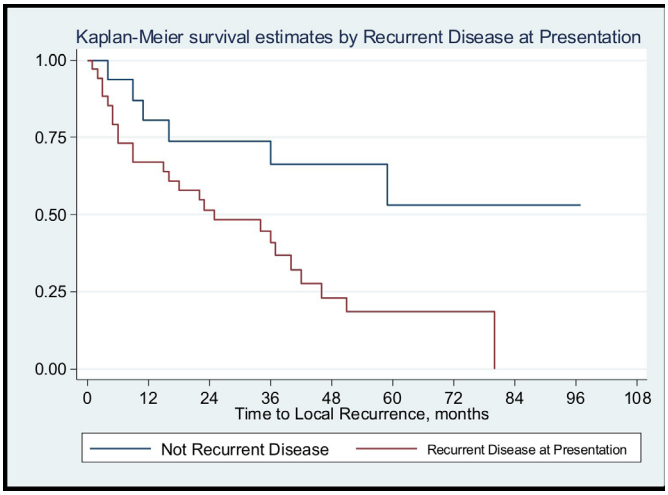

Figure 2: Comparison of local control in patients with primary RPS vs recurrent RPS at presentation

Conclusion: Use of HDR-brachytherapy along with aggressive surgical treatment can achieve good overall survival and local control among RPS patients with high risk features. Use of HDR-brachytherapy for RPS merits further evaluation, preferably in prospective randomized trials.

Poster 172 #2783761

USING RADIOMICS TO DISTINGUISH BETWEEN BENIGN AND MALIGNANT LUNG NODULES IN PEDIATRIC SARCOMA PATIENTS

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Objective: Computed tomography (CT) of the chest is an important study to evaluate for sarcoma metastases. Up to one-third of pediatric sarcoma patients have small lung nodules seen on chest CT that are difficult to characterize as being clearly malignant or benign. The presence of these indeterminate nodules can complicate staging and response assessment, often requiring more frequent follow-up imaging and/or invasive procedures to establish the diagnosis. Radiomics is the high-throughput extraction and quantification of features such as texture and intensity that can be obtained from conventional imaging studies using special computerized programs. In previous studies, radiomics has successfully characterized a variety of primary solid tumors, providing important prognostic information. We hypothesized that radiomics may help clarify the true nature of indeterminate lung nodules in pediatric sarcoma patients, and if validated could potentially guide clinical decision making.

Methods: In this pilot study, we retrospectively selected CT scans from pediatric sarcoma patients who had undergone resection of a suspicious lung nodule. On blinded review, two attending pediatric radiologists were asked

Summary of Data Including Blinded Radiology Evaluations, Examples of Radiomic Scores, and Histologic Diagnosis of Lung Nodules

Diagnosis	Size (mm)	Radiologist 1	Radiologist 2	Coarseness 1	Coarseness 2	Pathology
ES	5	Indeterminate	Likely Malignant	-0.401690	-0.435651	Benign
ES	9	Malignant	Likely Malignant	-0.148089	-0.219681	Benign
UHGSTS	6	Benign	Likely Malignant	0.154698	0.057899	Benign
ES	3	Malignant	Likely Benign	0.514354	0.526801	Malignant
ES	4	Malignant	Likely Malignant	0.631645	0.599342	Malignant
UHGSTS	9	Malignant	Malignant	0.701372	0.585908	Malignant

ES, Ewing sarcoma; UHGSTS, undifferentiated high-grade soft tissue sarcoma

to characterize these nodules as malignant, likely malignant, benign, likely benign, or indeterminate. The images were also subjected to radiomic evaluation, where quantitative data was collected on various radiomic features.

Results: Six conventional CT scans were reviewed from 5 pediatric sarcoma patients (median age 13 years, range 4-21), all of whom underwent resection of a suspicious lung nodule (median size 6 mm, range 3-9). One patient had a nodule removed at diagnosis, and then had a new nodule resected 20 months later. Three of the nodules were histologically proven malignant, and three benign. The interpretations of the two blinded radiologists varied between themselves and the pathology results, as shown in the table below. In contrast, blinded radiomic assessment showed eight quantifiable features of coarseness which segregated consistently between the benign nodules compared to the malignant nodules. Representative examples of data from two of these features are included below.

Conclusion: Radiomic scores for eight features of coarseness all were consistently higher for malignant nodules than those proven benign. These preliminary findings suggest quantifiable assessment of radiomic features such as coarseness may be different for benign vs malignant lung nodules, and could possibly allow for more precise diagnosis of lung nodules in pediatric sarcoma patients compared to conventional visual assessment by radiologists. A larger data set involving more patients and features is being studied to optimize this methodology.

Poster 173 #2789665

MRI RADIOMICS PREDICT FOR OUTCOME IN SOFT TISSUE SARCOMA TREATED WITH PREOPERATIVE RADIATION

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Objective: Soft tissue sarcoma (STS) is comprised of a rare and heterogeneous group of malignancies, with limited predictive tools available. Radiomics is a computer assisted analysis of radiologic images, whose utility in the prediction of STS outcome is not fully understood. Identifying the radiomic predictors for local and distant failure may eventually lead to a personalized treatment approach, where local or systemic treatment can be augmented to optimize patient outcome.

Methods: After IRB approval, records of non-metastatic STS patients treated between 2003- 2015 with preoperative radiotherapy (RT) were retrospectively reviewed. Patients with a treatment planning MRIs were identified, areas of gross disease were contoured with Mirada, and first order radiomic analysis was conducted on the T1 weighted MRI sequence. Radiomic features' association to local control (LC), distant control (DC) and overall survival (OS) were analyzed via univariate (UVA) cox proportionate regression analysis. Features significant ($p<0.05$) on UVA were included in a multivariate (MVA) cox regression analysis.

Results: A total of 60 patients were identified with a median follow up of 36 months. The cohort primarily consisted of cT2 (92%), cN0 (93%), and high grade (55%) disease, with a low percentage receiving concomitant chemotherapy (38%). Overall 3-year LC, DC, and OS rates were 94%, 68%, and 73%, respectively.

Most notably, an increase in entropy was associated with a LC benefit (HR 0.42, 95%CI 0.15-1.15, p=0.088), and a detriment in DC (HR 1.66, 95%CI 1.04-2.66, p=0.033) and OS (HR 1.64, 95%CI 1.07-2.50, p=0.023). An increase in the surface area to volume ratio (SVR) was associated with a LC detriment (HR 3.40, 95%CI 1.03-11.23, p=0.045), and a DC (HR 0.32, 95%CI 0.12-0.89, p=0.029) and OS (HR 0.36, 95%CI 0.15-0.88, p=0.025) benefit, which continued its association with LC and DC on MVA (all $p<0.05$).

Conclusion: When compared to an asymmetric or infiltrative mass (high SVR), the more spherical heterogeneous tumors (high entropy and low SVR) are associated with improved local control, but have a higher propensity for distant spread, which may benefit from a more aggressive systemic approach. Further validation studies will be conducted to confirm the utility of radiomics in STS.

Poster 174 #2798286

DIFFERENTIAL ONCOLOGIC OUTCOME IN ANGIOSARCOMA BY ANATOMIC SUBSITE AND ASSOCIATION WITH PRIOR RADIATION: IMPLICATIONS FOR PROGNOSTICATION AND TREATMENT STRATEGY

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Objective: Angiosarcomas are rare, aggressive soft tissue sarcomas with a poor prognosis and scarce data to inform management. Treatment typically consists of surgery and/or radiation or chemotherapy. We sought to characterize the impact of anatomic site of origin, prior radiation exposure, and treatment factors on clinical outcomes.

Methods: We performed an IRB approved retrospective review of 139 patients with localized angiosarcoma treated at our institution from 1968 to 2015. All cases were reviewed by central pathology. Overall survival (OS) and local control (LC) were estimated using the Kaplan-Meier method, together with multivariate analyses using the Cox proportional hazard regression model to identify prognostic factors.

Results: With a median follow up of 24.1 months, the median OS was 30.3 months and 2-yr rates of OS and LC were 47.1% and 46.0%, respectively. 73 men and 66 women were treated with a median age of 68 years (range: 19 to 93), including scalp (n=49, 35.3%), trunk (n=32, 23.0%), breast (n=28, 20.1%), extremity (n=26, 18.7%), and head and neck (n=4, 2.9%) primary. Thirty-three (23.7%) had radiation-associated angiosarcomas (RAAS), including 15 breast and 18 non-breast RAAS. Prior malignancies for RAAS included breast (n=22), prostate (n=2), rectal cancer (n=3), or other (n=6): with median time from prior malignancy to onset of RAAS of 7.5 years (range: 4 - 50). Patients were treated with surgery (n=51,36.7%), radiation (RT) (n=19,13.7%), or surgery with pre- and/or post-operative RT (n=63,45.3%). 25.9% of the patients were treated with chemotherapy.

On univariate and multivariate analysis, younger age ($p<0.001$), tumor size 5 cm ($p<0.001$), lower grade ($p<0.05$), surgery ($p<0.001$), and negative margins ($p<0.001$) were associated with improved OS. On multivariate analysis, LC was worse for patients with positive margins (HR 4.54, $p<0.005$) and varied significantly depending on site of primary ($p < 0.05$). Radiation-associated breast angiosarcoma had worse LC than spontaneous breast angiosarcoma with a 2-yr LC rate of 60.3% versus 82.3% ($p<0.05$) respectively though 2-yr OS of 70.0% versus 90.9% respectively was not statistically different.

Conclusion: In our single-institution experience with angiosarcoma, prognostic factors included age, tumor size, tumor grade, margin status, and resectability. Local control was worse for radiation-related breast compared to spontaneous breast angiosarcoma, suggesting potential treatment or biologic differences that should be further investigated.

Poster 175 #2799245

IDENTIFYING CHALLENGES IN COMPREHESIVE GENOMIC PROFILING OF SARCOMA SPECIMENS

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Objective: Comprehensive genomic profiling (CGP) of sarcomas is rapidly becoming necessary routine practice. Sarcomas are a heterogeneous group of tumors and tissue specimens are often difficult to obtain or may be subject to tissue decalcification that can damage nucleic acid. These factors contribute to the difficulty of successfully performing CGP on sarcoma specimens. The conditions for optimal CGP success are unclear, and to our knowledge there is no published data on the failure rate of genomic profiling in sarcoma patients in a routine clinical setting. We hypothesized that sarcoma subtypes and biopsy site may influence the rate of successful genomic profiling.

Methods: To better define characteristics of sarcoma profiling success, we performed a single institution retrospective study evaluating the profiling outcomes of 395 patients seen at a sarcoma clinic from which 441 processed biopsy samples were procured between November 2012 and May 2017 and were subsequently profiled using the FoundationOne™ Heme platform. Tumor type, location of biopsy, type of biopsy, and profiling outcome were captured for all samples. CGP failures were defined as insufficient extracted DNA or RNA, low tumor content, or low quality sequencing metrics. Descriptive statistics were used to characterize the results on a per sample basis.

Results: Across all samples, the overall profiling failure rate was 13% (57/441 samples). Bone sarcomas exhibited significantly higher failure rates at 28% (15/54) as compared to soft tissue sarcomas (Chi-square, $p = 0.001$). In particular, chordomas and chondrosarcomas exhibited a failure rate of approximately 40% (5/11 and 7/17 samples respectively). In contrast, soft tissue sarcomas as a whole exhibited a failure rate of 11% (42/387), with the highest failure rate in myxofibrosarcoma at 25% (4/16). Biopsy location also correlated with profiling efficiency. Bone spec-

imens had a 21% (7/32) failure rate whereas lung biopsy specimens had a 16% (8/50) failure rate.

Conclusion: This study is the largest in-depth evaluation of sarcoma CGP failures to date. We note that CGP in sarcoma is successful in a large majority of patients. However, the tumor location and tissue subtype are determinants of profiling success, likely secondary to pre-analytic variables that impact quality of DNA and RNA such as decalcification as well as tumor cellularity, respectively. Our results support implementing standard biopsy collection protocols for sarcoma specific subtypes to improve the rate of CGP success.

Poster 176 #2801252

QUALITY ASSURANCE ROUNDS FOR SARCOMA RADIOTHERAPY PATIENTS: TEN-YEAR RESULTS

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Objective: Quality assurance (QA) rounds are corner stone in radiation oncology practice. This study aimed to determine the changes in sarcoma radiation therapy (RT) plans based on QA review rounds in a single tertiary cancer center.

Methods: Prospectively collected data of the RT plans for sarcoma patients who were treated at our institution between January 2007 and December 2016 were retrieved. Plans subjected to minor or major modifications were recorded; major modifications were defined as any significant change in target volume definition, RT dose prescription, planning objectives or organs-at-risk (OAR) constrains which require re-planning. While minor modification included trivial treatment plan change which doesn't require re-planning.

Results: Out of a total 7943 plans discussed at our QA rounds, there were 318 (4%) sarcoma cases. Planning was performed using 3D-conformal radiotherapy (3D-CRT) in 235 cases (74%), while intensity modulated radiation therapy (IMRT) was implemented in 83 plans (26%). The majority of our patients received post-operative RT (n=305, 96%), while 13 patients (4%) treated in neo-adjuvant setting. The reviewed treatment plans were distributed as follows; 293 (92%) were approved without modification, 7 (2%) needed minor modifications, while 18 (6%) required major modifications. Major modification included significant changes in: target volume definition (e.g. to include edema; n=6, 33%), RT prescription dose (e.g. higher dose based on operative and/or radiological finding, n=5, 28%), planning objectives criteria (n=4, 22%) and OAR constrains (n=3, 17%). Among plans which required major modifications, seven out of 235 (3%) were planned with 3D-CRT, and 11 out of 83 (13%) were planned with IMRT.

Conclusion: QA rounds detects potential deviations prior to start of RT. They harmonize the practice within radiation oncology team and enhance the accuracy of radiation process, especially in patients treated with IMRT. Further studies are required to evaluate QA rounds in a multi-institutional fashion.

Poster 177 #2804368

IMPACT OF 18F-FDG-PET-CT IN TREATING SOFT TISSUE TUMORS: ANALYSIS OF A PROSPECTIVELY KEPT DATABASE

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Objective: The real value of FDG-PET-CT in the treatment of soft tissue tumors is controversially discussed, an often labelled as "might be useful" in sarcoma guidelines. We analyzed the value of the FDG-PET over a 7-year span in a setting characterized by a identical clinical team making the indication and staff of nuclear medicine physicians using an identical technical equipment and procedural routine as well as reporting system. A dedicated statitstical evaluation plan for the whole cohort was developed beforehand.

Methods: From 2009-15, 194 patients (101m, 93f, median age 49,9 yrs, range 16,9 - 79,8 yrs) with biopsy proven soft tissue tumors were studied: STS n=59 (30%), GIST n=57 (29%), desmoid n=50 (26%), other n=28 (15%). The clinical indications were, with two indications in some of the patients:

A) dignity of the lesion (n=30)
B) staging/restaging (n=62)
C) suspected recurrence (n=32)
D) response control (n=98)

Dynamic PET studies were performed after i.v. injection of 300–370 MBq 18F-FDG for 60 min with a dedicated PET system (ECAT EXACT HR plus, Siemens, Erlangen, Germany). The last images at 55–60 min were used for quantitative analysis, SUV=tissue concentration (MBq/g)/[injected dose (MBq)/BW (g)].SUV value provided by the quantification software in VOI ,being more robust SUVmax. PET images were analysed using the software package Pmod (PMod Technologies, Zurich, Switzerland).

For response control, CMR was defined as complete metab. response, PMR as a ≤ 25% decrease, SMD stable metab. disease ≤25% increase, and PMD ≥25% increase. For sensitivity analysis classical RP, FP, RN, FN and 'n.a.' were used in correlation to histology results, WB-CT and biopsy of M1-suspected lesions or RECIST criteria in response control. For statistical analysis we used StatXact-9, Cytel Studio, Version 9.0.0, 2010 and SAS Institute Inc. Software, Version 9.4, 2012. Median follow-up of the patients studied is 3.2 yrs.

Results: 192/194 patients were evaluable, histological subtypes differed significantly between genders for desmoid vs. GIST, p=0,00716 (χ2-Test). SUVMax for the subtypes of sarcoma, desmoid, and GIST did not show significant differences (Wilcoxon p=0,068).
For group A (dignity), the PPV was 0,84 and NPV was 1,0 resulting in a sensitivity of 87,5% and specificity of 88%.
For group B (staging), the PPV was 0,97and NPV was 0,6 resulting in a sensitivity of 88% and specificity of 85%.,It was obvious that the detection of M1 disease was less rewarding with PPV of 0,94 and NPV of 0,69 only yielding a sensitivity of 81% and a specificity of 90%.
For group C (recurrences), the PPV was 0,892 and NPV was 0,82 resulting in sensitivity of 91.6% and specificity of 81.8%.
For group D (response control), there was a significant difference betwen the subgroups at baseline SUVMax. All patients being treated with tyrosine kinase inhibitors. Under imatinib, we could not find statistically different results between GIST and desmoid patients with respect differences between baseline and 1st treatment control (DiffSUVMax, Wilcoxon, 0,36.)

Conclusion: To achieve accurate and reliable results from FDG-PET-CT, a clear process of selecting the correct indications isrequired and recommended. There is good specificity and sensitivity for the questions addressed in our patient examinations over a long time period, particularly when staging/restaging and dignity of lesions are addressed. Beyond instructive cases on response to TKI therapy in GIST dominating the perception of 18F-FDG-PET, the method needs to be developed further for indications with therapeutic TKI use. Our results show, that at least desmoid tumors could be evaluated with the same accuracy as GIST.

Poster 178 #2804561

CLINICAL CHARACTERISTICS AND PATTERNS OF CARE IN PARATESTICULAR SARCOMA: A DUAL INSTITUTION STUDY

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Objective: Paratesticular sarcomas are rare tumors and treatment protocols are not well defined in the literature. These tumors are typically managed by surgical resection with pre or post-operative radiation therapy depending on surgical margins, histology, and staging. Due to the low occurrence rate of these sarcomas, there is no consensus on the optimal treatment of these tumors. The purpose of this study is to assess prognostic factors in paratesticular sarcomas and to analyze the impact of different treatment protocols on survival rates for paratesticular sarcomas.

Methods: We identified 60 patients with paratesticular sarcomas who presented to two large sarcoma institutions within our network between 2005-2014 for a retrospective review of clinicopathologic variables, treatment details, and outcomes. A cox multivariate regression model and Kaplan-Meier log rank were used for statistical analysis of the relationship between treatment, clinical factors, overall survival (OS) and progression free survival (PFS).

Results: The median age was 55 years (range 17-87 years). 48 (80.0%) presented with a primary tumor in the inguinal/groin region, 10 (16.7%) presented with a scrotal tumor, and 2 (3.3%) presented with testicle confined tumor. Tumor histology included dedifferentiated liposarcoma (17, 28.3%), well differentiated liposarcoma (9, 15.0%), leiomyosarcoma (5, 8.3%), spindle cell sarcoma (5, 8.3%), epithelioid sarcoma (5, 8.3%), and dermatofibrosarcoma (4, 6.7%). 4 (6.7%) had a transcrotal biopsy before resection, 22 (36.7%) had an excisional biopsy, 24 (40.0%) had an unplanned excision and 15 (25.0%) included hernia repair on initial surgery. Treatment protocols varied widely: 100% of patients underwent resection. 33 (55.0%) of these patients were treated with surgery only, 11 (18.3%) surgery followed by postoperative radiation, 6 (10.0%) initial non-oncologic surgery then subsequent radiation prior to oncologic surgery, and 10 (16.7%) neoadjuvant radiation then surgery. Of note, there was an institutional variance in % treated with surgery only: one institution 25.3%, the other 68.3%. Of those receiving surgery, 38 (59.4%) underwent orchiectomy; 84.2% used inguinal approach, 15.8% used scrotal approach. 5 (8.3%) had tumors with lymphovascular invasion (LVI), 10 (16.7%) cases had internal inguinal ring violation, and 6 (10.0%) had external ring violation. 10 (16.7%) had pelvic

extension of the tumor. There was institutional variance in orchiectomy rate: 52.6% at one institution and 61.0% at the other (p=0.045). 13 (21.7%) required an abdominal wall resection. 29 (48.3%) resection margins were R0, 7 (11.7%) were R1, and 16 (26.7%) were R2.

27 (43.8%) patients were treated with radiation therapy. Use of RT varied by institution: 73.7% vs. 31.7% (p=0.005). Median total RT dose was 50.4 Gy. Median preoperative RT dose was 50.0 Gy. CTV varied with case, only 7 (10.9%) including the scrotum.
With a median follow up in this study of 50.0 months, 5 year OS was 63.7%, and PFS was 49.3%. Multivariate regression analysis identified dedifferentiated liposarcoma histology (HR=4.74, 95% CI 1.41-15.96, p=0.012) as a poor prognostic factors for OS, while dedifferentiated liposarcoma (HR= 7.28, 95% CI 1.82-29.12, p=0.005) and lymphovascular invasion (HR=11.58, 95% CI 2.57-52.20, p=0.006) were poor prognostic factors for PFS. No association was found between timing of radiation therapy (pre-op vs. post-op) and OS or PFS.

Conclusion: Paratesticular sarcomas do not have a consensus management protocol due to their rare incidence and high frequency of initial unplanned excision. We identified dedifferentiated liposarcoma as a poor prognostic factor in OS and PFS and LVI as a poor prognostic factor in PFS. A larger multi-institutional study of the patterns of care and outcomes of this unique anatomic site may help guide treatment protocols.

Poster 179 #2804687

MRI FEATURES PREDICTIVE OF RESPONSE TO METHOTREXATE AND VINORELBINE IN DESMOID FIBROMATOSIS

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Objective: Desmoid fibromatosis (DF) is a mesenchymal tumor that is locally aggressive and historically treated with surgical resection, with high recurrence rates. Systemic treatment of progressive DF can be associated with improved progression-free rates however the use of medical therapy remains controversial. Also, treatment response as defined by RECIST 1.1 by measuring maximum tumor dimension (D_{max}) may not accurately evaluate response to medical treatment in desmoid patients. We sought to assess if imaging parameters such as approximate tumor volume (V_{tumor}) and MRI features, specifically T2 signal were more predictive of response to medical therapy than D_{max}.

Methods: A retrospective chart review between 1997 and 2015 identified 22 patients with biopsy proven DF treated with Methotrexate and Vinorelbine and followed with MRI throughout treatment. Dmax, Vtumor and quantitative T2 hyperintensity using interquartile range scoring on MRI were compared pre, mid (between 3-9 months) and post-treatment. On T2-weighted or T2-weighted fat-saturated MRI images, tumors were ranked as containing: 0-25%, 25-50%, 50-75% or 75-100% of internal high T2-signal intensity. Treatment response was defined as: partial response (PR) if the size or T2 quartile score decreased, stable disease (SD) if there was no change in size or T2 quartile, progression of disease (PD) if there was an increase in size or increase in T2 quartile, and complete response (CR) if size decreased and/or the entire lesion was hypointense on T2-weighted images.

Results: Mean age was 31 yrs with 17 females and 5 males. Patients presented with primary (n=18) or recurrent/residual (n=4) with DF of the extremity (n=9), abdominal wall (n=7), head and neck (n=3), chest wall/back (n=2) or mesentery (n=1). At end of treatment (median 20 mos (range 9-27)), D_{max} mean decreased by -30% and V_{tumor} decreased by -76% overall. On T2 weighted imaging, CR was observed in 13 and PR in 5 patients. Mid treatment, 2 had PD and 7 had SD as per D_{max} and V_{tumor} with T2 change indicative of PR in all cases. Both patients with PD continued therapy and had CR at end of treatment. Four patients progressed post treatment, median PFS was 31 months (95% CI: 14.9-137) and all had complete response (CR) on T2 imaging treatment end.

Conclusion: Evaluation of treatment response for DF utilizing an estimated volume of tumor and monitoring the degree of T2-weighted signal intensity change within the tumor may be better predictors of response to medical therapy than maximum tumor dimension. Findings from this study warrant prospective multi-institutional validation.

Poster 180 #2804772

METASTATIC CHORDOMA TO LYMPH NODES IN SPINE PATIENTS WHO UNDERWENT SURGICAL RESECTION AND RADIATION THERAPY

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Objective: Chordoma is an extremely rare malignancy with an approximate annual incidence of 1:1,000,000, accounting for approximately 20% of primary spinal tumors and only 3% of all bone tumors. Chordomas have been reported to metastasize to a number of secondary sites in the body, with lung metastases accounting for over

50% of metastatic chordoma. Additional secondary sites include distal bone, (roughly 20% of all cases), soft tissue (15%), and liver, (fewer than 10%).

However, chordomas have anecdotally been known to spread to lymph nodes. There is little published data on the occurrence of metastatic chordoma to lymph nodes or prognostic significance aside from a few case reports. We report the outcomes of a large case series of chordoma with nodal involvement.

Methods: Primary mobile spine, skull base, and sacral chordoma patients treated at MGH from 1993 to 2017 were identified under an IRB approved protocol. Patient demographics, tumor and pathologic status, lymph node metastasis location, size, treatment details, and oncologic outcome were collected.

Results: Fifteen cases with either initial nodal involvement (9) and/or subsequent nodal failures (8, 2 with both) were identified from 140 mobile spine and sacrococcygeal and 777 base of skull chordoma cases. Median age at diagnosis was 44 years (range 10–67). The patient profile was 5, 33.3% female and 10, 66.67% male. The three histologies identified were 13, 86.7% Nonchondroid Chordoma, 1, 6.7% Poorly Differentiated and 1, 6.7% De-Differentiated chordoma. Primary chordoma sites of these cases included 3 skull base, 5 cervical, 1 lumbar, and 6 Sacral/coccygeal. 40% percent of the involved lymph nodes were over 8 cm in size, 20% were under 8 cm, and 40% were undetermined. Of the nine cases with nodal metastasis on initial diagnosis, only two were apparent on physical exam. Two cases were found only on pathology from sampling of suspicious lymph nodes at the time of the resection of the primary tumor. Six cases were detected on radiographic imaging (CT, MRI, or PET). The frequency of lymph node metastasis is 1% overall: 0.4% for base of skull, 3.07% for cervical spine, 0% for thoracic spine, 1.1% for lumbar spine, and 3% for sacrum and coccyx. With median of 39 months of follow up, 5 year OS was 53.3% (+/-16.9%), disease specific survival was 76.7% (+/-11.9%)%, DMFS was 55.2% (+/-14.2%), locoregional control was 31.7% (+/-13.7%). Compared to 140 mobile spine and sacrococcygeal chordoma patients without metastases, there was not a statistically significant difference in OS. Age, poorly diff and dediff versus conventional and R0 resection were significant factors for OS on multivariate analysis. However, there was significant difference in disease specific survival ($p < 0.001$), DMFS ($p<0.001$), and locoregional control ($p=0.013$) associated with N+ status. There were too few BOS cases with nodal metastasis for statistical comparison to the remainder of the BOS cases.

Conclusion: In this large series of chordomas with nodal involvement at either initial presentation or subsequent failure, we demonstrated that lymph node metastasis from chordoma is rare; however the prognosis is poor. Initial evaluation and follow up should consider assessment of potential lymph node drainage sites.

Poster 181 #2739620

RADIOMIC T2-WEIGHTED MRI GEOMETRICAL AND TEXTURE FEATURES TRAINED CLASSIFICATION MODELS USING MACHINE LEARNING FOR HISTOLOGIC PREDICTION OF SOFT TISSUE TUMORS

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Objective: To identify radiomic texture features of soft tissue lesions and develop a machine learning-based predictive model to classify soft tissue tumors as malignant or benign.

Methods: T2-weighted fat suppressed (T2-FS) MR images from a patient cohort with histologically verified soft tissue tumors (16 malignant, 18 benign) were analyzed and used to train predictive classification models. Twenty additional patients with blinded pathology results were used as an independent validation cohort. Texture and geometrical features were extracted from segmented lesions using 13 directional gray level co-occurrence matrices (GLCM), 256 gray level quantization, and 3 pixel offsets. Feature selection was performed by both Correlation-based Feature Selection (CFS) and wrapper-subset schemes using different machine learning strategies, including logistic regression (LG), sequential minimal optimization (SMO), multi-layer perceptron (MLP), and stochastic gradient descent (SGD). (See Figure 1) Area under the curve (AUC), sensitivity, and specificity were used to assess predictive accuracy of selected features and classification scheme.

Results: Feature selection substantially reduced the dimensionality of the features for predictive model training from 826 to fewer than 10 prominent features. The highest performing models in terms of AUC were the SGD wrapper+MLP classifier and the SGD wrapper+SGD classifier with 94.8±1.1% and 94.1±2.4% accuracy, respectively. The results of the additional 20 patient testing data set showed that all models had a classification accuracy of at least 85% (17/20), with the SGD wrapper+SGD classifier being the top performer, exhibiting an accuracy of 95% (19/20).

Conclusion: Radiomics models show promise in predicting the histology of soft tissue tumors; further work is needed to provide additional grade discrimination, and prospective validation studies will be necessary to determine whether these models are clinically reliable.

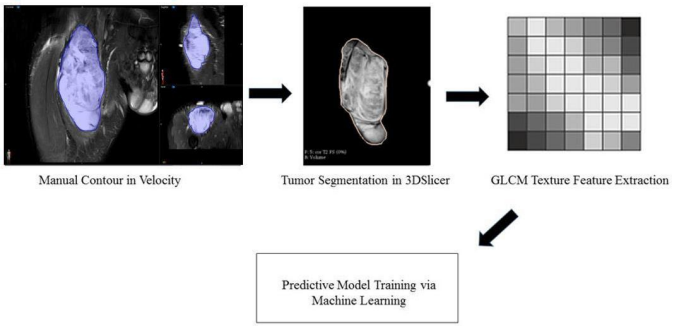

Figure 1: General workflow starting with manual segmentation in Velocity, tumor segmentation in 3DSlicer, GLCM texture extraction via Matlab, and finally predictive model training using Weka.

Poster 182 #2762742

EXPLORATION OF THE ROLE OF REPEATED STEREOTACTIC BODY RADIOTHERAPY FOR SALVAGING TREATMENT OF REPEATEDLY RECURRENT LIPOSARCOMA

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Objective: Many patients with soft-tissue sarcomas experience recurrence. Unfortunately, soft tissue sarcoma is often encountered recurrence in 40-80% of patients after complete resection of the metastatic site, so repeated surgical resection is often required. Liposarcoma represents the most common subtype of soft tissue sarcoma and it is known that it is sensitive to radiotherapy.Therefore, we would like to analyze the therapeutic effect of stereotactic body radiotherapy (SBRT) unging high dose of RT in relapsed liposarcoma, which are inoperable.

Methods: Between 2005 and 2017, 16 patients with liposarcoma underwent SBRT for recurrent disease after curative resection of primary lesion. Total 92 metastatic lesions were treated. Location for the tumor were 32 in abdomen, 34 in skeltal and spine, 19 in lung and pleura, and 7 in others. Tumor size were 1-27cm (median 3.8cm) and dose of SBRT were 10-60 Gy in 1-6 fractions (median 30 Gy in 3 fractions). In the histologic subtype, 15 lesions were well differentiated, 61 lesions were myxoid/round cell, and 16 lesions were pleomorphic. Treated lesions were divided into 6 groups according to SBRT dose and the 3-year local control rate was calculated for each group. Tumor control probability model was developed using least square estimation.

Results: Complete remission was achieved in 33 lesions. The 3-year local control and overall survival rates were 77% and 83%, respectively (Figure 1). A 80% and 90% tumor control probability was predicted at 20 Gy in 2 fractions and 24.9 Gy in 3 fractions, respectively (Figure 2). Dose of SBRT (10 Gy/1 fraction vs. > 10 Gy/1 fraction) (p= 0.023, HR = 0.154), gross tumor volume (< 100cc vs. >= 100cc) (p=0.011, HR =6.689), and demarcation of tumor from surrounding tissue (well vs. poor) (p=0.017, HR =7.296) were statistically significant factors for local control in multivariate analysis. Severe toxicity > grade 2 was not observed after SBRT.

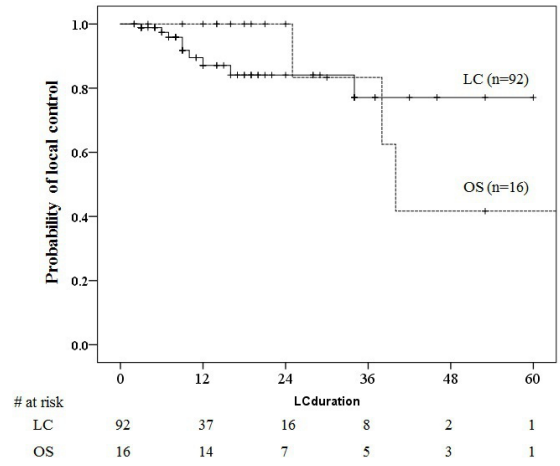

Figure 1. Overall survival and local control rates in all patients and all treated lesions, respectively.
The 3-year overall survival and local control rates were 83% and 77%, respectively.

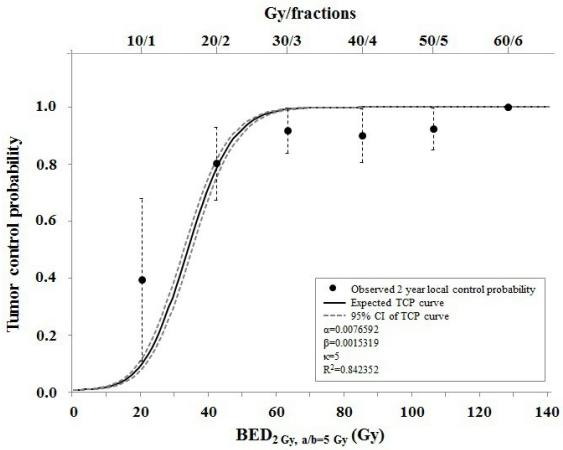

Figure 2. Tumor control probability according to radiation dose.
Treated lesions were divided into 6 groups according to the biologically equivalent dose (BED) with α/β = 5 Gy. The parameter fitting for local control rate at 2 years vs. $BED_{5\ Gy}$ is plotted.

Conclusion: SBRT-based salvage treatment could be considered as a efficient and safe approach to increase local control and survival in patients with repeatedly recurrent liposarcoma. Liposarcoma can be controlled by low doses of SBRT, so SBRT doses may need to be reduced considering the possibility of repeated SBRT for repeated recurrences.

Poster 183 #2779328

SUPPRESSION OF HIF-1α SENSITIZES EXPERIMENTAL SARCOMA TO STEREOTACTIC BODY RADIATION THERAPY

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Objective: HIF-1α is the master transcription factor that promotes the survival of hypoxic cells, resistance of tumor cells to radiotherapy or chemotherapy, vascularization, invasion, recurrence, and metastasis. HIF-1α is up regulated in tumors soon after high-dose irradiation such as stereotactic body radiation therapy (SBRT) due to increased hypoxia and oxic stress stemming from reoxygenation of hypoxic tumor cells. Anti-diabetes drug Metformin and anti-cancer drug Docetaxel effectively down regulates HIF-1α expression in hypoxic tumor cells in vitro

The purpose of our study was to reveal whether suppression of radiation-induced up regulation of HIF-1α improves the outcome of SBRT using FSaII fibrosarcoma of C3H mice.

Methods: FSaII tumors were grown subcutaneously in the hind limbs of C3H mice. When the tumors reached 5-7 mm in diameters, they were irradiated with 15 Gy of X-rays in a single fraction and the host mice were treated with metformin at 125 mg/kg (i.p) daily or docetaxel at 15 mg/kg (i.p) once a week. The response of tumors to irradiation with or without drug treatments was assessed by examining the tumor growth rate and by determining the clonogenic cell population in tumors with in vivo-in vitro excision assay method. The changes in expression of HIF-1α and VEGF in the tumors were studied with immunohistochemical staining of tumor tissues.

Results: The drug treatments of host-mice markedly increased the radiation-induced tumor growth delay. The surviving cell number in tumors progressively declined for 3-5 days after 15 Gy irradiation in a single exposure due to vascular damage then repopulated. Metformin and docetaxel exerted minimal effect on the initial cell death and the subsequent additional secondary cell death after 15 Gy irradiation, but the drugs profoundly inhibited the repopulation of tumor cells. It appeared that the lack of VEGF activation as a result of the decrease in HIF-1α by the drugs inhibited revascularization leading to prevention of repopulation of tumor cells and regrowth of tumors.

Conclusion: The suppression of HIF-1α accumulation by metformin or docetaxel markedly improved the efficacy of SBRT to control FSaII tumors in mice.

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Poster 184 #2791356

A SERUM MICRORNA CLASSIFIER FOR THE DIAGNOSIS OF BONE AND SOFT TISSUE SARCOMAS OF VARIOUS HISTOLOGICAL SUBTYPES

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Objective: Diagnosis of sarcomas is considered to be quite difficult because of the rarity and diversity of the disease. The development of a novel diagnostic test for sarcoma is eagerly awaited. The aim of this study is to address whether serum miRNA profiles can be used to detect only malignant cases (sarcomas) of bone and soft tissue tumors regardless of histological subtypes.

Methods: The case-control study included 1,002 patients with bone and soft tissue tumors representing more than 43 histological subtypes, including sarcomas, intermediate, and benign tumors. As controls, 275 healthy and 240 patients with other cancers were enrolled. MiRNA levels were measured using microarray. Patients were divided into three cohorts: a discovery to identify differentially expressed miRNAs; a training to establish a diagnostic index; and a validation to validate the utility of the index. An exploratory cohort was used to evaluate the index in recurrent sarcomas, intermediate tumors, and other cancers.

Results: Circulating serum miRNA profiles, determined by microarray analysis, in malignant cases of bone and sarcomas, were clearly distinct from those in benign and healthy controls. A promising molecular detector, diagnostic index II, was developed using the serum levels of three miRNAs. Diagnostic index II also clearly separated sarcomas from benign and healthy controls with remarkable high sensitivity (94%), specificity (90%), and accuracy (91%).

Conclusion: Comprehensive analysis of serum miRNA profiles in approximately 1000 cases of bone and soft tissue tumors identified a promising classifier, diagnostic index II, calculated using the serum levels of three miRNAs with remarkable performance for the detection of sarcoma. The present data overcome a serious problem associated with sarcoma diagnosis and provide the basis for the development and implementation of miRNA-based strategies for diagnostic purposes in the clinic.

Poster 185 #2804325

DIFFERENTIATION OF ENDOMETRIOMAS AND DESMOIDS IN THE ANTERIOR ABDOMINAL WALL IN FEMALES OF REPRODUCTIVE AGE

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Objective: Desmoids and endometriomas are rare, predominantly present in females of reproductive age. Endometriomas maybe be left in situ and often atrophy during pregnancy and post-menopause, unlike desmoids.

Endometriomas rarely recur after excision, whereas desmoids frequently recur and so often require extensive resection. Differentiation prior to management is essential.

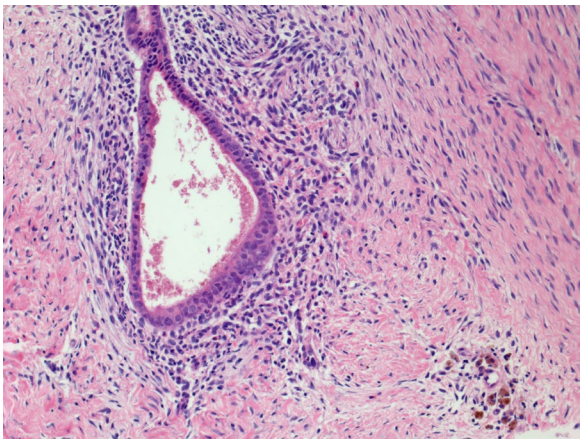
This study was designed to determine distinguishing clinical and radiological features between desmoids and endometriomas of the anterior abdominal wall.

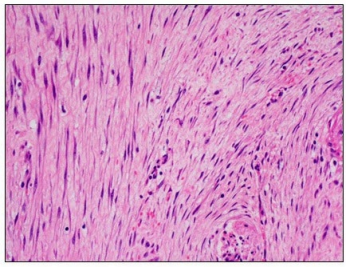
Methods: This was a retrospective comparative analysis over eleven years (January 2006 to December 2016) in a high volume sarcoma centre. Patients with endometriomas (n=27) and desmoids (n=110) were identified. The inclusion criteria were; female, reproductive age, anterior abdominal wall, inferior to the umbilicus. Patients were excluded if there were inadequate records of radiological or clinical features. Endometriomas (n=23) and desmoids (n=19) were compared.

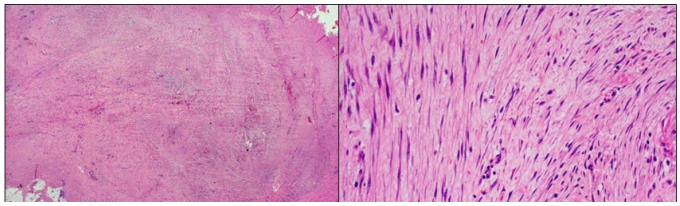
Radiological features included; size, location (subcutaneous v intramuscular), magnetic resonance imaging T1 and T2 signal, restriction diffusion imaging, imaging characteristics (heterogenous/homogenous, internal fluid locules), and border definition.

Continuous data were reported as means with p values from Paired T tests, and categorical data reported as percentages and p values from McNemar or Fishers exact tests.

Results: Clinically, 50% of patients with endometriomas reported cyclical symptoms, compared with zero patients with desmoids (p=0.007). The mean age for patients with desmoids and endometriomas was 34 years and 37 years respectively (p=0.71). Mean tumour size of desmoids and endometriomas was 6.8cm and 3.1cm respectively (p<0.0001). 70% of endometriomas and 58% of desmoids were heterogenous (p=0.32). Desmoids had a greater incidence of internal fluid locules (93% v 50%, p=0.03). There was no difference in exhibition of bright T2 areas (75% v 53%, p=0.19) between desmoids and endometriomas respectively. There was a greater number of desmoids with a low T1 signal (88% v 53%, p=0.04). All desmoids and endometriomas exhibited restricted diffusion and enhancement.







Conclusion: Endometriomas and desmoids occur infrequently and can be challenging to differentiate. However, endometriomas may be associated with smaller size and cyclical pain, while desmoids may have a greater incidence of low T1 signal. We recommend obtaining histological or cytological diagnosis prior to management

Poster 186 #2804609

ADJUVANT RADIATION THERAPY WITH IMMEDIATE INTERSTITIAL BRACHYTHERAPY FOLLOWING SURGICAL EXCISION FOR PEDIATRIC KELOID

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Objective: Keloids are hypertrophic scars made of fibrous tissue that elevate and expand beyond the wound border, and can be both painful and disfiguring. While a range of treatment options exist, including pressure treatment, silicone sheeting, topical and injected medications, cryotherapy, laser therapy, and of course surgical excision, response may be poor and recurrences are common. Surgical excision with adjuvant radiation has been shown to be an effective treatment, but radiation exposure is of increased concern in the pediatric population. In this study, we reviewed outcomes and toxicity when using

interstitial brachytherapy following resection of recurrent/refractory keloids.

Methods: An IRB-approved retrospective review was conducted, including all patients with histologically confirmed recurrent/refractory keloid diagnosis between January 2011 and January 2017 treated with repeat resection and adjuvant brachytherapy. Pediatric patients (ages 5.2-20.4 years, median age 17.3), treated for keloid scarring with excision followed by immediate adjuvant radiation therapy were included. All patients were treated with surgical excision of keloid and intraoperative placement of an interstitial brachytherapy catheter at the excision site. Patients were then simulated and planned to undergo adjuvant radiation therapy. High-dose-rate (HDR) brachytherapy was performed utilizing an Ir-192 afterloader, with 1200-1500 cGy (median 1200 cGy) delivered in 3 fractions given a minimum of 4 hours apart, with all radiation therapy delivered within 48 hours from start to finish. (see Figure 1) Dose was prescribed to 0.3-1cm from the center of the applicator (median of 0.5 cm).

Results: A total of 22 patients with a pathological keloid diagnosis were treated with surgical excision of keloid followed by immediate post-operative radiation during the study; the 22 patients had 32 total keloids excised. Average length of follow up was 7.5 months. Three patients had recurrence of keloid (14% of patients, 9% of total keloids). Follow up time for these patients and recurrence of keloid was observed at 6 months, 9 months, and 4.5 years. Hyperpigmentation was observed in 82% of patients after treatment, the remaining had some mild hypopigmentation. 82% of patients reported improvement of pain and itching after treatment. No patients developed secondary malignancy to date.

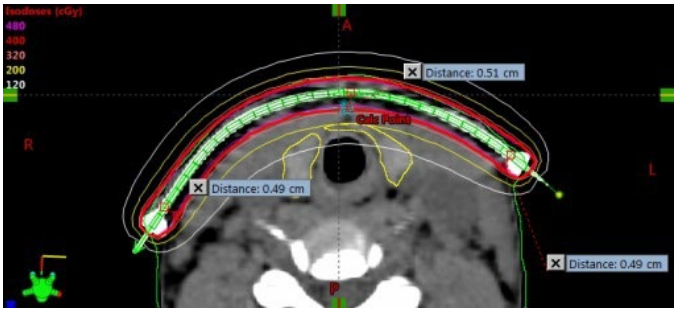

Figure 1. Treatment plan for high-dose-rate (HDR) interstitial brachytherapy for a transverse neck keloid on a 14 year old boy. Note rapid dose falloff with sparing of the underlying thyroid tissue.

Conclusion: In our cohort of 22 pediatric patients treated with surgery and adjuvant radiation, we observed recurrence rates that were much lower than other modes of treatment and consistent with other reports of positive outcomes after adjuvant radiotherapy. Side effects were minimal, including no reports of secondary malignancy. Longer followup will be necessary to assess for ultimate recurrence rates and any late toxicity.

Poster 187 #2782453

THE CONSEQUENCES OF PREVIOUS EXTERNAL BEAM RADIATION IN THE SURGICAL TREATMENT OF LOCAL RECURRENCE OF EXTREMITY SOFT TISSUE SARCOMA: A COMPARATIVE RETROSPECTIVE STUDY OF 117 PATIENTS

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Objective: Practitioners deciding for or against the use of adjuvant radiation in the treatment of a soft tissue sarcoma (STS) face a trade-off between the risk of local recurrence and the effect of radiation. Sometimes the oncologic benefits of radiation are uncertain. This decision reaches its pinnacle when dealing with patients who had inadequate resection at another centre. One may choose a postoperative irradiation with the risk of dealing with a local recurrence on an irradiated field. Other may discard radiation altogether, with an increased risk of local recurrence but knowing that if the tumor recurs it will occur on non-irradiated tissue.
We decided to compare the outcome of patients operated on for a local recurrence with and without previous radiation with regards to surgical site infection/wound complication (SSI/WC).

Methods: This was a single centre retrospective study. 117 patients, 48 (41%) with previous radiation and 69 (59%) without previous radiation, operated on for the local recurrence of an extremity STS at our hospital between 2000 and 2015 were included. There were 64 females (55%) and 53 males (45%), with a mean age of 62 years. 66 tumors (56%) were high grade, 104 deep-seated tumors (89%), and half were large.
The principal outcome criterion was the cumulative incidence of revision for SSI/WC. Cox regression models were used to find variables associated with this outcome.

Results: The overall cumulative incidence of reoperation for SSI/WC was 25% (17% - 33%), 28% (19% - 37%), and 33% (22% - 44%) for all patients at 12, 24, and 60 months respectively and was significantly different between both groups (p=0.027). The cumulative incidence of reoperation for SSI/WC was 16% (8% - 27%), 21% (11% - 36%) and 21% (11% - 36%) for patients without previous radiation and 36% (22% - 50%), 36% (22% - 50%), and 48% (27% - 67%) for patients with previous radiation at the same times. Multivariable regression models found previous radiation (p=0.007), arteriopathy (0.0017), and the use of a flap (0.0012) associated with the risk of SSI/WC. There was however, no difference with regards to local recurrence between groups (p=0.43)

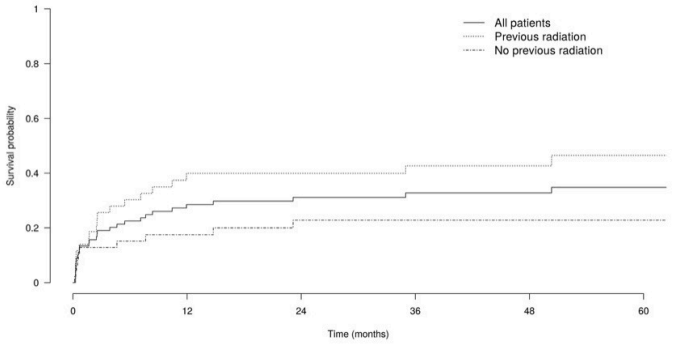

Fig. 1 The overall cumulative incidence of reoperation for SSI/WC

Conclusion: Previous radiation is associated with an increased risk of reoperation for SSI/WC when treating a local recurrence. Patients the more at risk are those with known arteriopathy or when a flap is planned. This information should be accounted for when deciding for the use of radiation when its oncologic effects are thought of undetermined significance.

Poster 188 #2804500

PHASE I SAFETY STUDY OF STEREOTACTIC RADIOSURGERY WITH CONCURRENT AND ADJUVANT PD-1 ANTIBODY NIVOLUMAB IN SUBJECTS WITH RECURRENT OR ADVANCED CHORDOMA

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Objective: Application of checkpoint inhibition to solid tumors has produced promising results in a variety of cancers. Recent data from studies in sarcoma of pembrolizumab alone revealed an overall response rate (ORR) of 18% in soft tissue sarcoma but only 5% in bone sarcoma. The combination of nivolumab (N) + ipilimumab revealed an ORR of 16% in a more heterogeneous population of sarcomas. Checkpoint inhibitors have activity in sarcoma but combinatorial therapy with different agents warrants further exploration to enhance these initial results. Chordomas represent a poorly responsive sarcoma to systemic therapy in the recurrent or metastatic setting. A previous analysis of sarcoma cell lines revealed induction of PD-1 ligands by pro-inflammatory cytokines. Primary chordoma tissue samples demonstrated no PDL-1 expression, but immune infiltrates in the tissue had expression of both PD-1 and PD1-L. Stereotactic Radiosurgery (SRS) has produced immune responses in pre-clinical models through upregulation of antigen presentation pathways and clinically in combination with immunomodulatory agents. We report an ongoing phase I safety study of SRS with N in patients with recurrent or advanced chordoma.

Methods: This is a dual arm, dual-institution non-randomized phase I study of nivolumab (N) administered alone or concurrently with SRS. The first 12 patients will be sequentially allocated between N and N+SRS as part of a safety run-in. If no dose limiting toxicity is observed in these 2 groups, then expansion will occur to a total of 12 in the N arm and 21 in the N + SRS arm. If DLTs are observed, radiation scheduling will be moved earlier in the treatment schema. The patients must have advanced or metastatic chordoma without effective surgical options. Determination of a safe treatment schedule of N with or without SRS in advanced chordoma is the primary endpoint. Secondary endpoints include the toxicity and tolerability of the regimens, estimations of the clinical response (CR + PR) within 6 months or stable disease beyond 6 months, estimations of the growth modulation index, PFS at 6 months, and overall survival at 1, 3, and 5 year time points. Correlative studies focus on exploring the peripheral blood immune response during and post-treatment.

Results: At the time of this abstract, 3 of the first 12 patients have been enrolled; 2 in the N arm and 1 in the N + SRS arm. No DLTs have been observed thus far.

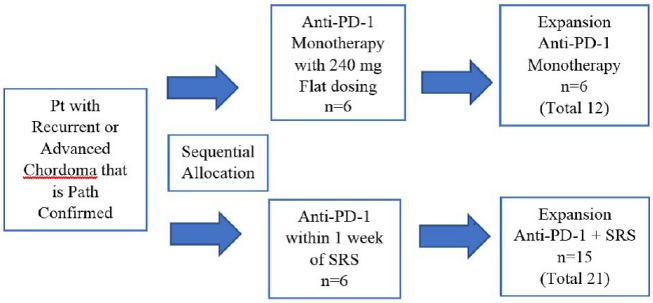

Figure 1: Treatment Schema. There will be an initial safety run-in of 12 patients who will receive Anti-PD-1 monotherapy (n=6) or Anti-PD-1 with SRS using sequential allocation. Two cohorts of six patients will be treated at dosing schedule of 240mg flat dose of nivolumab. If DLTs in the combination arm are < or = 33%, the cohort will be expanded to n=21. If DLTs are > 33%, radiation will occur within 2 days of nivolumab infusion.

Conclusion: Administration of SRS and nivolumab in chordoma is proceeding per protocol without safety issues thus far.

Poster 189 #2804634

COMBINED SURGICAL RESECTION AND ADJUVANT HIGH DOSE PHOTON/PROTON RADIOTHERAPY STRATEGY RESULTS IN HIGH LOCAL CONTROL IN CERVICAL SPINE CHORDOMAS

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Objective: Cervical spine chordoma is a rare and challenging tumor often treated with combination surgical resection and radiotherapy. We report the outcomes in the largest series of cervical spine chordoma treated with maximum surgical resection combined with high-dose photon/proton beam radiotherapy (RT) in the pre-operative and/or adjuvant setting.

Methods: We performed an IRB approved retrospective review on 148 consecutive patients with cervical spine chordoma treated during the years of 1984-2014 at our institution. CTCAE version 4.0 was used to grade late treatment toxicity.

Results: Median age at diagnosis was 51 years old (range:4-87). Median follow-up was 44 months (range: 0.9-262). 131 patients (88%) had non-chondroid histology. Median size was 4.4 cm (range:1.4-12). 112 patients (82%) underwent resection followed by adjuvant RT, 15 patients (10%) underwent pre-operative RT and 7 patients (5%) underwent RT alone. 4 patients (2.7%) received no treatment or surgery alone. 9 patients (6%) received systemic therapy. Spinal stabilization was performed in 76% of patients and included a cervical (55%) or occipital (18%) approach. Gross total resection was achieved in 55 patients (37%). Of 121 patients (82%) with known margin status, 17% had an R0 resection and 60% had an R1/R2 resection. Median RT dose was 75.2 GyRBE (range:5.7-83.2 GyRBE). Of 144 patients who received radiotherapy, 76% received combined photon/proton beam RTwith a median 63% of the dose delivered using proton beam. Five-year local control, progression-free survival, overall survival and metastasis-free survival was 64% (95% CI:54-74), 62% (95% CI:52-72), 81% (95% CI:72-89) and 92% (95% CI:87-100), respectively. There was no difference in local control between patients who underwent pre-operative RT or RT alone versus those who underwent upfront en bloc resection (71% vs 73%, respectively; p=0.82) and there was no difference in late grade 3+ toxicity between groups. Late grade 3+ toxicity occurred in 17% of patients overall, including one grade 5 toxicity (recurrent chordoma at presentation, perioperative mortality).

Conclusion: Combined surgical resection and high dose photon/proton RT results in good local control for patients with acceptable low rates of late grade 3+ toxicity. In patients treated with pre-operative RT or RT alone, local control and serious late toxicity appears to be similar to those treated with an upfront en bloc resection. This may be an alternative approach in patients for who an en bloc resection is not feasible, although this approach was used in only a small number of patients with limited follow-up.

– RHABDOMYOSARCOMA –

Poster 190 #2804626

A COMPARISON OF RHABDOMYOSARCOMA HISTOLOGIC SUBTYPES IN A MODERN ADULT COHORT: AN 8-INSTITUTION ANALYSIS FROM THE *U.S. SARCOMA COLLABORATIVE*

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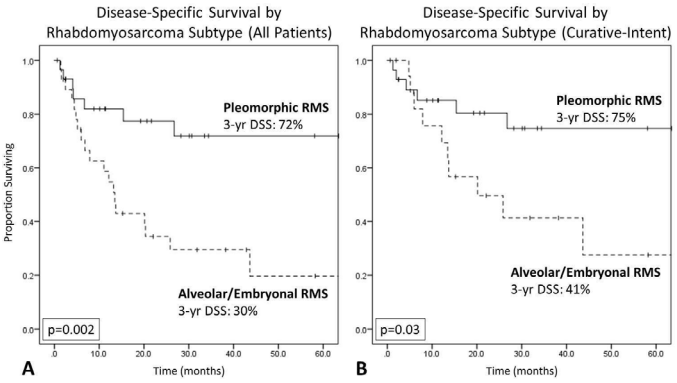
Objective: Pleomorphic rhabdomyosarcoma (RMS) is traditionally viewed as a more aggressive subtype of RMS compared to alveolar/embryonal, with the latter being predominant in a pediatric population. Our aim was to compare the clinical, pathologic, and survival differences between resected RMS subtypes exclusively in modern series of adult patients.

Methods: All adult patients with RMS of the trunk/extremity or retroperitoneum who underwent resection from 2000-2016 at the 8 U.S. institutions of the U.S. Sarcoma Collaborative were evaluated retrospectively. Primary outcome was disease-specific survival (DSS).

Results: Of 60 total RMS, 32 (53%) were pleomorphic (P-RMS) and 28 (47%) were alveolar/embryonal (AE-RMS). Compared to adult patients with AE-RMS, those with P-RMS were older (65 vs 40yrs; p<0.001), and more frequently had primary tumors located in the trunk/extremities (97% vs 58%; p=0.001). Patients with P-RMS were

also more likely to undergo R0 resections (78% vs 39%; p=0.001), despite no difference in mean tumor size (8.8 vs 9.7cm; p=0.67), N1 disease (6% vs 14%; p=0.40), or receipt of multimodality therapy between the two groups (67% vs 68%; p=1.00). Although the incidence of recurrent/metastatic tumors was similar between groups (31% vs 43%; p=0.51), when present, the majority of P-RMS patients had isolated lung metastases (63%), while 100% of those with AE-RMS had extra-pulmonary disease (p=0.02). Among all 60 patients, P-RMS was associated with improved 3-yr DSS (72%) compared to AE-RMS (30%; p=0.002; Fig 1A). Similarly, P-RMS was associated with improved 3-yr DSS compared to AE-RMS among only patients who underwent curative-intent resections (75% vs 41%; p=0.03; Fig 1B). The improved survival associated with P-RMS vs AE-RMS persisted in a multivariable Cox regression (HR 0.35, 95%CI 0.14-0.87; p=0.02), accounting for curative-intent resection, metastatic disease, N stage, margin status, and receipt of chemotherapy and/or radiation.



Conclusion: In a modern adult cohort, pleomorphic RMS is the predominant subtype encountered. Contrary to previous reports, pleomorphic RMS is associated with improved survival, even after accounting for location and patterns of disease, margins and completeness of resection, and receipt of multimodality therapy.

Poster 191 #2755596

TARGETING THE CELL CYCLE AS A VULNERABILITY IN RHABDOMYOSARCOMA

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Objective: Rhabdomyosarcoma (RMS) is an aggressive malignancy of childhood with a poor prognosis in patients with metastatic or recurrent disease. Inhibitors of Wee1 kinase and heat shock protein 90 (HSP90) have in vitro activity in RMS and have emerged as potential novel treatment strategies. We performed a comprehensive preclinical phase III study to compare the Wee1 inhibitor AZD1775 and HSP90 inhibitor ganetespib (GSP) in combination with irinotecan (IRN) and vincristine (VCR).

Methods: Orthotopic xenografts (O-PDXs) were created by injecting luciferase labeled RMS cells into the hind-leg muscle of athymic nude mice. Pharmacokinetic studies on RMS O-PDXs were performed to determine matched human AUC-guided dosing. A total of 499 O-PDXs derived from 4 high risk RMS patients, 2 alveolar and 2 embryonal, were randomly enrolled into 14 treatment groups. Six courses of blinded placebo-controlled therapy were given on a clinically relevant schedule. Mice were classified as having progressive disease if tumor approached 20% body weight at any time in the study. For mice completing all 6 courses, bioluminescence was used to determine complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD).

Results: The addition of AZD1775 to IRN and VCR demonstrated the most significant response for all 4 O-PDX lines tested; 70% of mice achieved a CR or PR. GSP combined with IRN and VCR had a 54% response (CR + PR) which was not significantly better than IRN plus VCR for most O-PDXs tested. Overall response data for all treatment groups is shown in Figure 1.

Conclusion: Comprehensive preclinical testing using multiple O-PDX models of RMS that represent the clinical spectrum of disease is feasible. Comparison of novel treatment regimens to standard of care at clinically relevant doses is warranted as justification for future clinical trials. The 4 RMS O-PDX models tested here showed a range of response to standard of care regimens as well as combinations of the novel agents AZD1775 and ganetespib with IRN and VCR. Responses using ganetespib combinations were seen in some xenografts; however the combination of AZD1775 + VCR +IRN had the highest overall CR + PR response (70%). Clonal analysis of tumors that progressed on or after therapy as well as observation to assess durable response is ongoing to enhance our understanding of the biology of RMS as well as determine if AZD1775 remains a promising treatment strategy.

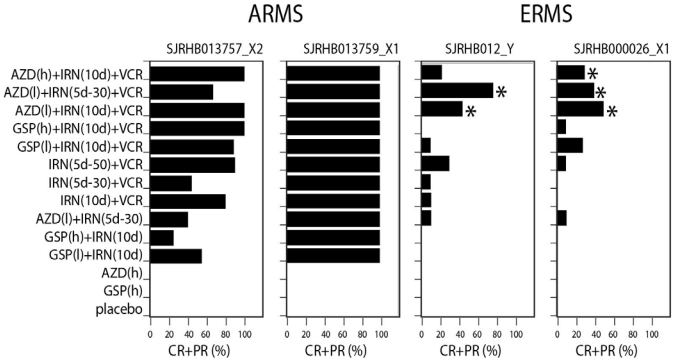

FIGURE 1. Histogram of the percentage of CR+PR for each of the 4 O-PDX models tested in this study for all 14 treatment groups. Two clinically relevant doses of AZD1775 (AZD) and ganetespib (GSP) were tested (high (h) and low (l)) along with several different schedules and dosing regimens of IRN that are used in pediatric cancer patients (5 day and 10 day low dose protracted schedules). Asterisks indicate the treatment groups that were significantly different (p<0.05)

Poster 192 #2781482

ALTERATIONS IN THE DNA DAMAGE RESPONSE PATHWAY ARE PREVALENT IN RHABDOMYOSARCOMA: A REPORT FROM THE CHILDREN'S ONCOLOGY GROUP

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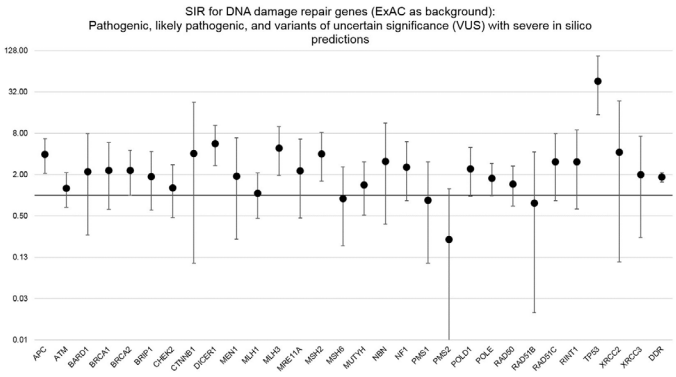
Objective: Approximately 5% of rhabdomyosarcoma (RMS) cases are considered to be associated with various cancer predisposition syndromes (e.g., Li-Fraumeni syndrome, Neurofibromatosis-1), but this has not been confirmed in a large-scale study. Additionally, no standardized germline testing protocols exist for children diagnosed with RMS. We tested the hypothesis that germline mutation burden is greater in RMS than previously reported and present several new genes as potential drivers of pediatric RMS.

Methods: We sequenced 59 cancer predisposition genes from germline DNA among 251 children diagnosed with intermediate-risk RMS and enrolled on a clinical trial (COGARST0531), unselected for family history of cancer. Variant validation was performed with Sanger sequencing.

Results: Using the VAAST analysis pipeline, we identified potential new associations between known cancer predisposition genes and RMS, including BRCA2 (p=3.00X10-7) and PTCH1 (2.00X10-7). Further evaluation of observed variants revealed 6.0% of RMS cases carry a pathogenic or likely pathogenic variant (P/LP) in known cancer predisposition genes: BRCA2, DICER1, MSH2, CHEK2, NF1, and TP53. When P/LP variants and variants of uncertain significance (VUS) with severe in silico scores were combined, a significant overrepresentation of variants was observed in RMS cases in BRCA2 (p=0.019), DICER1 (p=3.37X10-5), MSH2 (p=9.61X10-4), and TP53 (p=2.36X10-7) when compared with non-TCGA ExAC controls in an SIR analysis. Additionally, grouping DNA damage response genes also revealed a significant overrepresentation of predicted severe variants.

Conclusion: This analysis suggests that a substantial portion of RMS cases harbor a clinically actionable P/LP germline variant (6.7%) that could impact the future medical management and early tumor screening of the RMS case and asymptomatic relatives, thus describing the utility of multigene panel testing in the context of RMS. This analysis also suggests that variants in the DNA damage response genes (VUS carrier rate 13.9%), although not penetrant enough to alter management without family history, may still play a role in RMS tumorigenesis. Larger and more comprehensive next-generation sequencing analyses are now underway on this same cohort.

Standardized incidence ratios (SIR) between the number of carriers observed in RMS cases and the expected number of carriers assumed from non-TCGA ExAC allele frequencies. Error bars represent 95% confidence intervals.



Standardized incidence ratios (SIR) between the number of carriers observed in RMS cases and the expected number of carriers assumed from non-TCGA ExAC allele frequencies. Error bars represent 95% confidence intervals.

Pathogenic and likely pathogenic variants identified in RMS cases

Gene	Variant		Type	Histology	Age (years)	Sex	Race	Ethnicity
BRCA1	NM_007294.3:c.4912G>T	NP_009225.1:p.Glu1638Ter	Stopgain	Alveolar	5.26	Female	Black or African American	Not Hispanic or Latino
BRCA2	NM_000059.3:c.4914dupA	NP_000050.2:p.Val1639SerfsTer3	Frameshift	Embryonal	0.98	Male	White	Hispanic or Latino
BRCA2	NM_000059.3:c.5200G>T	NP_000050.2:p.Glu1734Ter	Stopgain	Embryonal	2.26	Female	White	Not Hispanic or Latino
BRCA2	NM_000059.3:c.7133C>G	NP_000050.2:p.Ser2378Ter	Stopgain	Embryonal	1.84	Male	Asian	Not Hispanic or Latino
BRCA2	NM_000059.3:c.7241C>A	NP_000050.2:p.Ser2414Ter	Stopgain	Embryonal	5.76	Male	Asian	Not Hispanic or Latino
CHEK2	NM_007194.3:c.1100delC	NP_009125.1:p.Thr367MetfsTer15	Frameshift	Embryonal	5.05	Female	White	Not Hispanic or Latino
CHEK2	NM_001005735.1:c.304G>T	NP_001005735.1:p.Gly102Ter	Stopgain	Embryonal	4.42	Female	White	Not Hispanic or Latino
CHEK2	NM_001005735.1:c.808G>T	NP_001005735.1:p.Gly270Ter	Stopgain	Spindle cell	12.06	Female	White	Hispanic or Latino
DICER1	NM_001195573.1:c.1174C>T	NP_001182502.1:p.Arg392Ter	Stopgain	Embryonal	7.68	Female	White	Hispanic or Latino
MSH2	NM_000251.2:c.1744delG	NP_000242.1:p.Val582SerfsTer8	Frameshift	Embryonal	23.21	Male	White	Not Hispanic or Latino
NF1	NM_000267.3:c.608_615delC-CCTAAAG	NP_000258.1:p.Ala203GlufsTer10	Frameshift	Embryonal	1.32	Male	Asian	Not Hispanic or Latino
NF1	NM_000267.3:c.1541_1542delAG	NP_000258.1:p.Gln514ArgfsTer43	Frameshift	Embryonal	1.59	Male	White	Not Hispanic or Latino
RAD50	NM_005732.3:c.2801delA	NP_005723.2:p.Asn934IlefsTer6	Frameshift	Alveolar	5.09	Female	White	Not Hispanic or Latino
RAD50	NM_005732.3:c.3G>A	NP_005723.2:p.Met1?	Start Lost	Embryonal	1.91	Male	White	Not Hispanic or Latino
TP53	NM_000546.5:c.469_476delGTC-CGCGC	NP_000537.3:p.Val157HisfsTer21	Frameshift	Embryonal	2.31	Female	White	Hispanic or Latino
TP53	NM_000546.5:c.365_366delTG	NP_000537.3:p.Val122AspfsTer26	Frameshift	Botryoid	0.92	Female	White	Not Hispanic or Latino
TP53	NM_000546.5:c.743G>A	NP_000537.3:p.Arg248Gln	Missense	Embryonal	1.03	Male	Black or African American	Not Hispanic or Latino

Poster 193 #2788357

THE RHABDOMYOSARCOMA-SPECIFIC PAX3-FOXO1 ONCOPROTEIN MODULATES EXOSOME MIRNA CONTENT TO ENHANCE ONCOGENIC SIGNALING

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Objective: Tumor-derived exosomes are small, secreted vesicles that are implicated in promoting cancer survival and metastasis, through delivery of miRNA and protein content to recipient cells. Alveolar-type rhabdomyosarcoma (ARMS) is an aggressive childhood soft tissue tumor, characterized by a specific fusion oncogenic protein, PAX3-FOXO1, which mediates its aggressive phenotype. We investigated the role of PAX3-FOXO1 on exosome content and associated paracrine signaling to recipient cells.

Methods: Using the murine myoblasts C2C12 cell line, we investigated the effects of the PAX3-FOXO1 fusion oncoprotein on secreted exosomes, to determine differential consequences on recipient cell proliferation, invasion, migration and anchorage independent growth. We also interrogated the exosome miRNA cargo modulated by PAX3-FOXO1 expression, using Affymetrix microarray and subsequent signaling pathway analysis. We utilized knock-down and over-expression experiments to study the role of specific miRNA in modulating the observed effects on cellular phenotype.

Results: PAX3-FOXO1 expression in C2C12 murine myoblasts enhanced colony formation in soft agar. Exosomes secreted by PAX3-FOXO1 expressing myoblasts significantly increased proliferation of recipient normal fibroblasts, and enhanced their invasion. Array analysis revealed unique miRNA enrichment signatures in exo-

somes derived from PAX3-FOXO1 transduced cells compared to control, and uncovered modulation of several signaling networks involved in cancer and inflammation. We focused on the microRNA miR-486-5p, which was enriched in exosomes of PAX3-FOXO1 transduced cells. We found that this miRNA was also upregulated in human alveolar rhabdomyosarcoma cell lines, and enriched in their respective exosomes, as compared to embryonal rhabdomyosarcoma cell lines. Knockdown of mir-486-5p significantly reverted the effects of exosomes on recipient fibroblasts, and modulated growth of parental PAX3-FOXO1 expressing C2C12 cells, as well as human ARMS xenografts.

Conclusion: We have discovered specific effects of the PAX3-FOXO1 oncogenic fusion protein on exosome content and paracrine signaling in myoblasts, and identified the microRNA miR-486-5p as an effector of PAX3-FOXO1 in paracrine and autocrine signaling in tumor proliferation and invasion. Findings will help devise targeted therapeutic interventions in ARMS, which are urgently needed.

Poster 194 #2779212

TARGETING PHOSPHORYLATION OF EZRIN IN METASTATIC RHABDOMYOSARCOMA

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Objective: With current treatment strategies, metastatic rhabdomyosarcoma (RMS) continues to have poor outcomes with three-year event free survival rates ranging between 20%-69% (depending on Oberlin risk factors). There is an unmet need for new treatment strategies against this disease. Metastatic RMS cell lines have increased expression of the ERM family membrane-cytoskeleton linker protein Ezrin. Knockdown of ezrin decreases the metastatic potential of these cells and forced expression results in increased degree of metastasis. As the activity of ezrin is controlled by its phosphorylation at Threonine 567, our goal is to determine if inhibition of Thr567 phosphorylation in ezrin affects the growth, survival and metastasis in RMS.

Methods: RMS cell lines representative of the alveolar and embryonal histological subtypes were used. RMS cells were treated with a small molecule inhibitor of ezrin, NSC668394, which specifically dephosphorylates ezrin at the Thr567 residue. Baseline expression of ezrin and pERM levels as well as the effect of NSC668394 on pERM levels in the RMS cell lines was determined by western blotting of cell lysates. Viability of cells was assessed by trypan blue exclusion, and morphology visualized by bright field microscopy. The extent of apoptosis was detected by imaging caspase 3/7 activation using fluorescent microscopy. Motility of RMS cells was examined by performing a wound-healing assay.

Results: Ezrin exists in the Thr567-phosphorylated form at baseline in three of the four RMS cell lines examined. NSC668394 dephosphorylates ezrin at the Thr567 residue in these cell lines. Treatment with NSC668394 results in the inhibition of growth and induces apoptosis in RMS cells. Further, NSC668394 inhibits the migration of RMS cells.

Conclusion: Our findings suggest that dephosphorylation of ezrin at the Threonine 567 residue may have the potential to be a novel therapeutic strategy for metastatic RMS.

Poster 195 #2804253

CLINICAL FEATURES, TREATMENT AND PROGNOSIS OF PLEOMORPHIC RHABDOMYOSARCOMA IN THE SINGLE INSTITUTE

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Objective: Pleomorphic rhabdomyosarcoma is a rare pathological subtype of rhabdomyosarcoma, which often occurs relatively aged patients and is known to be resistant to chemotherapy, resulting in poor prognosis, compared to embryonal or alveolar rhabdomyosarcoma. However, little is known about the clinical characteristics, treatments and prognoses of pleomorphic rhabdomyosarcoma because of its rareness. The objective of this study is to give an insight into these features of this rare tumor.

Methods: We retrospectively reviewed the medical records of patients with pleomorphic rhabdomyosarcoma who were diagnosed and treated at our hospital between January 2009 and December 2016.

Results: Fifteen patients were pathologically diagnosed as pleomorphic rhabdomyosarcoma. Median age at time of diagnosis was 47 years (range 19-73). Male/female was 8/7. Primary tumors were located in lower extremity (n=9); trunk (n=5), and upper extremity (n=1) and all tumors were sited in the deep lesion with the diameters over 5cm. Two patients had lymph-node metastases at first presentation. One had concurrent multiple bone and lung metastasis, the other had primary tumors in the prostate with multiple lymph-node metastases in the pelvic and subclavicular lesions. Ten primary tumors were surgically treated without regional lymph-node dissection and R0 resections were achieved in 9 patients. However, no lymph-node metastasis was detected during follow-up in these operated cases. As for perioperative chemotherapy, doxorubicin (A: n=1) or combination of doxorubicin and ifosfamide (AI: n=5) were administered and the rest 5 cases, which were surgically treated, didn't have any perioperative chemotherapy. Among them, 4 cases were able to assess the chemotherapeutic effect, 2 cases were

SD (AI=2) and 2 were PD (A=1, AI=1) in their best therapeutic effects. Median follow-up was 383 days (range 15-2789). Final oncological outcomes were NED (n=8), AWD (n=5), and DOD (n=2).

Conclusion: In this retrospective analysis, R0 resections were accomplished in all 8 NED cases, as such wide resection seems to be indispensable for the cure as stated in previous reports. Regional lymph-node dissection did not seem to add any clinical benefit on the primary tumor resection. Also, we couldn't see any effectiveness of perioperative chemotherapy in these limited cases. However, our study lacks the power to prove these hyposthesis. Multi-institutional, prospective study is mandatory for the development of standard therapies for this rare tumor.

Poster 196 #2804531

COMBINED APPLICATION OF ARSENIC TRIOXIDE AND LITHIUM CHLORIDE AUGMENTS VIABILITY REDUCTION AND APOPTOSIS INDUCTION IN HUMAN RHABDOMYOSARCOMA CELL LINES

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Objective: Rhabdomyosarcomas (RMS) are the most prevalent soft tissue sarcomas affecting children and adolescents. Despite intensive treatment consisting of multimodal chemotherapy and surgery RMS patients diagnosed with metastatic disease expect long term survival rates of only 20%. Often multidrug resistance arises upon initial response emphasizing the need for new therapeutic drugs to improve treatment efficiency. Previously, we demonstrated the efficacy of the FDA approved drug arsenic trioxide (ATO) specifically inhibiting viability and clonal growth as well as inducing cell death in human RMS cell lines of different subtypes. In this study, we combined low dose ATO with lithium chloride (LiCl), which is approved as mood stabilizer for the treatment of bipolar disorder, but also inhibits growth and survival of different cancer cell types in pre-clinical research.

Methods: The impact of ATO and LiCl on growth and survival of thre RMS cell lines using MTS assay, colony formation assay, 3D spheroid cultures, flow cytometry and western blotting was analysed.

Results: We could show additive effects of LiCl and ATO on viability reduction, decrease of colony formation as well as cell death induction. In the course of this, LiCl induced inhibitory glycogen synthase kinase-3β (GSK-3β) serine 9 phosphorylation, whereas glioma associated oncogene family 1 (GLI1) protein expression was particularly reduced by combined ATO and LiCl treatment in RD and RH-30 cell lines, showing high rates of apoptotic cell death.

Conclusion: These results imply that combination of ATO with LiCl or another drug targeting GSK-3 is a promising strategy to enforce the treatment efficiency in resistant and recurrent RMS.

– SOFT TISSUE SARCOMA –

Poster 197 #2782572

COMPARATIVE PERFORMANCE OF THE 7TH AND 8TH EDITIONS OF THE AMERICAN JOINT COMMITTEE ON CANCER STAGING SYSTEMS FOR SOFT TISSUE SARCOMAS OF THE TRUNK AND EXTREMITIES

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Objective: The 8th edition AJCC staging system for soft tissue sarcoma divides T stage into 4 categories and upstages patients with nodal disease to stage IV. We validated the 8th edition of the AJCC staging system for soft tissue sarcoma of the trunk and extremities using the National Cancer Database (NCDB).

Methods: 26,144 patients were identified from the NCDB with extremity/trunk sarcoma from 2004-2013. Patients with pediatric or bone sarcomas and patients not treated at the reporting hospitals were excluded. Patients were staged according to both AJCC 7th and 8th editions. Overall survival (OS) was compared using Kaplan-Meier curves and Cox proportional hazard models. Concordance indices (C-index) were calculated to evaluate the discriminatory power of both staging systems.

Results: Including T3 (10cm > x >15 cm) and T4 (>15 cm) categories in the 8th edition resulted in an increased number of patients classified as stage III disease (5,120 patients as IIIA [19.6%], 4,280 as IIIB [16.4%] vs. 7,882 [30.1%] in the 7th edition). There was a small increase in the number of patients classified as stage IV due to nodal disease (2,776 [10.6%], vs. 2,565 [9.8%] in the 7th edition). In the 7th edition, the HR for death increases with stage, with large incremental increases between stages II-III and III-IV (Table). In the 8th edition, the HR for death also increases by stage, with smaller incremental increases between each stage (Table). Median follow up was 40.8 months. When stratified by T stage, 5-year OS for 7th edition T1 and T2 patients was 78.8% and 58.8% ($p<0.01$), respectively. In the 8th edition, 5-year OS is improved for T2 patients (62.6%, $p<0.01$), with T3 and T4 patients demonstrating similar 5-year OS of 53.5% and 56.1% ($p=0.52$), respectively. Patients with nodal disease as the only site of metastasis (n=211) had a significantly higher 5-yr OS than those with distant metastases (33.1% vs 12.4%, $p<0.001$). The c-index for the 7th edition (0.72) was comparable to the 8th edition (0.74).

A Comparison of Overall Survival as Estimated by Cox Proportional Hazards Stratified by the 7th and 8th Edition AJCC Soft Tissue Sarcoma Staging Systems

	Stage	Hazard Ratio for Death	95% CI	5-year Overall Survival (%)
AJCC 7th edition	IA*			85.3
	IB	1.2	1.1-1.3	83.0
	IIA	1.4	1.3-1.6	79.0
	IIB	1.6	1.4-1.9	75.6
	III	3.6	3.3-4.0	52.3
	IV	15.3	12.7-15.6	12.4
AJCC 8th edition	IA*			85.3
	IB	1.2	1.1-1.3	83.0
	II	1.4	1.3-1.6	79.0
	IIIA	2.6	2.4-2.9	62.4
	IIIB	4.0	3.6-4.4	50.1
	IV - N+/M-	6.2	5.1-7.6	33.1
	IV - overall	14.1	12.7-15.6	13.9
	IV - M+	15.3	13.8-16.9	12.4

*Reference; **Hazard ratio calculated from Cox regression model.
CI: Confidence interval; AJCC: American Joint Committee on Cancer; N+: node positive; M+: distant metastases

Conclusion: The overall discrimination of the AJCC 7th and 8th editions are similar, but the 8th edition uses T stage to more finely stratify overall survival in patients with large, high-grade tumors (T3/4) as compared to those with T2 tumors, which facilitates risk assessment. The distinction between T3 and T4 may not be clinically significant. Patients with nodal disease have a survival in between that of patients with stage III and stage IV disease and their inclusion as stage IV requires further evaluation.

Poster 198 #2804509

A MULTISTATE MODEL IN EXTREMITY SOFT TISSUE SARCOMAS: INSIGHT ON RISK FACTORS AND A NEW PROGNOSTIC TOOL

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Objective: Patients surgically treated for primary extremity STS are at risk of local recurrence (LR), distant metastases (DM) or death without LR or DM. Cox-proportional or competing-risk models are not able to assess the effect of the sequence of LR or DM on subsequent events, while multistate models do.

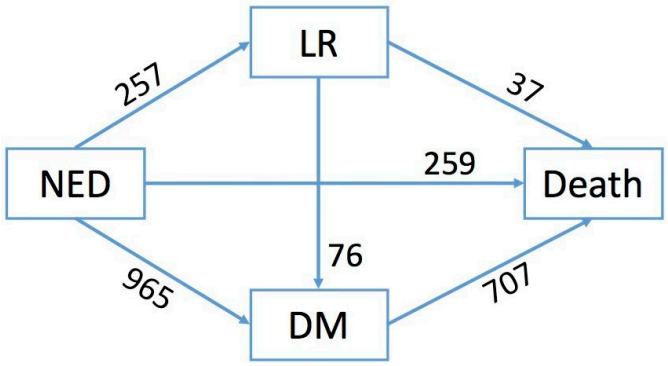
Methods: Data from 4 institutional (3 European and 1 North American) prospective sarcoma databases on patients with primary localized ESTS resected with curative intent between 1994 and 2013 were merged.

We built a multistate model with 4 states (NED, LR, DM, death) and 6 transitions: NED to LR (1), NED to DM (2), NED to death (3), LR to DM (4), LR to death (5), DM to death (6). Transitions 1, 2, and 3 were treated as competing events. The model included the following covariates in all transitions but transition 3: age, size, depth (superficial, deep), margins (R0, R1), FNCLCC grading (G1, G2, G3), histology (LMS, DD Liposarcoma, Myxoid/RC Liposarcoma, Myxofibrosarcoma, Synovial Sarcoma, MPNST, UPS, Vascular Sarcoma, Other), RT at primary (done/not done), CT at primary (done/not done). In the transitions from LR (4, 5) also treatment of 1st LR was considered (surgery, no treatment, CT and/or RT). The simultaneously detection of LR and DM was classified as DM. The transition was included as stratification factor.

Results: 3752 cases were included. In the transition NED to LR, significant risk factors were age (p .005), depth (p .009), margins (p <.001), grading (p <.001), histology (p<.001) and RT (p <.001). In the transition from NED to

DM, size (p <.001), depth (p< .001), grading (p <.001) and histology (p <.001) were statistically significant. In the transition LR to DM, only tumor size (p .006) was a significant prognostic factor although treatment of 1st LR was close to significance (p .083). In the transition LR to death, age (p <.001), size (p .05) and treatment of 1st LR (p .001) were relevant prognostic factors. In the transition DM to death, age (p <.001), size (p <.001) and histology (p .019) were significant.

Conclusion: Multistate modeling of this series of operated extremity STS patients allowed us to better understand the prognostic value of each covariate in transitions. Moreover, this model unveils transition probabilities, thus providing an accurate prediction for all possible patient states at any timeline after surgery.



	NED to LR (1)		NED to DM (2)		LR to DM (4)		LR to death (5)		DM to death (6)	
	HR (95%CI)	p	HR (95%CI)	p	HR (95%CI)	p	HR (95%CI)	p	HR (95%CI)	p
Age 42 vs 69	1.44 (1.15, 1.79)	.005	1.37 (0.92, 2.05)	.29	1.12 (0.20, 6.32)	.542	3.10 (1.27, 7.59)	<.001	1.62 (1.42, 1.86)	<.001
Size 4 vs 11cm	1.09 (0.84, 1.43)	.796	2.92 (2.44, 3.49)	<.001	4.52 (0.96, 21.28)	.006	7.51 (0.85, 66.35)	.053	1.18 (0.96, 1.46)	.001
Depth deep vs superficial	1.54 (1.11, 2.12)	.009	1.44 (1.17, 1.77)	.001	0.78 (0.41, 1.51)	.473	1.11 (0.42, 2.92)	.828	1.23 (0.95, 1.59)	.113
Surgical margins R1 vs R0	2.97 (2.25, 3.93)	<.001	1.14 (0.96, 1.35)	.143	0.83 (0.45, 1.54)	.560	2.09 (0.85, 5.12)	.106	1.14 (0.94, 1.38)	.176
FNCLCC grade III vs I	2.77 (1.77, 4.35)	<.001	5.19 (3.73, 7.21)	<.001	2.32 (078, 6.94)	.269	1.18 (0.27, 5.18)	.514	1.43 (0.90, 2.29)	.322
Histology LMS vs DD/pl lipo MLPS vs DD/pl lipo MPNST vs DD/pl lipo myxofibro vs DD/ pl lipo other vs DD/pl lipo synovial vs DD/pl lipo UPS vs DD/pl lipo vascular vs DD/pl lipo	0.77 (0.38, 1.54) 0.79 (0.39, 1.61) 1.63 (0.78, 3.43) 2.24 (1.23, 4.08) 1.19 (0.64, 2.21) 1.55 (0.76, 3.15) 1.20 (0.66, 2.20) 5.03 (2.29, 11.05)	<.001	2.30 (1.68, 3.17) 0.87 (0.62, 1.23) 1.55 (1.07, 2.24) 1.02 (0.71, 1.45) 1.69 (1.24, 2.29) 1.88 (1.33, 2.67) 1.36 (1.01, 1.83) 3.35 (1.95, 5.75)	<.001	1.33 (0.37, 4.75) 0.75 (0.16, 3.60) 0.56 (0.14, 2.27) 0.40 (0.11, 1.40) 1.19 (0.35, 3.98) 1.88 (0.53, 6.63) 0.56 (0.16, 1.90) 0.80, 0.16, 4.00)	.062	-	.171	0.90 (0.62, 1.31) 0.95 (0.63, 1.44) 1.43 (0.95, 2.16) 0.99 (0.66, 1.47) 1.05 (0.74, 1.51) 1.22 (0.82, 1.84) 0.91 (0.65, 1.28) 2.23 (1.20, 4.17)	.019
RT yes vs no	0.44 (0.33, 0.59)	<.001	1.01 (0.86, 1.20)	.884	1.37 (0.80, 2.34)	.245	1.12 (0.43, 2.92)	.822	0.85 (0.71, 1.02)	.076
CT yes vs no	0.77 (0.59, 1.01)	0.62	0.99 (0.86, 1.15)	.930	1.11 (0.63, 1.96)	.718	1.01 (0.42, 2.42)	.981	1.02 (0.86, 1.20)	.848
Treatment of 1st LR no treat vs surg RT and/or CT vs surg	-	-	-	-	1.30 (0.37, 4.57) 2.36 (1.11, 5.02)	.083	6.84 (2.40, 19.46) 2.45 (0.70, 8.53)	.001	-	-

NED non evidence of disease, LR 1st local recurrence, DM distant metastasis, HR hazard ratio, CI confidence interval, LMS leiomyosarcoma, DD/pl lipo dedifferentiated/pleomorphic sarcoma, MPNST, malignant peripheral nerve sheath tumor, myxofibro myxofibrosarcoma, synovial synovial sarcoma, UPS undifferentiated pleomorphic sarcoma, vascular vascular sarcoma, RT radiotherapy, CT chemotherapy, no treat no treatment, surg surgery.

Poster 199 #2804709

SMOOTH MUSCLE TUMORS OF UNCERTAIN MALIGNANT POTENTIAL (STUMP): AN EXPERT CLINICAL-PATHOLOGIC CONSENSUS-BUILDING EFFORT

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Objective: STUMP are rare uterine mesenchymal neoplasms in which “an unequivocal benign or malignant diagnosis” cannot be made, but a malignant evolution is seen in 10-20% of cases. Pathologic criteria for a diagnosis of STUMP are based on necrosis, atypia, mitotic count. STUMP are a highly uncomfortable diagnosis for patients and a challenge for pathologists and oncologists.

Methods: We set up an open interest group of expert pathologists and clinicians, to explore whether current diagnostic practices in STUMP can be improved. A first meeting was held to pathologically review selected clinical cases, in order to make hypotheses for change.

Results: A few tentative conclusions were made. 1. STUMP should not be viewed as a borderline nosographic entity, since they are actually an uncertain differential diagnosis between leiomyomas and leiomyosarcomas. Contrary to variants such as metastasizing leiomyomas, and the like, which are not distinguishable pathologically from leiomyomas, STUMP carry suspicious pathologic features of being malignant, i.e., leiomyosarcomas. 2. It was felt that in expert hands the number of STUMP diagnoses could be lowered vis-a-vis leiomyomas, but the impression was that expertise is hardly transferrable to the community. 3. Also due to the wide criteria, it is difficult to speculate how many of the currently diagnosed STUMP could be held as actual “low-grade” leiomyosarcomas, i.e., an entity that is not encompassed in current classifications. In principle, they should correlate with a non-negligible risk of relapse, on an intermediate-long term, and a potential for dedifferentiation across relapses. The expression of hormonal receptors in a proportion of these might be therapeutically relevant. 4. In expert hands, high-grade leiomyosarcomas, i.e., carrying a relatively high risk of relapse within 2-3 yrs, should prove to be well demarcated from these conditions.

Conclusion: We are finalizing a green paper to prompt discussion in the pathology, oncology and gyneco-oncology communities, including societies such as CTOS. We aim at a re-conceptualization allowing to better contrast high- and low-grade patterns of malignancy, with a view to more rational treatment strategies, a decrease in prognostic uncertainty, better exploitation of potential biomarkers.

Poster 200 #2753196

COPY NUMBER ALTERATIONS IN SOLITARY FIBROUS TUMORS: ASSOCIATION BETWEEN *MYC* PROTOONCOENE COPY NUMBER GAIN AND METASTATIC RELAPSE

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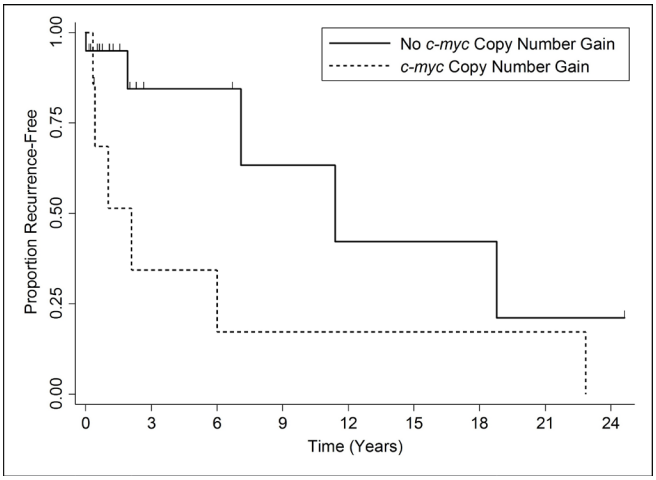
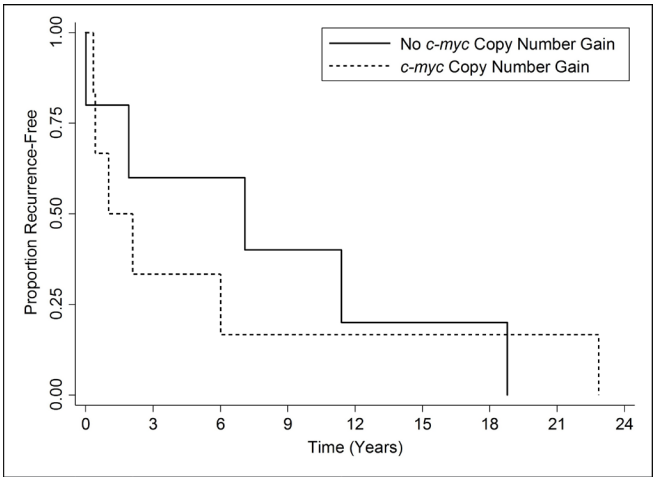
Objective: Solitary fibrous tumors (SFTs) exhibit a wide range of biologic behavior, posing a significant challenge in assessment of risk of relapse and long-term prognosis. A strong correlation between histologic features (notably mitotic activity), conventional staging systems, molecular diagnostic markers, and clinical outcome is still lacking. We genomically characterized a series of SFTs to assess a correlation between copy number alterations and risk of metastatic recurrence

Methods: We queried the Dana-Farber Cancer Institute (DFCI) Oncology Data Retrieval Systems (OncDRS) to identify patients (pts) with SFT who underwent targeted massively parallel sequencing of exonic DNA sequences of 300 cancer genes (OncoPanel). All cases were reviewed by experienced soft tissue tumor pathologists from Brigham and Women’s Hospital and followed at DFCI. Fisher’s Exact Test and Wilcoxon Rank Sum were used for descriptive statistics; log rank test was used to compare time to event distributions

Results: A total of 27 pts were included, with a median follow-up of living patients of 2.24 years. Sequencing data were obtained from 20 primary tumors and 7 metastatic lesions. Eleven pts (40.7%) developed metastatic disease with a median recurrence free survival of 2.1 years (range 0-22.8 years). Recurrent copy number gains (CNGs) in MYC were observed in 7 cases (26%); Four (of 7) metastatic lesions (57%), and 3 (of 20) primary tumors (15%). Six of the 7 cases with MYC gain were from thoracic origin (86%). Patients with MYC gain had larger primary tumors (6.0 vs. 13.9 cm; p=0.03) and higher mitotic count in their primary lesions (2 vs. 11 mitoses/HPF; p=0.01) compared to pts without CNGs in MYC. These CNGs were almost exclusively observed in pts who developed metastases (6/11 pts, four in metastatic lesions, two in primary tumors) compared with pts who did not develope metastases (1/16 pts; p=0.009). Patients with metastatic disease and MYC CNGs (either in primary or metastasis) had shorter relapse-free survival compared to patients with metastatic disease without copy number alterations

in MYC (median 1.0 vs. 7.1 years, respectively; p=0.80). All 3 primary tumors with Gains in MYC had high mitotic count (mean 10.6 per 10 HPF).





Conclusion: This is the largest SFT cohort with targeted next generation sequencing data currently available. In this sample size, copy number gains of MYC are associated with metastatic presentation and shorter time to relapse of metastatic disease. The observation of these alterations in primary, as well as in metastatic lesions, suggests a possible early event leading to increased risk of metastatic development.

Table 1.
Patient and Tumor Characteristics by Metastatic State

	Non-Metastatic (n=16)	Metastatic (n=11)	p-value
Gender, n (%)			>0.99
Male	9 (44%)	7 (36%)	
Female	7 (56%)	4 (64%)	
Age at Diagnosis, n (%)			0.60
Median (range)	51 (28-74)	57 (20-81)	
Primary Site, n (%)			0.77
Meningeal	4 (25%)	1 (9%)	
Soft-Tissue	5 (31%)	4 (36%)	
Thoracic	7 (44%)	6 (55%)	
Tumor Size, cm			0.11
Median (range)	6.0 (1.3-15.0)	10.5 (4.5-19.5)	
Primary Mitoses			0.35
Median (range)	3.5 (0-17)	5 (1-18)	
Margins, n (%)			0.85
Negative	11 (69%)	6 (55%)	
Positive	3 (19%)	2 (18%)	
Unknown	2 (12%)	3 (27%)	
MYC gain, n (%)			0.009
No	15 (94%)	5 (45%)	
Yes	1 (6%)	6 (55%)	
Status, n (%)			<0.001
AWD	1 (6%)	9 (82%)	
DOD	0 (0%)	2 (18%)	
NED	15 (94%)	0 (0%)	

AWD indicates alive with disease; DOD, died of disease; NED, no evidence of disease.

Table 2. Patient and Tumor Characteristics by MYC Copy Number Gain

	No MYC gain (n=20)	MYC gain (n=7)	p-value
Gender, n (%)			0.39
Male	13 (65%)	3 (43%)	
Female	7 (35%)	4 (57%)	
Age at Diagnosis, years			0.21
Median (range)	51 (20-81)	57 (39-77)	
Primary Site, n (%)			0.10
Meningeal	5 (25%)	0 (0%)	
Soft-Tissue	8 (40%)	1 (14%)	
Thoracic	7 (35%)	6 (86%)	
Tumor Size, cm			0.03
Median (range)	6.0 (1.3-13.5)	13.9 (4.8-19.5)	
Primary Mitoses			0.01
Median (range)	2 (0-15)	11 (2-18)	
Margins, n (%)			0.83
Negative	13 (65%)	4 (57%)	
Positive	4 (20%)	1 (14%)	

Unknown	3 (15%)	2 (29%)	
Unavailable	2 (10%)	0 (0%)	
Metastatic Recurrence, n (%)			0.009
No Metastatic Recurrence	15 (75%)	1 (14%)	
Metastatic Recurrence	5 (25%)	6 (86%)	
Status, n (%)			0.01
AWD	6 (30%)	4 (57%)	
DOD	0 (0%)	2 (29%)	
NED	14 (70%)	1 (14%)	

AWD indicates alive with disease; DOD, died of disease; NED, no evidence of disease.

Poster 201 #2759453

PATIENT PREFERENCES IN ADVANCED SOFT TISSUE SARCOMA: A DISCRETE CHOICE EXPERIMENT

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Objective: Soft-tissue sarcomas (STS), a rare heterogeneous group of cancers originating in the muscle, fat, blood vessels or other fibrous/connective tissues, account for 1% of all cancers diagnosed annually in the US. A discrete choice experiment (DCE) was conducted to quantify the relative value of overall survival (OS), progression-free survival (PFS), tumor response rate (RR), risk of hospitalization due to side effects, and convenience of therapy (days per month to administer treatment) among patients diagnosed with STS.

Methods: An online DCE survey was administered to adult patients who were recruited through physician referrals and patient advocacy announcement. Patients were asked to verify the STS diagnosis and to confirm receipt of chemotherapy treatment within the past two years. The survey asked patients to choose between pairs of hypothetical treatment profiles characterized by a common set of attributes: OS (14, 20, or 26 months), PFS (3, 5, or 7 months), RR (12, 18, or 26%), risk of hospitalization due to side effects (12, 30, or 46%), and days/month to administer treatment (1, 2, or 4 days). A Hierarchical Bayes model was used to estimate preferences, the relative importance of treatment attributes (from 0-100%), and trade-offs between attributes.

Results: A total of 76 eligible patients completed the survey: 23.7% male; mean age 52.8 years, and 55.3% had received their last chemotherapy treatment within the past 6 months. OS had the highest relative importance (39.5%, standard deviation, SD, 18.2%), followed by RR (21.2%, SD 10.4%), and risk of hospitalization due to side effects (19.8%, SD 12.5%). PFS and days to administer treatment had lower relative importance (11.0%, SD 3.7%; and 8.4%, SD 4.3%, respectively). For a 1-month increase in OS, patients were willing to trade off a 2.2 percentage point decrease in RR, a 6.0 percentage point increase in hospitalization risk, a 1.2 month reduction in PFS, and an additional 1.4 days/month to administer treatment.

Conclusion: Patients with STS in the US prefer a treatment that maximizes their life and achieves tumor response while avoiding hospitalizations.

Poster 202 #2778170

OLARATUMAB AFTER TREATMENT WITH OLARATUMAB + DOXORUBICIN: MONOTHERAPY (MONO) OUTCOMES FROM THE JGDG PHASE 2 CLINICAL TRIAL

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Objective: Background: Olaratumab is a PDGFRα targeting monoclonal antibody blocking PDGFRα signaling. In a Phase 1b/2 study (NCT01185964) olaratumab + doxorubicin (dox) demonstrated significant progression-free survival (PFS) and overall survival (OS) benefit versus dox in patients (pts) with advanced unresectable or metastatic soft tissue sarcoma. Pts who had not experienced progressive disease (PD) after 8 cycles of olaratumab + dox in this study continued with olaratumab mono. Pts in the dox alone arm were allowed to receive olaratumab mono after PD. Here we report the results of the subgroup analysis for Phase 2 pts who received olaratumab monotherapy.

Methods: Patients eligible received olaratumab mono 15mg/kg IV on days 1 and 8 of each 21-day cycle until PD or other discontinuation criteria were met. The primary objective was to assess PFS. Additional objectives included OS, safety, and PK. PFS and OS were measured from randomization and tumor response was assessed according to RECIST (v1.1).

Results: Of 133 pts enrolled, 64 pts received olaratumab mono (34 pts post-olaratumab+dox; 30 pts post-dox). Baseline characteristics were similar to the overall study population, although a slightly increased proportion of women received olaratumab mono. Pts post olaratumab+dox received a median of 4.5 cycles of olaratumab mono. 10 pts received ≥12 cycles. The 2-year survival rate was 67.6% (95% CI; 49.2, 80.6); median PFS and OS were 9.8 months (m) (95% CI, 7.2, 13.2) and 31.7 m (95% CI, 23.3, NE), respectively. Most pts discontinued due to PD (n=25); only 2 patients discontinued due to AE. Most frequent related AEs (in >2 pts) included diarrhea (n = 4) and fatigue (n = 3).

Pts post-dox received a median of 2.0 cycles of olaratumab mono; 3 pts received ≥10 cycles. The 2-year survival rate was 28.7% (95% CI; 13.6, 45.7). Median OS was 13.5 m (95% CI, 8.4, 21.7). The only related AE reported in >2 pts was nausea (n = 3).

The pharmacokinetics of olaratumab was similar in all pts who received olaratumab mono, and consistent with that of olaratumab combined with dox.

Conclusion: Olaratumab mono was safe and well tolerated in the patient population. Pts treated with olaratumab mono following olaratumab+dox had efficacy outcomes longer than any historically reported OS for pts with advanced or metastatic soft tissue sarcoma. There do not appear to be any particular baseline characteristics that predict which pts would continue on to olaratumab mono.

Poster 203 #2784005

A COMPARISON OF THE 7TH AND 8TH EDITIONS OF THE AJCC STAGING SYSTEM FOR SOFT TISSUE SARCOMA OF THE TRUNK AND EXTREMITY: AN ANALYSIS FROM THE US SARCOMA COLLABORATIVE

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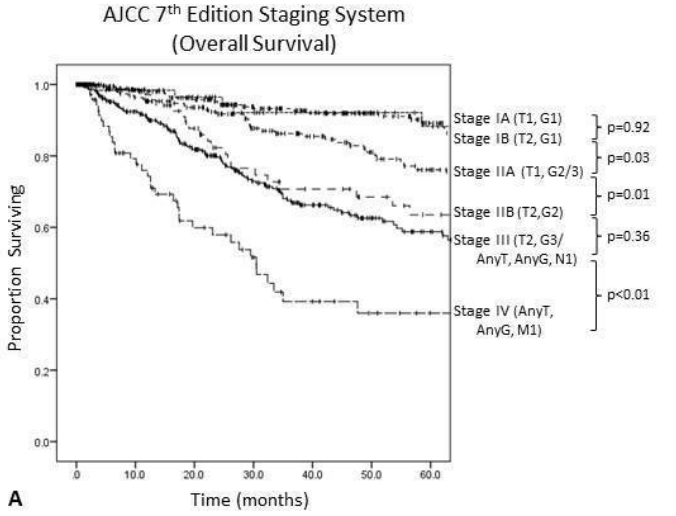
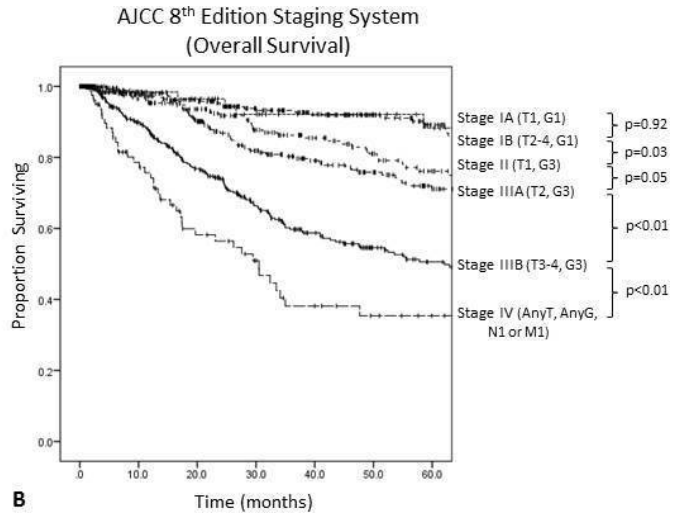
Objective: To compare the prognostic value of the 7th and 8th eds of the AJCC staging systems for truncal/extremity soft tissue sarcoma (STS).

Methods: All adult pts with primary truncal/extremity STS who underwent resection from 2000-2016 at 7 institutions of the US Sarcoma Collaborative were included. Primary endpoint was overall survival (OS).

Results: Of 1350pts identified, mean age was 59yrs and 54% were male. The most common histologies were undifferentiated pleomorphic sarcoma (32%), liposarcoma (21%), myxofibrosarcoma (9%), and leiomyosarcoma (8%). 22% of tumors were <5cm, 34% were 5-10cm, and 44% were >10cm . The majority (77%) were high-grade; 15% of pts had nodal disease (N1). In the 7th ed, low-grade tumors are Stage I and are further stratified by size (IA: <5cm; IB: >5cm), while IIA, IIB and III are based on a combination of tumor size, grade, and LN status (IIA: <5cm, high-grade; IIB: >5cm, intermediate-grade; III: >5cm, high-grade or N1). Stage IV is defined only by metastatic disease (M1). On stepwise comparison, there was no difference in OS between IA and IB (p=0.92). While IB vs IIA, and IIA vs IIB were adequately stratified (p=0.03 and 0.01), there was no difference between IIB and III (p=0.36; Fig.1A). The 8th ed maintains the same Stages IA/B designations, but stratifies high-grade exclusively by size (II: <5cm, IIIA: 5-10cm; IIIB: >10cm), and combines N1 and M1 disease in Stage IV. Using this revised system, while there was still no difference in OS between Stages IA and IB (p=0.92), high-grade tumors were better stratified (II vs IIIA, p=0.05; IIIA vs IIIB, p<0.001; Figure 1B). Although Stage IV disease had the worst OS in both systems, N1 disease also demonstrated poor survival and was similar to M1 disease. The strength of the 8th ed over the 7th persisted in multivariable analyses, even accounting for histologic subtype, gender, tumor location, margin status, receipt of chemotherapy, comorbidities, and major complications.





Conclusion: Compared to the 7th edition AJCC staging system, the 8th edition better defines high-grade truncal and extremity sarcomas by stratifying exclusively by size. Although rare, lymph node involvement is associated with a poor prognosis and is appropriately designated in the 8th edition as Stage IV. However, neither system adequately stratified patients with low-grade tumors. Other prognostic biomarkers are needed to better define and categorize low grade tumors, and histology-specific analyses should be performed.

Poster 204 #2785040

A PHASE 2 STUDY OF CMB305 AND ATEZOLIZUMAB IN NY-ESO-1+ SOFT TISSUE SARCOMA: INTERIM ANALYSIS OF IMMUNOGENICITY, TUMOR CONTROL AND SURVIVAL

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Objective: CMB305 is an active immunotherapy designed to generate and expand anti-NY-ESO-1 immune response (IR). CMB305 consists of a dendritic cell-targeting lentiviral vector encoding NY-ESO-1 (LV305), and a boost with an NY-ESO-1 recombinant protein plus GLASE (G305), a TLR-4 agonist. Phase 1 studies of LV305 and CMB305 showed this approach is safe, generates IR and appears to impact survival with 81% 1-yr survival in NY-ESO-1+ sarcoma patients (pts) following LV305 treatment. We evaluated efficacy and IR for combination of CMB305 (C) and atezolizumab (A) or A alone in NY-ESO-1+ synovial sarcoma (SS) and myxoid round cell liposarcoma (MRCL).

Methods: A prospective randomized open label phase 2 study of C (LV305 Intradermal Days 0, 14, 42, 70 + G305 Intramuscular Days 28, 56, 84 then q6wk up to one year) + A (1200mg IV q3wk) vs. A alone in locally advanced or metastatic NY-ESO-1+ SS/MRCL. Primary endpoints are progression free survival (PFS) and overall survival (OS) with secondary endpoints of safety, IR, and response rate.

Results: As of December 30, 2016, 58 patients were enrolled. A prespecified interim analysis of PFS included the first 36 pts with median 7.0 mos follow up (Arm A+C: median age 47 yrs, 78% SS, 100% metastatic, 78% =>2 chemotherapy; Arm A: median age 44 yrs, 56% SS, 67% metastatic, 56% =>2 chemotherapy). Combination A+C was well tolerated. Clinical benefit was similar between arms (Arm A+C: 8/18 pts with SD, 1 pt unconfirmed PR, 6 mos PFS rate 17%; Arm A: 10/18 pts SD, 6 mos PFS rate 22%). In addition, anti-NY-ESO-1 IR seen in 10/19 (53%) pts Arm A+C vs. 3/12 (25%) pts Arm A by T Cell ELISpot, and 9/22 (41%) pts Arm A+C vs. 0% Arm A by antibody ELISA. Pts with IR had target lesion increase 2% compared to 18% in pts without IR based on preliminary ANOVA-model based analysis. No deaths observed in pts with induced anti-NY-ESO-1 T cell IR (0/13 deaths IR+ pts vs. 5/18 deaths IR- pts).

Conclusion: In the interim analysis, Arm A+C resulted in a higher level of anti-NY-ESO-1 IR when compared to Arm A; pts with IR tend to have better target lesion control. Early data indicate that induction of anti-NY-ESO-1 IR may be associated with better survival.

Poster 205 #2789742

THE ANGIOSARCOMA PROJECT: GENERATING THE GENOMIC LANDSCAPE OF A RARE SARCOMA THROUGH PATIENT PARTNERSHIP

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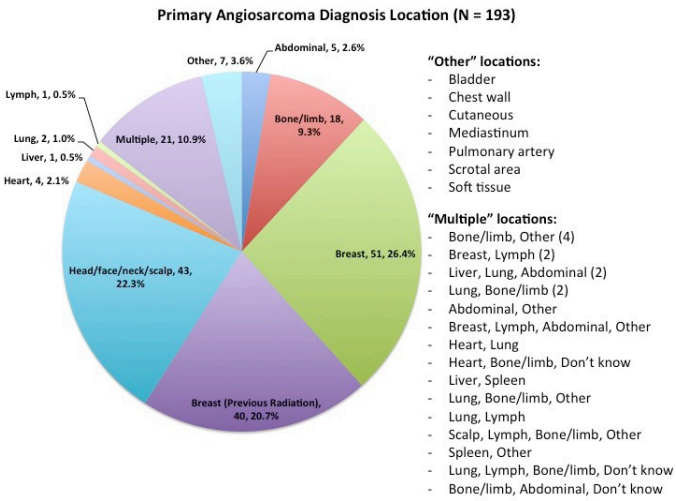
Objective: Angiosarcoma (AS) is a rare soft tissue sarcoma, with an incidence of 300 cases/yr and a 5-year disease-specific survival of 30%. The low incidence has impeded large-scale research efforts that may lead to improved clinical outcomes. To address this, we launched a direct-to-patients (DTP) nationwide study, which seeks to empower patients to accelerate research by sharing their normal and tumor 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 were mailed a saliva and blood draw kit for germline and cell free (cf) DNA analysis, respectively. We then obtained medical records and stored tumor samples. Whole exome sequencing is being performed on tumor, cfDNA, and saliva samples. Transcriptome analysis is being performed on tumor samples. A clinically annotated genomic database will be generated and 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. 205 patients enrolled in 12 weeks, including 63 on the first day. Average age of patients is 54 years (range from 21-86 yrs). Primary locations of AS were primary breast 51 (26%), breast with prior radiation 40 (21%), head/face/neck/scalp 43 (22%), bone/limb 18 (9%), abdomen 5 (3%), heart 4 (2%), lung 2 (1%), liver 1 (0.5%), lymph 1 (0.5%), multiple locations 21 (11%), and other locations 7 (4%) (figure). 107 (52%) reported being disease free at the time of enrollment. 105 saliva kits, 51 medical records, 9 blood samples, and 4 tissue samples have been received. Blood samples have been submitted for ultra-low pass whole genome sequencing, and will advance to whole exome sequencing if quality metrics are met. Once ten paired saliva and tumor samples are received, they will be submitted for sequencing.



As part of the online enrollment process in The Angiosarcoma Project, patients are asked to identify the original site of angiosarcoma diagnosis. Primary locations of AS are primary breast 51 (26%), breast with prior radiation 40 (21%), head/face/neck/scalp 43 (22%), bone/limb 18 (9%), abdomen 5 (3%), heart 4 (2%), lung 2 (1%), liver 1 (0.5%), lymph 1 (0.5%), multiple locations 21 (11%), and other locations 7 (4%). Patient-reported data will be vetted using concordance with medical records.

Conclusion: A DTP approach enabled rapid identification and enrollment of over 200 AS patients, an exceedingly rare cancer, in less than three months. We are able to obtain tumor, blood, and saliva samples to perform genomic analyses, which are then merged with detailed clinical information. This study serves as proof of principle that DTP genomics efforts can democratize cancer research for exceedingly rare cancers, which to date have been understudied.

Poster 206 #2790487

DEDIFFERENTIATED LIPOSARCOMA: A SPEEDING CAR WITHOUT BRAKES

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Objective: Liposarcomas, despite being rare consist of entities spanning low to high grade sarcomas. Whilst the most common subtype well-differentiated liposarcoma (WDLS) has the most favourable prognosis, up to 17% of WDLS may progress to de-differentiated liposarcoma (DDLS), associated with increased frequency of recurrence and lower overall survival. We aimed to identify genomic and transcriptomic changes associated with de-differentiation.

Methods: We analysed data from gene expression omnibus (Gobble et al, GEO ID = GSE30929) to identify genes dysregulated between WDLS (n=52) and DDLS (n=39). Genomic and transcriptomic data from The Cancer Genome Atlas (TCGA, n=58 DDLS) was used to further examine changes and association with outcome for 1272 genes representing STOP (n=567) or GO (n=705) signals (Solimini et al, Science 2012). Validation was performed in an independent set representing WDLS (n=3) or laser capture microdissected WDLS and matched DDLS from same sample at recurrence (n=3/3).

Results: In the Gobble cohort WDLS formed a distinct cluster. Genes significantly upregulated in DDLS ($p<1x10-5$) were enriched for E2F1 transcription factor targets and G1/S transition, and expression of E2F1 had a negative correlation with a senescence signature.
In the TCGA cohort 5 GO genes were frequently amplified (>30%, MDM2, HMGA2, CPSF6, RAP1B, IFNG) in liposarcoma, but showed no significant dysregulation between WDLS and DDLS. Of GO genes associated with poorer survival 4 had frequent copy number gains (>10%, TLE4, MARS, RKF, RAD21), and two were upregulated in DDLS (MARS, TLE4). There were no frequently copy number losses, although TP53 had loss or mutation in 11% of the samples. Two STOP genes with reduced expression in DDLS were predictive of poor survival (NTRK2, IGF1). Loss of function mutations were observed in genes involved in DNA repair (ATRX, 8%, MSH3, 8%) as well as copy number loss of the tumour suppressor CDKN2A (14%).

Conclusion: Liposarcoma is associated with frequent amplification of GO genes driving increased proliferation, although an intact senescence response in WDLS limits

progression of cells through the G1/S boundary. In DDLS upregulation of E2F1 allows cells to escape the senescence checkpoint response and is associated with poor prognosis. Emerging evidence that histone deacetylases and second generation tyrosine kinase inhibitors may interfere with E2F1 related pathways suggests a potential mechanism by which these drugs may be used to potentiate treatment in DDLS.

Poster 207 #2793234

SYNOVIAL SARCOMA OF THE EXTREMITIES: A RETROSPECTIVE REVIEW AND ANALYSIS OF 196 CASES TREATED AT THE ISTITUTO ORTOPEDICO RIZZOLI

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Objective: The diagnosis of synovial sarcoma (SS) is currently based on clinical, morphological and immunohistochemical data. The identification of tumor-specific translocation plays a major role in confirming the diagnosis. In the last two decades, several factors such as morphologic grade, type of translocation (SS18-SSX1 vs. SS18-SSX2) and the reduced expression of INI1, were proposed as prognostic variables. The aim of this study was to verify whether morphological (grading and histology), immunohistochemical (INI1 expression) and molecular (type of SSX translocation) features of SS influence the prognosis of the disease.

Methods: We retrospectively evaluated 196 patients affected by SS of the extremities treated at Istituto Ortopedico Rizzoli, Bologna, Italy. All cases were histologically reviewed, and tumor grade was assessed according to the FNLCC system. Tissue specimens were retrospectively evaluated to check for SS18-SSX fusion type and immunohistochemical expression of INI1.

Results: Most SS were monophasic, 28% were biphasic. Eighty tumors (41%) were grade 3. Sixty percent harbored a SSX1 translocation; 40% a SSX2; 51% maintained the expression of INI1. Sarcoma specific survival (OS) was 56.6% at 5 years and 46.9% at 10 years. Prognosis was worse in the monophasic morphology (p=0.011) as well as in grade 3 tumors (p=0.083). No correlation was found neither between SSX fusion types nor INI1 expression and survival. Local recurrence-free survival was 78.9% at 5 years and 75.9% at 10 years. A higher local recurrence rate was observed in tumors with SSX2 translocation (p=0.049) and in grade 3 SS (p=0.028).

Conclusion: Our data confirm that not all cases of SS present the same severe outcome. High-risk patients identified on the basis of morphology and grading may qualify for an aggressive treatment approach.

Poster 208 #2804696

A PILOT STUDY OF NY-ESO-1 SPEAR T-CELLS IN SUBJECTS WITH ADVANCED MYXOID/ROUND CELL LIPOSARCOMA (NCT02992743)

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Objective: Myxoid/round cell liposarcomas (MRCLS) account for 5-10% of soft tissue sarcomas. Although a chemosensitive tumor, metastatic MRCLS has a poor prognosis and is inevitably fatal. NY-ESO-1 is a cancer/testis antigen that is expressed in ~90% of MRCLS tumors. This study is evaluating the safety and efficacy of genetically engineered specific peptide enhanced affinity receptor (SPEAR) T-cells (NY-ESO-1c259T-cells) recognizing an NY-ESO-1 derived peptide complexed with HLA-A*02 in MRCLS.

Methods: This open label phase I/II non-randomized pilot study. The primary endpoint is overall response rate (CR+PR) by RECIST v1.1 via independent review. Secondary endpoints include safety, time to response, duration of response, progression free survival, overall survival, and gene-marked cell persistence. Patient eligibility criteria include: ≥ 18 yrs old; HLA-A*02:01, *02:05 or *02:06 positive; have advanced (metastatic or inoperable) MRCLS expressing NY-ESO-1 at 2+/3+ intensity in ≥30% of tumor cells by IHC; measurable disease; prior systemic/intolerant anthracycline therapy; have ECOG performance status 0 or 1; and adequate organ function. Initially, 10 patients are planned to be enrolled, with potential to enroll an additional 5 patients.

Lymphocytes are obtained by leukapheresis, isolated, activated, transduced to express NY-ESO-1c259T, and expanded. Target dose is 1–8 × 109 cells. Patients who do not receive the minimum cell dose or who do not receive the T-cell infusion may be replaced. Disease is assessed at weeks 4, 8 and 12 post-T-cell infusion, and then every 3 months. On study tumor biopsies and blood samples will be evaluated to compare the pre- and post-T cell infusion immune profile for association with treatment outcome.

Results: Six subjects have been screened for HLA. Four subjects are positive for HLA-A*02:01 (one homozygous for A*02:01; one 02:01/68:01; one 02:01/33:03; one 02:01/24:02). Three subjects who met HLA eligibility also expressed NY-ESO-1 at 2+/3+ intensity in ≥30% of tumor cells by IHC (one patient 3+ in 70% and two patients 3+ in 100% of cells), with one patient still pending antigen testing.

Conclusion: Based on the screening results to date, it appears that subjects with MRCLS tend to highly express NY-ESO-1. Screening, efficacy, and safety data will be evaluated on an ongoing basis for all subjects treated, and available data will be presented.

Poster 209 #2804699

PREDICTORS OF SURGICAL SITE INFECTION FOLLOWING SURGICAL RESECTION OF SOFT TISSUE MALIGNANCY: ANALYSIS OF 866 PATIENTS IN ACS-NSQIP DATABASE

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Objective: In this study, we aimed to (1) to define the incidence of surgical site infection (SSI) in patients undergoing excision of an extremity or pelvic STS from a prospectively collected, national cohort, (2) to identify predictive factors of the 30-day post-operative development of SSI in general, (3) to identify predictive factors of superficial and deep SSI independently following surgical treatment of soft tissue malignancy of the limbs and pelvis using data derived from the ACS-NSQIP database.

Methods: A retrospective cohort study of patients who underwent resection or amputation of an extremity or pelvic soft tissue malignancy between 2005 and 2013 was conducted using data extracted from the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database. Primary malignant soft tissue neoplasms were identified using the following ICD-9 codes: 171.2, 171.3 and 171.6. Patients treated with both wide excision and amputation were identified using the current procedural terminology (CPT) codes. Logistic regression models were used to identify significant predictors of superficial and deep SSIs in general following soft tissue malignancy resection.

Results: A total of 866 patients met our inclusion criteria. Seven hundred and eleven patients (90.2%) underwent surgical excision, while 77 (9.8%) underwent amputation. One in fifteen patients (6.9%) operated for resection of soft tissue malignancy developed any SSI within 30-days post-operatively, with superficial and deep SSI occurring at 4.9 % and 2.2%, respectively. Modifiable factors, non-modifiable factors and surgical factors were analysed separately. A final model including pre-operative radiotherapy, wound site and operation time showed that operation time was the strongest predictor of surgical site infection (p=0.03).

Conclusion: Certain patients undergoing soft tissue malignancy resection surgery have a significant increase in risk for developing SSIs; knowledge and awareness of characteristics of those patients can help in prevention and early identification of such SSIs.

Poster 210 #2804760

ASSOCIATION OF NY-ESO-1 EXPRESSION WITH BASELINE IMMUNITY AND CLINICAL OUTCOMES IN SOFT TISSUE SARCOMA (STS) PATIENTS (PTS) TREATED WITH LV305 OR CMB305

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Objective: NY-ESO-1 is a cancer testis antigen that is frequently expressed in human cancers including STS and which high expression has been associated with poor prognosis. CMB305 is an active immunotherapy regimen designed to generate and expand anti-NY-ESO-1 T cells and antibodies. 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 GLASE, a TLR-4 agonist. A phase 1 study of LV305 demonstrated a 1-yr survival of 81% and induction of anti-NY-ESO-1 T cells in sarcoma pts. The first-in-human study of CMB305 demonstrated a 1-yr survival of 83% with induction of broader and deeper anti-NY-ESO-1 T cells and antibodies when compared to LV305. We have evaluated the baseline tumor expression of NY-ESO-1 in STS pts enrolled in either the LV305 or CMB305 Phase 1 with clinical outcomes.

Methods: Adults with non-GIST, STS, whose tumors were tested by IHC were considered positive for NY-ESO-1 if expression was >1% by central review were enrolled in either of the phase 1 studies and treated with LV305 or CMB305. The CMB305 regimen included 4 injections of LV305 at 109 or 1010 vector genomes, alternating with 3 boost injections at 250 μg for 3 months, then bimonthly boost injections up to 1 yr. IHC staining for NY-ESO-1

expression was performed using a mouse monoclonal antibody E978 (Sigma). Anti-NY-ESO-1 antibody was measured by ELISA and T cells by Elispot. The potential association between tumor NY-ESO-1 expression and clinical outcomes were evaluated.

Results: A total of 145/328 STS pts (n=66 liposarcoma, n=118 synovial sarcoma, n=144 other) were screened positive for NY-ESO-1 IHC. After meeting eligibility criteria, 57/145 STS pts (n=17 myxoid/round cell liposarcoma, n=34 synovial sarcoma, n=6 other) with previously treated with at least one line of prior therapy were enrolled in the two trials. The mean NY-ESO-1 expression level was 76.6%; lowest level of expression 1-25% n=8, 26-50% n=3, 51-75% n= 7 and highest level of expression 76-100% n=39. At baseline, 15/45 (33%) of evaluable patients with available data had anti-NY-ESO-1 antibodies and 17/43 (40%) anti-NY-ESO-1 T cells. The IHC expression of NY-ESO-1 was significantly associated with baseline anti-NY-ESO-1 antibodies (p=0.0367). The median progression free survival in the lowest and highest level of expression of NY-ESO-1 expression was 4.6 months (2.1, 7.8) and 3.7 months (2.2, 14.0); and median overall survival was 27.8 months (11.5, 27.8) and Not Acheived (NA) (16.9, NA), respectively.

Conclusion: NY-ESO-1 is highly expressed in STS subtypes providing a target for CMB305. NY-ESO-1 expression by IHC is significantly associated with a baseline anti-NY-ESO-1 antibody response. Despite a poorer prognosis expected in patients with tumors with high levels of NY-ESO-1 expression, those in the upper level of expression treated with either LV305 or CMB305 had a trend toward improved clinical outcomes as compared to those in the lower level of expression.

Poster 211

WITHDRAWN

Poster 212 #2804798

THE ROLE OF RADIATION DOSE IN SOFT TISSUE SARCOMAS WITH A POSITIVE MARGIN AFTER RESECTION

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Objective: Surgery with or without radiation is the treatment for patients with soft tissue sarcomas (STS). Often, post-operative radiation is utilized to decrease the risk of local failure. We aimed to investigate the patterns of care and overall survival (OS) of patients with STS with positive margins after surgical resection who received adjuvant radiation therapy, utilizing a large national registry of patients.

Methods: Adult patients with a STS of the extremity who underwent definitive surgical resection and adjuvant radiation therapy from 2004 to 2012 were included. Logistic and Cox regression modeling was used to identify factors predictive of receipt of adjuvant radiation therapy and OS. Survival analysis was performed with Kaplan Meier and

log rank analysis. Univariate and multivariate Cox regression analysis was performed to control for covariates that may impact OS.

Results: A total of 2,609 patients were identified. 1,776 (67%) had a tumor size >5.1cm, and 833 (32%) had a tumor size < 5.0cm. 1,566 patients (60%) of patients received a radiation dose <64Gy, and 1,043 patients (40%) received a radiation dose > 64Gy. Patients who received a radiation dose >64Gy were found to have an improved 5 year OS as compared to patients who received a radiation dose <64Gy (62.0% versus 56.1%). Median survival for patients who received a radiation dose >64Gy was 39.4 months, as opposed to 37.6 months for patients who received a radiation dose < 64Gy (p=<0.001). The benefit of dose escalation was persistent of univariate and multivariate analysis (HR: 0.84, 95% CI 0.72 to 0.96). On subgroup analysis, the benefit of adjuvant radiation was most significant in stage III patients (HR: 0.75, 95% CI 0.63 to 0.89).

Conclusion: In the setting of positive margins after resection of STS of the extremity, radiation dose of >64Gy is associated with an OS benefit.

Poster 213 #2797065

TRANSCRIPTIONAL LANDSCAPE OF DESMOPLASTIC SMALL ROUND CELLTUMORS- A REPORT FROM THE CHILDREN'S ONCOLOGY GROUP

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Objective: Desmoplastic small round cell tumor (DSRCT) is a rare malignant tumor that predominantly affects young males in their second decade of life. Despite intense multi-modal therapy, DSRCT exhibit a dismal 5-year overall survival rate of less than 20%. Presently, the defining molecular marker of DSRCT is the, t(11;22)(p13;q12) translocation encompassing EWSR1 and WT1. In this study, we used next-generation RNA sequencing in an effort to elucidate the transcriptional landscape of DSRCT as well as identify therapeutically relevant EWS-WT1 target genes.

Methods: RNA was extracted from DSRCT tumor samples obtained from Cooperative Human Tissue Network biorepository and subsequently used for paired-end RNA sequencing. Presence of the EWSR1-WT1 fusion was verified using both RNA-sequencing and PCR. Validation studies, including WT1 ChIP-seq, RNA sequencing, and EWS-WT1 knockdown experiments, were performed on an established DSRCT cell line (JNDSRCT1).

Results: We analyzed 14 tumor RNA samples out of which two were confirmed negative for the EWSR1-WT1 translocation. Principal component analysis of the sequencing data indicated that fusion-negative and fusion-positive tumors are transcriptomically distinct entities. Overlap of the significant peaks discovered in ChIP-sequencing with genes found to be highly expressed in the RNA sequencing data revealed that IGF2 and FGFR4 were both highly expressed, and targets of the EWS-WT1 fusion gene, a finding that has potential clinical relevance. In addition, we identified the immune checkpoints CD200 and CD276 as potentially targetable genes whose overexpression is independent of the EWS-WT1 fusion gene.

Conclusion: Despite the transcriptional complexity of this disease, we were able to identify IGF2, FGFR4, CD200, and CD276 as potential therapeutic targets for patients suffering from DSRCT.

Poster 214 #2804805

CONSEQUENCES OF RTK AMPLIFICATION AND P53 LOSS IN NF1-RELATED MPNSTS

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Objective: Malignant Peripheral Nerve Sheath Tumors (MPNSTs) are aggressive, chemoresistant sarcomas that develop in patients with Neurofibromatosis Type 1. Loss of TRP53 and amplification of the receptor tyrosine kinase (RTK) MET is observed 25-50% of cases. Our objective is to investigate the role of MET and p53 in MPNST progression.

Methods: We developed three distinct mouse NF1-related MPNST models: an NF1 null and MET overexpressing MPNST model (NF1-MET), an NF1 and TRP53 heterozygous knockout model (NF1-p53), and a NF1 null model (NF1). Using orthotopic tumorgrafts from these models, we tested the efficacy of MET (capmatinib) and MEK (trametinib) inhibition on MPNST growth and assessed phosphoproteomic response using western blot analysis. We assessed the effects of combined kinase inhibition

on proliferation of MPNST cells, as well as the impact of METi and MEKi therapy on the phospho-preoteome using reverse phase protein arrays (RPPA).

Results: Trametinib moderately inhibited tumor growth in all of the models; however, combined inhibition of MEK and MET was highly effective in both the NF1-MET and NF1 models. NF1-p53 tumors were the least responsive to combined inhibition and upregulated AKT signaling in response to single agent therapy. These data suggest that 1) alternate RTK signaling pathways downstream of MET may compensate for MEK inhibition and 2) p53 loss promotes kinome reprogramming in response to targeted inhibition in MPNSTs. To determine the effects of MEK, MET, PI3K, and mTOR inhibition on kinome signaling, we generated MPNST cell lines from each of our MPNST models. Western blot analysis revealed that 1) NF1-MET MPNST cells are highly sensitive to MET inhibition, 2) NF1-p53 MPNST cells maintain ERK and AKT activity in the presence of MET inhibition and 3) NF1-p53 MPNST cells uniquely upregulate MEK signaling in response to PI3K and mTOR inhibition. Furthermore, analysis of the EGFR inhibitor, erlotinib, in NF1/p53-deficient, human MPNST cell lines confirms compensatory MET activation. These results suggest that p53 plays a unique role in kinome reprograming and resistance to kinase inhibitors.

Conclusion: By understanding these complex signaling networks we will identify new points of compensation that occur in the setting of tyrosine kinase inhibition, and combinations of targeted therapies that can be used to effectively treat NF1-related MPNSTs.

Poster 215 #2751240

DISCOIDIN, CUB AND LCCL DOMAIN-CONTAINING PROTEIN 2 (DCBLD2) IS A NOVEL BIOMARKER OF MYXOFIBROSARCOMA INVASION IDENTIFIED BY GLOBAL PROTEIN EXPRESSION PROFILING

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Objective: Myxofibrosarcoma (MFS) is a mesenchymal malignancy characterized by frequent recurrence even after radical wide resection. To optimize therapy for MFS patients, we aimed to identify candidate tissue biomarkers of MFS invasion potential.

Methods: Invasion characteristics of MFS were evaluated by magnetic resonance imaging and protein expression profiling of primary tumor tissues performed using two-dimensional difference gel electrophoresis (2D-DIGE).

Results: Protein expression profiles were compared between invasive and non-invasive tumors surgically resected from 11 patients. Among the 3,453 protein spots observed, 59 demonstrated statistically significant difference in intensity (≥ 2 fold) between invasive and non-invasive tumors ($p < 0.01$ by Wilkoxon test), and were identified by mass spectrometry as 47 individual proteins. Among them, we further focused on discoidin, CUB and LCCL domain-containing protein 2 (DCBLD2), a receptor tyrosine kinase with aberrant expression in malignant tumors. Immunohistochemistry analysis of 21 additional MFS cases revealed that higher DCBLD2 expression was significantly associated with invasive properties of tumor cells. DCBLD2 sensitivity and specificity, and positive and negative predictive values for MFS invasion were 69.2%, 87.5%, 90%, and 63.6%, respectively. The expression level of DCBLD2 was consistent in different portions of tumor tissues.

Conclusion: DCBLD2 expression can be a useful biomarker to evaluate invasive properties of MFS. Further validation studies based on multi-institutional collaboration and comprehensive analysis of DCBLD2 biological functions in MFS are required to confirm its prognostic utility for clinical application.

Poster 216 #2752828

MALIGNANT MYOEPITHELIAL TUMOR OF SOFT TISSUE: CLINICAL EXPERIENCE AND GENOMIC SEQUENCING

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Objective: Malignant myoepithelial tumor of soft tissue (MM) or myoepithelial carcinoma is a rare tumor that affects individuals of any age without sex predilection. MM has a more aggressive course than its benign counterpart. While pathology is well defined, the paucity of patients has limited the study of clinical behavior and treatment responses. Rearrangement of EWSR1 is found in approximately 45% of cases, though pathogenicity of the translocation is unknown. A subset of MM exhibit loss of SMARCB1/INI1 expression. We report on our clinical experience and tumor genome sequencing in patients with MM.

Methods: We identified patients (pts) with MM treated at the University of Michigan from 2000 to 2017 and collected data on demographics, therapy and outcomes. We conducted pathologic review on 10 available samples and comprehensive next generation sequencing (NGS) on 4 pts.

Results: We identified 13 pts with MM (10M/3F) with a median age of 51 yrs (range 22-88) and median follow-up of 2.8 yrs (0.4-7.6 yrs). Eleven pts with localized disease at diagnosis underwent resection; 4 pts received adjuvant radiation therapy (RT), median dose 60 Gy (range 35-63 Gy). Three pts developed local recurrence and had re-resection. Three developed distant metastases (mets) at a mean interval of 33 mo (range 5-75 mo) from diagnosis; 2 underwent metastasectomy. Eight pts were disease free at last follow-up and 1 died of progressive disease.

Of 5 pts with mets, 4 underwent systemic therapy and NGSas outlined in Table 1. No therapies resulted in objective response. Stable disease > 6 mos was observed in pts treated with: carboplatin/paclitaxel (1/3 pts), gemcitabine/docetaxel (1/2 pts), doxorubicin (1 pt).

NGS revealed 2 pts with homozygous deletion of CDKN2A/B; one with outlier expression of MET and the other with a germline variant in PPM1D. One sample had over 1700 point mutations. The fourth patient was found to harbor a novel PHF1-TFE3 gene fusion. Pathology review revealed 9/10 available samples were high grade with mean mitoses of 52.5/10 HPF, 7/10 with necrosis and 7/7 with INI retained.

Conclusion: MM is a rare malignancy with a variable clinical course. Pts with mets had limited benefit from systemic therapy. The variety of agents used in our series highlights the lack of therapy consensus. EWSR rearrangement was absent in all pts indicating its presence is not necessary for aggressive disease. Unique molecular alterations were identified, which may be integral to the pathogenesis of MM.

Metastatic Disease Course

Age at Dx/ Gender	1° Site	Location of Mets	Time from Dx to Mets (mo)	Systemic Treatment and Best Response	NGS Results	Survival from Dx/Mets (mo)
62/M	Extremity	Lymph Node, Abdomen/ Pelvis	0	GT: SD Doxo: SD Carbo/Pem: Prog	CDKN2A/B; PPM1D germline variant	63
48/M	Chest Wall	Intrathoracic, Abdomen/ Pelvis, Bone	0	Carbo/Pac/Bev: SD Carbo/Pac: PD Doxo/Dacarbazine: PD Phase I: PD	Highly mutated	27
77/F	Abdomen/ Pelvis	Abdomen/Pelvis	75	Carbo/Pac: SD	PHF1-TFE3 fusion	91/16
57/F	Extremity	Intrathoracic, Lymph Node	5	GT: PD MET inhibitor: PD	CDKN2A/B; MET overexpression	12/8

SD: stable disease; PD: progressive disease; Bev: bevacizumab; Carbo: carboplatin; Doxo: doxorubicin; GT: gemcitabine/ docetaxel; Pac: paclitaxel; Pem: pemetrexed

Poster 217 #2768598

EXPRESSION OF PDGFRα, LIGANDS, AND RELATED GENES VERSUS CLINICAL OUTCOMES IN A PHASE 1B/2 STUDY OF OLARATUMAB PLUS DOXORUBICIN IN SOFT TISSUE SARCOMA

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Objective: Olaratumab is a monoclonal antibody binding PDGFRα, recently approved for treatment of soft tissue sarcoma (STS) in combination with doxorubicin. Post hoc biomarker analyses explored potential associations of biomarkers related to the PDGFRα signaling pathway with progression-free survival (PFS) and overall survival (OS) in the randomized, controlled Phase 1b/2 study of doxorubicin with or without olaratumab in metastatic soft tissue sarcoma (NCT01185964).

Methods: Archived tumor samples of patients were collected at baseline as formalin-fixed, paraffin-embedded slides or tissue blocks, from which RNA was extracted. A novel multiplex RT-PCR method was developed and used for relative quantification of PDGFRα, PDGFRβ, PDGF-A, PDGF-B, PDGF-C, PDGF-D, Gli1, EGFR, EGF, VEGFA, TGFα, TGFβ, TOPO2A, PTEN and CXCR4 expression. Expression of these genes was then explored for associations with efficacy endpoints across treatment arms.

Results: Evaluable samples were from 77 patients including 37 patients from the olaratumab plus doxorubicin

arm and 40 patients from the doxorubicin arm. Patient demographics of this subset were similar to those of the overall study. No significant association was observed for PDGFRα or PDGFRβ expression and OS or PFS. Low PDGF-B or CXCR4 expression was associated with improved PFS in the combination arm (HR = 0.51 [90% CI: 0.28, 0.91], HR= 0.48 [90% CI: 0.26, 0.87], respectively). Low CXCR4 was also associated with improved OS (HR = 0.32 [90% CI: 0.17, 0.60]). In contrast to previous studies, poorer outcome among doxorubicin-only treated patients with low CXCR4 expression was observed.

Conclusion: A novel multiplex RT-PCR method was tested to measure PDGFRα, its ligands, and related genes on archival pre-treatment samples from this study. While PDGFRα gene expression on archival pre-treatment samples was not linked to PFS or OS of olaratumab-treated patients, some statistical associations for PDGF-B and CXCR4 and efficacy endpoints were identified. The discrepancy with published data for outcome in patients with low CXCR4 treated with doxorubicin alone introduces uncertainty regarding findings of this exploratory analysis which was limited by sample age, numbers and heterogeneous mixture of primary and metastatic tumor samples. Further biomarker analyses of tissue samples from the ongoing Phase 3 study of olaratumab plus doxorubicin in STS (ANNOUNCE) of both tumor and stromal expression of PDGF receptors and related ligands are warranted.

Poster 218 #2770373

THE EFFECT OF PAZOPANIB ON DOXORUBICIN PHARMACOKINETICS IN CHILDREN AND ADULTS WITH NON-RHABDOMYOSARCOMA SOFT TISSUE SARCOMA

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Objective: Pazopanib is a multi-targeted tyrosine kinase inhibitor (TKI) with activity in patients with advanced soft tissue sarcoma. TKIs are known to modulate cellular ATP binding cassette (ABC) membrane transporters that can affect the efflux and intracellular accumulation of anticancer agents. The newer, multi-targeted TKIs appear to inhibit the activity of ABC transporters, increasing the bioavailability of co-administered drugs and potentially reversing multi-drug resistance. Doxorubicin is a known substrate for drug efflux pumps (ABC transporters); thus, its exposure may be altered by the concomitant use of pazopanib. ARST1321 (PAZNTIS) is a pediatric/adult phase II/III study in non-rhabdomyosarcoma soft tissue sarcomas sponsored by NRG Oncology and the Children's Oncology Group that includes a doxorubicin/ifosfamide chemotherapy arm with or without pazopanib administered neoadjuvantly with radiation therapy prior to resection of the primary tumor. As an exploratory aim, doxorubicin pharmacokinetic (PK) data was collected during the dose-finding phase of the study in patients receiving chemotherapy and pazopanib to assess the effect of pazopanib on doxorubicin PK parameters.

Methods: This was an optional study and patient consent was required. Doxorubicin and doxorubicinol concentrations were quantified in blood samples obtained during the 2nd cycle (week 4) of chemotherapy at the following time points from doxorubicin administration: predose, 5 minutes, 30 minutes, 60 minutes, 2 hours, 4 hours, 8 hours, 24 ± 3 hours, and 48 ± 3 hours after dosing. The population PK was evaluated using non-linear mixed effects modeling.

Results: PK studies were analyzed in 7 patients (4 patients < 18 years of age and 3 patients ≥ 18 years of age) who received ifosfamide (2.5 g/m2/d x 3d) and doxorubicin (75 mg/m2/d x 2 d) with continuous pazopanib (pediatric patients: 350mg/m2; adult patients: 600mg daily). Figures 1-3 show the doxorubicin and doxorubicinol concentrations achieved over time. Doxorubicin clearance (L/hr/m2) was similar in study patients and historic controls (24.2 and 24.1, respectively; Table 1).

Table 1: Doxorubicin and Doxorubicinol Population PK Estimates of ARST1321 Patients vs Historical Controls (Völler et al. Clin Pharmacokinet. 2015 Nov;54(11):1139-49)

Parameter	ARST1321	Voller et al
Doxorubicin Clearance (L/hr/m2) (relative std error)	24.2 (18.5%)	24.1 (6.3%)
Doxorubicin Volume of Distribution (L/m2)	8.0 (10.2%)	9.34 (10.4%)
Doxorubicinol Clearance (L/hr/m2)	54 (27.6%)	42.5 (7.1%)
Doxorubicinol Volume of Distribution (L/m2)	885.7 (29.5%)	760 (7%)
Doxorubicin Inter-Individual Variability Clearance (%)	22 (39.4%)	30.7 (13.8%)
Doxorubicin Inter-Individual Volume of Distribution (%)	10 (77.3%)	26.7 (88.4%)
Doxorubicinol Inter-Individual Variability Clearance (%)	61 (27.7%)	43 (12.8%)
Doxorubicinol Inter-Individual Volume of Distribution (%)	70 (27.3%)	48 (11%)
Doxorubicin Residual Error (%)	20 (13.3%)	29.6 (2.6%)
Doxorubicinol Residual Error (%)	14 (11.5%)	31.7 (1.6%)

Conclusion: Compared to published data, doxorubicin pharmacokinetics were not altered by concurrent pazopanib. These data support the safety of administration of pazopanib with doxorubicin-containing chemotherapy.

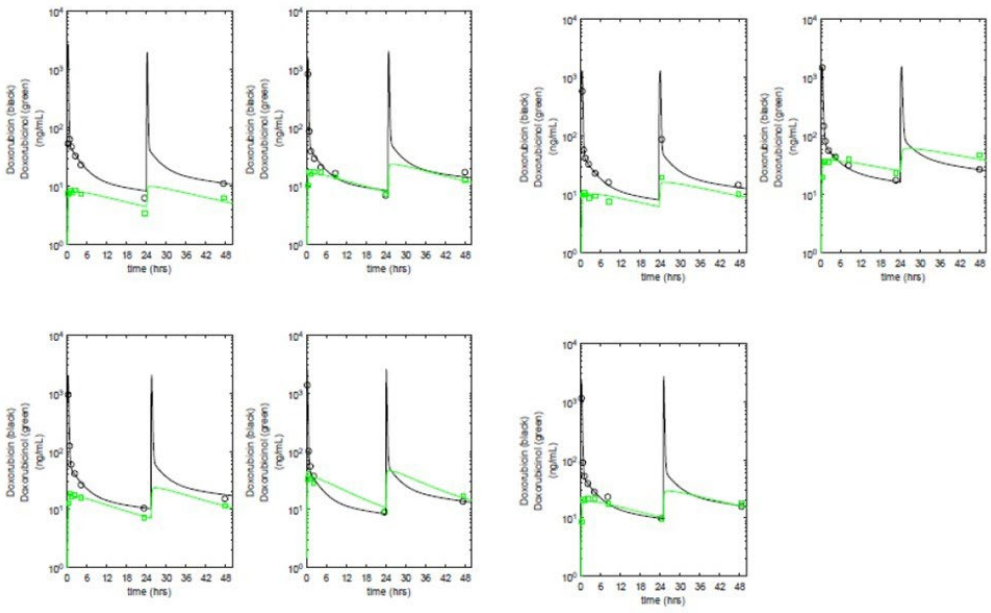

Figure 1: Plasma Concentrations of Doxorubicin and Doxorubicinol Plotted Against Time For All 7 Patients

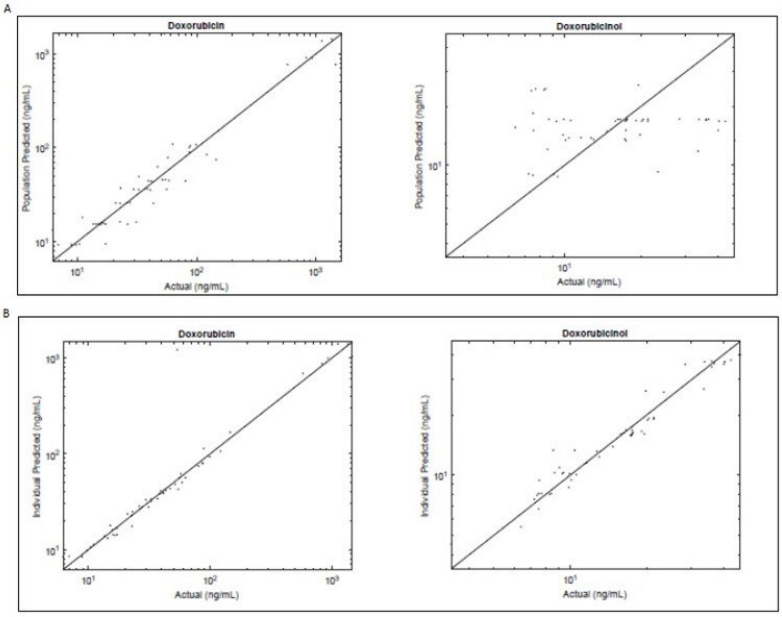

Figure 2: Doxorubicin and Doxorubicinol Observed Plasma Concentrations vs Population Predictions (A) and Observed Plasma Concentrations vs Individual Predictions (B)

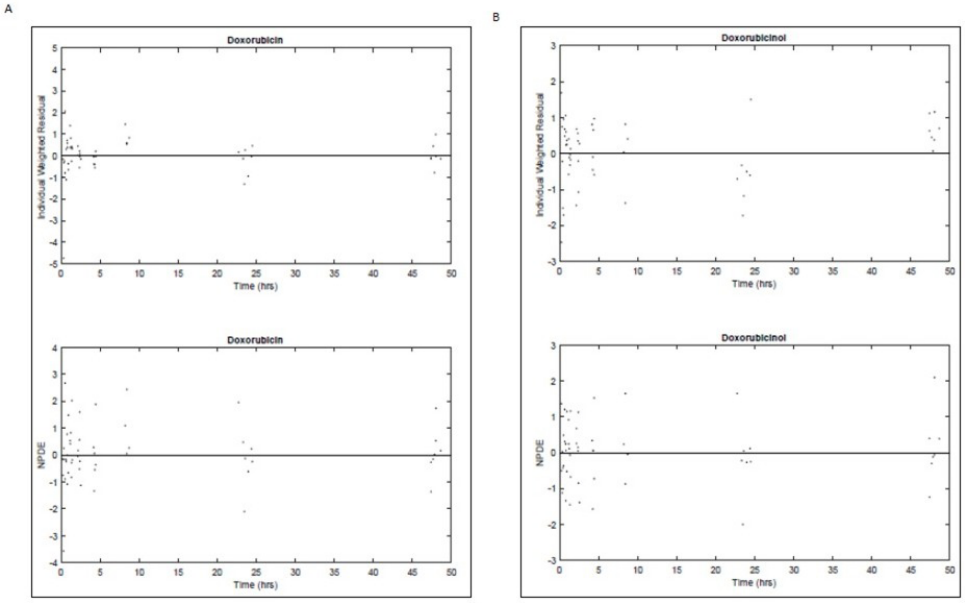

Figure 3: Doxorubicin Individual vs Normalized Prediction Distribution (A) and Doxorubicinol Individual vs Normalized Prediction Distribution (B)

Poster 219 #2777144

RESECTION OF RETROPERITONEAL SARCOMA EN-BLOC WITH INFERIOR VENA CAVA: 20 YEAR OUTCOMES OF A SINGLE INSTITUTION

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Objective: Margin negative resection offers the best chance of long-term survival in retroperitoneal sarcoma (RPS). En-bloc resection of adjacent structures, such as the inferior vena cava (IVC) is often required to achieve negative margins. Here we review our 20-year experience of enbloc IVC and RPS resection at a single institution.

Methods: Retrospective review of patients with RPS resection involving the IVC from 1995-2015. Prognostic factors for overall survival (OS) and disease free survival (DFS) were assessed.

Results: Thirty-two patients underwent resection of RPS en-bloc with IVC during the study period. Common histologies included leiomyosarcoma (26, 81%) and dedifferentiated liposarcoma (5, 16%). R0/R1 resection was obtained in 87.5% of cases. Types of reconstructions included synthetic graft or patch (19, 59%), allograft (3, 9%) and primary repair (6, 19%). In 4 (13%) cases, the IVC was ligated. Venoveno bypass was utilized in 6 (19%) cases and the vascular surgery team was present in all cases. Median blood loss was 2500 ml (IQR:6000-1125 ml), median tumor size was 10 cm (IQR 14.2-6.5 cm), and a median of 3 organs were resected. Perioperative mortality was 0%, although 6 (19%) patients experienced a severe complication. Patency for all evaluable patients was 90%. Margin status, number of organs resected and vascular ligation were associated with inferior survival. On multivariate analysis only an R2 margin (HR 10.74 DFS p=0.023, HR 5.75 OS p=0.050) and >5 organs resected (HR 8.10 DFS p=0.012, HR 13.24 OS p=0.002) were associated with inferior OS and DFS. Median OS was 42 months and DFS 16 months which was comparable to RPS resection without vascular involvement (n=142) with median OS 45 months and DFS 17 months (p=0.613, p=0.897).

Conclusion: Resection of IVC en-bloc with RPS is safe and can achieve equivalent rates of DFS and OS to patients without vascular involvement. These are often complex operations requiring multivisceral resection, and consequently referral to experienced sarcoma centers should be considered early in the evaluation and management of these patients.

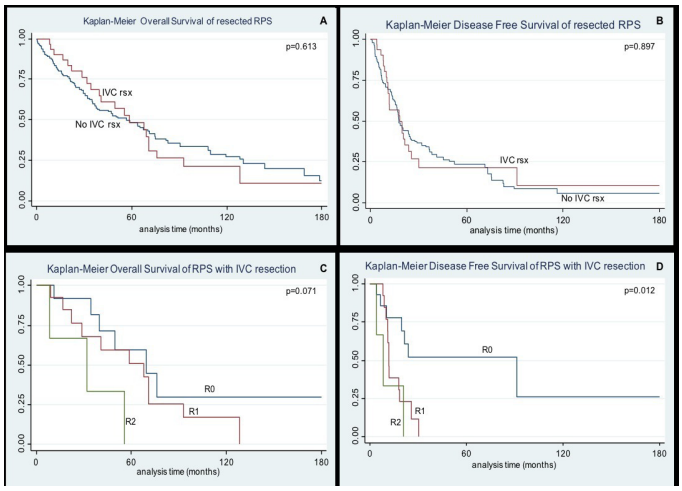

Figure 1: Kaplan-Meier survival estimates for resected retroperitoneal sarcoma (RPS). [A] Overall survival (OS) of RPS with inferior vena cava (IVC) resection [B] Disease free survival (DFS) of RPS with IVC resection [C] OS of RPS with IVC resection based on margin status. R0 vs R2 p=0.043. [D] DFS of RPS with IVC resection based on margin status. R0 vs R1, p=0.016, R0 vs R2, p=0.015.

Poster 220 #2778030

USING MRI TO DISTINGUISH LIPOMA VS. LIPOSARCOMA IN THE ERA OF MDM2 FISH: CAN EXPERIENCED OBSERVERS TELL THE DIFFERENCE?

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Objective: Lipomas and well-differentiated liposarcomas (WDL) are difficult to distinguish on MR imaging. Historically, pathologic diagnosis has also presented a diagnostic dilemma, however, this has changed with advances in molecular analysis and the use of Fluorescence in-Situ Hybridization (FISH) to identify MDM2 amplification present in all WDLs. Prior studies documenting the agreement between MRI interpretation and pathologic diagnosis are conflicting, and a weighted scoring system by Wang et al has been proposed as a potential solution. The new gold standard for pathologic diagnosis, MDM2 FISH, calls into question prior studies on the accuracy of MRI interpretation, as tumors previously regarded as lipomas are now known to be WDLs and vice versa. We therefore sought to evaluate the accuracy of expert readers of MRI in the era of MDM2 FISH, as well as to determine the utility of the proposed weighted scoring system.

Methods: A cohort of 49 patients with extremity lipomas or WDLs diagnosed by MDM2 amplification was retrospectively collected. Two musculoskeletal radiologists and two orthopaedic oncologists interpreted each MRI, and common radiologic features thought to correlate with a diagnosis of WDL were recorded, as well as the suspected diagnosis. The formula proposed by Wang and

colleagues was then compared against the MRI interpretation and the pathologic diagnosis.

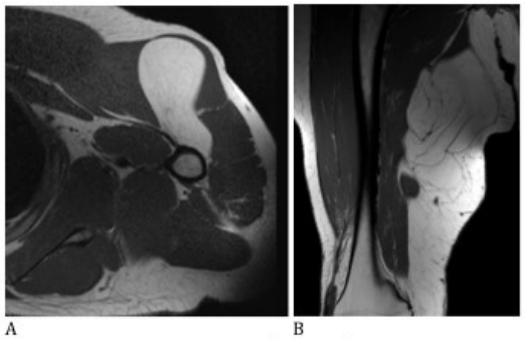
Results: 18 WDLs (36.7%) and 31 lipomas (63.3%) were included. Accuracy in obtaining the correct diagnosis for MRI readers was 73.5% (95% CI 61-86%), who preferentially diagnosed WDL [table 1]. Amongst expert observers, there was significant agreement in margin definition, homogeneity, stranding, nodularity, thickened septa, cystic changes, foci of high T2 signal, and overall diagnosis (p<0.0001) [table 2]. The proposed formula had an accuracy of 71%, which was not significantly different from the MRI readers (p=0.71). The formula had equal sensitivity for detecting WDLs (83%) but decreased specificity (64.5%) compared to the MRI interpreters (67.7%). This difference was not significant.

Table 1: Expert observer MRI diagnosis compared to pathologic diagnosis

Expert Readers Grouped Interpretation	Value	95%CI lower bound	95%CI upper bound
Sensitivity	0.8333	0.6612	1
Specificity	0.6774	0.5129	0.8420
Accuracy	0.7347	0.6111	0.8583
Positive Predictive Value (PPV)	0.6000	0.4080	0.7920
Negative Predictive Value (NPV)	0.8750	0.7427	1

Table 2: Inter-observer reliability and agreement on radiographic variables commonly used to differentiate Lipoma vs. WDL

	Margins	Homogenous	Stranding	Nodularity	Thickened Septa	Internal Cystic Change	Foci of High T2 signal	Radiographic Diagnosis
Kappa	0.2331	0.6122	0.4552	0.7673	0.5890	0.3333	0.7959	0.7022
P-value	0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001



A B

Figure 1: Representative MR imaging of Lipoma and WDL
A: Axial T1 MR of benign lipoma of the left upper extremity with universal agreement on benign nature amongst expert observers. Initial pathology was concerning for WDL, but changed to a Lipoma with MDM2 FISH. **B:** Coronal T1 MR of MDM2 FISH confirmed WDL of the right thigh with 3 of 4 expert observers predicting benign Lipoma. Formula and 1 of 4 observers predicted WDL.

Conclusion: MRI is commonly used as the initial screening tool for differentiating lipomas from WDLs [figure 1]. Given the recent evolution of MDM2 FISH, the agreement between pathologic diagnosis and MRI required re-evaluation. Based on our findings, the overall sensitivity of both our readers and the formula suggests that MRI remains unreliable.

Poster 221 #2779889

EVALUATION OF NEOADJUVANT RADIATION THERAPY IN THE TREATMENT OF MYXOID LIPOSARCOMA

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Objective: Myxoid liposarcoma (MLPS) has been reported to be radiosensitive. The authors report the results of the multidisciplinary treatment of myxoid liposarcoma and evaluate the role of neoadjuvant radiation.

Methods: Retrospective review of patients treated at a single institution with MLPS from 2000 to 2016. In this category the round cell variant was defined as hypercellular round cell (RCL) morphology >5% RCL phenotype in a given tumor. Margin status, treatment with radiation therapy, response to radiation, amongst other clinical and pathologic factors was analyzed in multivariate analysis for local recurrence-free survival (LRFS) and disease-specific survival (DSS).

Results: Two hundred and fifty three patients with MLPS underwent resection during the study time. One hundred and fourteen (45%) patients received systemic therapy and 207 (82%) received radiation in addition to surgery. Small tumor size (HR = 0.94, p = 0.01), negative margins (HR = 0.45, p < 0.001) and treatment with radiation therapy (HR = 0.71, p = 0.04) were all independently associated with improved LRFS. Female sex (HR = 0.34, p = 0.01), absence of cell round histology (HR = 0.21, p < 0.001) and negative resection margins (HR = 0.57, p = 0.004) were independently associated with improved DSS. A negative surgical margin was the only independent predictor of both LRFS and DSS. Neoadjuvant radiation was associated with a decreased incidence of positive margins (17.8%) compared to those treated without neoadjuvant radiation (25.5%) (p<0.001). According to RECIST criteria there were no complete responses, 80 (76%) partial responses, 11 (10%) stable and only 1 (1%) had progressive disease (13, 12% were un-evaluable). The median reduction in tumor size following neoadjuvant radiation was 2.90 (1.3-5.2) cm in maximal dimension from a median baseline of 12 (8.1-17) to a median of 9.1 (6.5-14.1) (p< 0.001). At least some pathological treatment response was evident in all patients with stable disease. Radiographic response to pre-operative radiation therapy was associated with a significantly improved 5 year DSS of 96% compared to 69% for those with stable or progressive disease (p<0.001).

Table 1: univariate and multivariate analysis for local recurrence-free survival (LRFS) and disease-specific survival (DSS)

Local recurrence-free survival				Disease-specific survival			
Univariate	p-value	Cox-regression	p-value	Univariate	p-value	Cox regression	p-value
sex	0.39			Sex	< 0.001	HR = 0.34	0.01
Age	0.90			Age	< 0.001		
Round cell histology	0.98			Round cell histology	< 0.001	HR = 0.21	< 0.001
Tumor size (cm)	0.001	HR=0.094	0.01	Tumor size (cm)	< 0.001		
Tumor location (extremity vs elsewhere)	0.007		0.054	Tumor location (extremities vs elsewhere)	0.42		
Histological grade	0.404			Histological grade	< 0.001		
Tumor focality (unifocal vs multifocal)	0.019		0.051	Tumor focality (unifocal vs multifocal)	0.20		
Tumor depth	0.285			Tumor depth	0.07		
Chemotherapy treatment	0.99			Chemotherapy treatment	< 0.001		
Radiation treatment	0.004	HR = 0.71	0.04	Radiation treatment	< 0.001		
Margin status	< 0.001	HR = 0.45	<0.001	Margin status	< 0.001	HR = 0.57	0.004

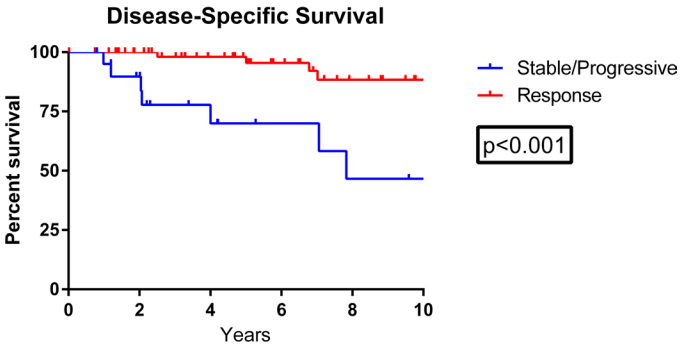

Figure 1: Kaplan Meier curve illustrating the statistical significant difference in disease-specific survival of patients treated with neoadjuvant radiation who acheived a partial radiographic response compared to those who achieved a stable or progressive radiographic response (p< 0.001)

Conclusion: Our study suggests that neoadjuvant radiation may be associated with significant reduction in tumor diameter, improved resection margins and improved LRFS. These findings support further evaluation of neoadjuvant radiation therapy for MRCL in a prospective randomized trial.

Poster 222 #2785200

A MATCHING-ADJUSTED INDIRECT COMPARISON OF TRABECTEDIN AND PAZOPANIB FOR THE TREATMENT OF ADVANCED, METASTATIC, LEIOMYOSARCOMAS

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Objective: Trabectedin (T) and pazopanib (P) are approved treatments for locally advanced or metastatic leiomyosarcoma (LmSTS). In the absence of head-to-head randomized controlled trials (RCTs); a matched-adjusted indirect comparison (MAIC) was performed to assess potential differences in clinical efficacy between the treatment groups.

Methods: MAIC was performed by extracting baseline characteristics from two phase III RCTs: SAR 3007 (T) and PALETTE (P): individual patient level data (IPD) was available for T only aggregated was published for P. Excluding those T patients who did not meet inclusion criteria for PALETTE, a sample size of 372 L-mSTS patients (T=263, P=109) was generated. Of all baseline characteristics, only time since diagnosis (≥30 vs. < 30 months), age (≥65 vs. < 65 years), and body weight (≥77 vs. <77 kilograms), were statistically significant outcome predictors with T. The generalized method of moments (GMM) was used to optimally match cohorts for evaluation of differences in overall survival (OS), progression-free survival (PFS), and safety. Statistical analysis was performed using "R".

Results: There was no statistically significant difference in PFS [HR=0.82, (95%CI 0.63-1.06, p=0.13)], or OS [HR=0.86, (95% CI 0.64-1.18, p=0.36)]. The percentage of patients with post-progression therapies was higher in T (74.5%) vs. P (59%) group. In the subgroup with PFS ≥6 months, patients treated with T experienced significantly improved median PFS (11.2 months vs PFS 8.4 months HR: 0.47 (95% CI: 0.3007-0.7434), p=0.002 and were significantly more likely to achieve long term survival (OS ≥ 18 months): 45.8% vs. 33.7% (95%CI: 23.5%-48.3%), p=0.025. Increased myelosuppression and hepatotoxicity observed with T whereas diarrhea, hypertension, pulmonary toxicity/pneumothorax, and neurotoxicity were observed with P.

Conclusion: The MAIC model warrants further investigation and validation. No differences in mPFS or mOS were noted in a MAIC comparison. Among patients achieving long term disease control (PFS > 6 mo), T significantly increased mPFS and the proportion of patients achieving prolonged overall survival (OS ≥ 18 mo). Differences in the safety profile were highlighted by this indirect comparison.

Poster 223 #2785250

EFFICACY AND SAFETY OF TRABECTEDIN IN AN ELDERLY PATIENT SUBGROUP (≥65 YEARS) WITH ADVANCED LEIOMYOSARCOMA (LMS) OR LIPOSARCOMA (LPS) FROM THE EXPANDED ACCESS PROGRAM (EAP)

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Objective: Elderly patients (pts) (≥65 yrs) with soft tissue sarcoma may have limited treatment options due to increased comorbidities and toxicities from available therapeutic agents. Previous retrospective analyses have suggested that trabectedin (T) has similar safety and efficacy outcomes irrespective of pt age.

Methods: In this multicenter, open-label study, pts received IV T (1.5 mg/m2) every 3 wks. We retrospectively analyzed the efficacy and safety of T in pts ≥65 yrs treated from 2005–2010 on this EAP.

Results: Mean age was 71 and 49 in the ≥65 (n=350) and <65 (n=1453) groups respectively. Pt demographics and disease characteristics were similar in ECOG score, race, gender, and histology. Median duration of therapy was 3 cycles in both groups. Pts receiving prolonged therapy (>12 mo) was 26 (7.4%) and 107 (7.4%) in the ≥65 and <65 groups, respectively. Elderly patients treated with T experienced similar median OS, ORR, and CBR (Clinical Benefit Rate, CR+PR+SD) compared to the <65 group with a median OS of 11.5 mo and 12.3 mo, ORR of 7 (3.9%) and 41 (5.4%), and CBR of 78 (43.1%) and 313 (40.1%) in the in the ≥65 and <65 groups, respectively. Toxicities in the elderly group were consistent with previously reported safety profiles, and incidence in the elderly group were comparable to those of the <65 group. Treatment-emergent adverse events (TEAEs), and serious TEAEs were similar in both groups. The percentage of pts requiring dose reduction and dose delay in pts who received ≥2 cycles was also similar with 96 (33.6%) and 444 (36.2%) of pts requiring dose delay and 135 (47.2%) and 563 (46.0%) requiring dose reduction in the ≥65 and <65 groups, respectively. In both groups, the majority of pts discontinued treatment due to disease progression

with only 32 (9.1%) and 118 (8.1%) of pts discontinuing treatment due to an AE in the >65 and <65 groups, respectively.

Conclusion: The efficacy and safety profile of T in pts ≥65 was similar to that observed in pts <65 in this EAP. Based upon this real world experience, T should be considered as a treatment option for elderly pts with soft tissue sarcoma and good performance status irrespective of age.

Poster 224 #2785293

PHASE II, MULTI-CENTER, RANDOMIZED TRIAL OF GEMCITABINE WITH PAZOPANIB OR GEMCITABINE WITH DOCETAXEL IN PREVIOUSLY TREATED SUBJECTS WITH ADVANCED SOFT TISSUE SARCOMA

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Objective: Pazopanib is a multi-tyrosine kinase inhibitor with efficacy in many subtypes of sarcoma. We designed a trial to assess the benefit of adding pazopanib to gemcitabine (G+P) as an alternative to the commonly used combination of G+T in pts with recurrent, advanced soft tissue sarcoma (STS).

Methods: This open-label, randomized, multi-site, phase 2 trial (NCT01593748) enrolled pts with advanced non-adipocytic STS who have received prior anthracycline based therapy. Pts were randomly assigned (1:1) to receive gemcitabine 1000 mg/m2 on days 1 and 8 with pazopanib 800 mg once daily or gemcitabine 900 mg/m2 on days 1 and 8 and docetaxel 100 mg/m2 on day 8, repeated every 3 weeks. Randomization was stratified by leiomyosarcoma sub-type and prior pelvic radiation. The primary endpoints are median PFS rate and rate of grade 3 /4 toxicities. Secondary endpoints include estimating the hazard ratio comparing G+P vs G+T, and evaluating response rates and quality of life measures (EORTC QLQ-C30 and EuroQol questionnaires) on G+P vs G+T. Response was assessed per RECIST every 6 weeks until progression. Optional cross-over was allowed for RECIST defined progression. Optional blood samples for biomarker (cytokine and angiogenesis factors) analyses were collected at baseline, cycle 2 and end of treatment on each arm.

Results: As of 5/2017, we have randomized 82 out of the 90 planned pts; 43 on G+P and 39 on G+T. The number of prior lines of therapy were similar on each arm (Table 1) There have been no unexpected toxicities or deaths. Rate of protocol-specified dose-reductions are high (67% on G+P and 56% on G+T). The most common grade 3/4 adverse events (AEs) in greater than 10% pts on G+P vs G+T were: neutropenia (54% vs 21%), thrombocytopenia (46% vs 46%), hypertension (21% vs 0), anemia (16% vs 23%) and fatigue (14% vs 26%). Most of the neutropenia in the G+P arm was grade 3. (Table 2) Rate of serious AEs was 33% on G+T and 30% on G+P. Primary reason for study discontinuation in G+P and G+T was disease progression (20 vs 17 pts, respectively) followed by toxicity (5 vs 8 pts, respectively). Nine patients on each arm crossed-over on study.

Patient Demographics

	G+T (n=39)	G+P (n=43)
Age (median age, years)	58	62
Gender: Female Male	18 21	23 20
Race: White African American Asian Other	29 8 0 1	37 2 1 3
Leiomyosarcoma: Yes No	10 29	14 29
Prior chemotherapy (total n) 1 2 3 Missing data	39 18 9 4 6	43 22 9 4 8

List of all recurrent grade 3 or higher toxicities (>1 event).

Adverse Event No. of events (% pts with at least 1 event)	G+T, N=39		G+P, N=43	
	Grade 3	Grade 4	Grade 3	Grade 4
Neutropenia	4 (8%)	6 (13%)	31 (42%)	5 (12%)
Thrombocytopenia	10 (23%)	12 (23%)	13 (23%)	11 (23%)
Hypertension	0	0	9 (21%)	0
Anemia	9 (23%)	0	7 (16%)	0
Fatigue	10 (23%)	0	6 (12%)	0
Increase in ALT	1	0	3	1
Lymphopenia	4	1	3	2
Nausea	0	0	2	0
Pancreatitis	0	0	2	0
Extremity edema	3	0	0	0
Lung infection	2	0	0	0

*Adverse events are ordered by the grade 3 events of G+P and one patient could experience multiple incidences.
*Parentheses show the percentage of patients who experience at least one incidence of the specific AE occurring at least 10% of patients

Conclusion: This ongoing study so far shows that G+P combination at the starting doses used in this study re-

sults in a high rate of myelosuppresion and similar to G+T, the majority require dose reduction because of toxicity. Analyses of median time on study, response rates and survival is ongoing and will be presented at the meeting.

Poster 225 #2786750

MDM2 IS RELEASED FROM LIPOSARCOMA IN EXOSOMES AND AFFECTS PREADIPOCYTE FATE

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Objective: We asked whether or not MDM2, as a driving factor of LPS, was released from LPS cells in exosomes and if this release is able to affect the surrounding microenvironment, in particular preadipocytes. We also examined whether or not MDM2 was present in exosomes circulating in the peripheral blood of LPS patients.

Methods: The expression level of mRNA and DNA was determined using mRNA sequence specific probes (TermoFisher) via real-time PCR according to the manufacturer's protocol. Exosomes were isolated by serial ultracentrifugations. The quality and the size of particles were assessed by Nanosight. Plasma samples were collected from 8 LPS patients. Peripheral blood vesicles were isolated from plasma by using ExoQuick (System Biosciences) and following manufacturer's protocol. Cell proliferation and invasion were assessed by MTS assay and Invasion Assay (Corning Matrigel™ Invasion Chambers), respectively.

Results: We proved that exosome derived from LPS cell lines contain the oncogenic MDM2 (by PCR and sequencing). We also showed that the level of MDM2 in exosomes is proportional to the level of MDM2 in the originating cells. When recipient preadipocytes were treated with LPS derived exosomes, they showed an increased ability of migration and invasion, suggesting that MDM2 can trigger this phenotypic change. We found levels of MDM2 in the recipient cells to be higher than cells that did not receive exosomes, which suggests that the aforementioned phenotypic change was the result of a transfer of MDM2 from LPS derived exosomes to the preadipocytes. Additionally, we found that MDM2 was present in the Peripheral Blood Exosomes (PBXs) from LPS plasma samples, introducing a new possibility for the use of MDM2 as a biomarker in LPS blood.

Conclusion: This study began to address an unsolved key issue in LPS: what is the mechanism of the devastating and often deadly recurrence of LPS tumor within the seemingly healthy tissue left behind following surgical treatment. We propose that MDM2 can be the driver not only for LPS initiation but also for LPS recurrence, as preadipocytes treated with LPS derived exosomes containing MDM2 have modified migration and invasion abilities. We also propose MDM2 in the PBX as possible biomarker for LPS disease.

Poster 226 #2790108

TRK AND BEYOND: TARGETABLE ONCOGENE MUTATIONS AND FUSIONS IN PEDIATRIC PATIENTS WITH SOFT TISSUE NEOPLASMS IN THE PROFILE CANCER RESEARCH PROJECT

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Objective: The frequency of actionable mutations in pediatric soft tissue and peripheral nerve neoplasms is unknown and clinical sequencing is not part of our current standard of care. The objective was to report the results of next-generation sequencing performed in a clinical laboratory as part of a cohort study, PROFILE. Here, we focus on the presence of actionable variants in soft tissue and peripheral nerve associated neoplasms.

Methods: We offered all pediatric patients with suspected extracranial solid malignancies enrollment on our clinical sequencing study, PROFILE, starting in June, 2013. Tumor samples were subjected to a targeted DNA sequencing panel, in which exons of 300-447 cancer genes are sequenced for variants and copy number alterations, and introns of 35-60 genes are sequenced for fusions.

Results: We enrolled 512 patients with extracranial solid tumors presenting to the Pediatric Oncology Clinic on PROFILE. There was adequate leftover tissue from clinical procedures (biopsy or surgery) for successful sequencing in 238 patients. 11 of the cases with successful sequencing were soft tissue or peripheral nerve neoplasms without a definitive histologic classification on initial pathology review. These cases were classified as spindle cell neoplasm (n=5), myofibroblastic neoplasm/sarcoma (n=1, Ewing-like sarcoma (n=2), neoplasm with histiocytoid appearance (n=1), undifferentiated pleomorphic sarcoma (n=1), and undifferentiated round cell sarcoma (n=1). PROFILE revealed the following actionable variants in 4 of these cases: KIAA1217-RET, BRAF p.V600E mutation, NTRK1 fusion (partner not defined), EML4-ALK fusion with PTEN p.R130Q mutation. Two patients with actionable variants responded to targeted therapy and 2 patients have no evidence of disease after surgical resection.

Conclusion: The unselective approach to enrollment undertaken in the PROFILE study led to identification of actionable variants with important implications for medical and surgical management in soft tissue and peripheral nerve neoplasms. To follow-up on this result, additional historical soft tissue and peripheral nerve neoplasms at our institution lacking a clear histologic subtype are being subjected to sequencing.

Poster 227 #2792920

NO BENEFIT OF PREOPERATIVE CHEMOTHERAPY FOR PRIMARY RETROPERITONEAL SARCOMAS: RESULTS FROM A SINGLE CENTER PROPENSITY SCORE MATCHED ANALYSIS

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Objective: Surgery for retroperitoneal sarcomas (RPS) is the keystone of curative treament. The potential benefits of preoperative chemotherapy remain unknown. The Aim of the study was to evaluate the prognostic impact of preoperative chemotherapy in patients with primary RPS.

Methods: All consecutive patients operated in our tertiary care center for a primary RPS between 1994 and 2017 were retrospectively studied. A caliper restricted, propensity score matched analysis was used to compare the groups receiving or not preoperative chemotherapy.

Results: 249 patients were identified and 49 (19.7%) had received preoperative chemotherapy. After matching, 40 pairs were available for analysis.7 patients had intermediate adipocytic tumors, 30 had malignant adipocytic tumor, 19 had smooth muscle tumors and 24 had other subtypes. Median tumors size was 20 cm.16 tumors were FNCLCC's grade 1, 28 grade 2 and 36 grade 3. In the matched cohort, preoperative chemotherapy was neither related to an "en-bloc" resection (94.9% vs. 95%, p=0.93) nor a R0 resection (48% vs. 46%, p=0.89). Severe postoperative morbidity and mortality were comparable (18% vs. 22%, p=0.65; 7% vs. 5%, p=1).Univariate analysis identified the size of the tumor (p=0.036), the pathological 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 pathological subtype (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: Preoperative chemotherapy was not associated to a greater overall or disease-free survival neither did it improve resection margin or morbidity. We do not recommend chemotherapy in the preoperative setting for resectable primary RPS.

Poster 228 #2792973

LONG-TERM OUTCOME OF UPFRONT ISOLATED LIMB PERFUSION FOR LOCALLY ADVANCED NON-METASTATIC PRIMARY SOFT TISSUE SARCOMA

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Objective: To evaluate long-term results after upfront isolated limb perfusion in untreated pateints with primary non-metastatic locally advanced limb soft tissue sarcoma (STS).

Methods: Weanalyzed the files of all patients treated in our single tertiary care center to select patient who had without any prior treatment an ufront ILP for an advanced STS of the extremity between 2000 and 2016. Preoperative, operative, postoperative data and the long term data were retrospectively recorded.

Results: Among 177 patients, who had an ILP, 44 patients were treated by neoadjuvant ILP. Median follow-up was 51, 7 months (range 3-137 months). Median tumor size was 15,9 cm (range 1-20 cm). Any patient among 44 patients underwent surgery, chemotherapy or radiotherapy before ILP. Local and systemic toxicity was mild to moderate in almost all cases. The tumor response assessed on MRI performed 2 months after ILP. MRI response 2 months after ILP was 29,5% complete response, 45,5% partial response,16% stable disease and 9% progressive disease. 31 patients (70, 5%) underwent conservative surgery. 3 of 44 patients underwent postoperative amputation either related to local recurrence or irresectability. 16 patients (36, 4%) were a complete histologic response. 4 of 31(13%) patients had local recurrences after ILP and limb sparing surgery, 15 of 44 (34,1%) developed metastatic disease. 15 of 44 (34,1%) died of disease.

Conclusion: Upfront ILP is feasible with good local control when associated with surgery in this population with unfavourable characteristics.

Poster 229 #2796502

APPROACH TO PRIMARY SOFT TISSUE SARCOMAS WITH METASTATIC DISEASE: DEFINING A COHORT FOR RESECTION, AN 8-INSTITUTION STUDY FROM THE U.S. SARCOMA COLLABORATIVE

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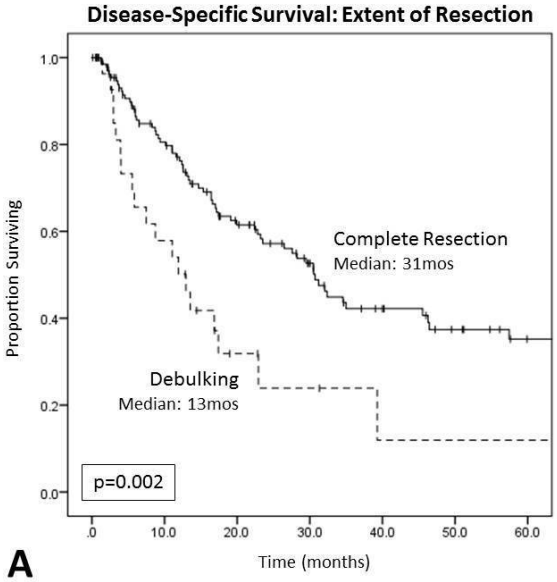
Objective: To define the clinical and pathologic characteristics of primary metastatic soft tissue sarcomas (STS) that are associated with improved disease-specific survival (DSS) after resection.

Methods: All adult patients with primary metastatic STS of the trunk, extremities, and retroperitoneum (RP), who underwent resection from 2000-2016 at 8 institutions of the US Sarcoma Collaborative were evaluated. Primary outcome was DSS.

Results: Of 2,139pts with primary STS, 168 (8%) underwent resection of the primary in the presence of metastatic disease. Mean age was 54yrs and 53% were male. Of the primary tumors, mean size was 13cm, 81% were high-grade, and 76% received chemotherapy and/or radiation. The most common location was trunk/extremity (64%), and most common histopathologic subtypes were leiomyosarcoma (21%), undifferentiated pleomorphic sarcoma (20%), liposarcoma (10%), and synovial sarcoma (10%). Of the metastases, 50% were isolated to the lung; 62% were resected in a staged fashion from the primary. Median DSS for all 168 pts was 28mos. Complete resection of all sites of disease (n=139, 83%) was associated with improved DSS compared to debulking (HR 0.44, 95%CI 0.26–0.74; p=0.002; Figure 1A) and resection of isolated lung metastases was associated with improved DSS compared to lung + other sites of disease (HR 0.49, 95%CI 0.28–0.87; p=0.01; Figure 1B). Both factors persisted in multivariable analysis, accounting for primary tumor grade, N stage, receipt of chemotherapy, and receipt of radiation. Among only curative-intent resections (n=139), isolated lung metastases were still associated with improved survival compared to lung + other sites (HR 0.47, 95%CI 0.25–0.89; p=0.02), which also persisted in multivariable analysis accounting for primary tumor grade, N stage, and receipt of chemotherapy. Location of the primary (trunk/extremity vs RP), timing of resection (synchronous vs staged), age, primary tumor margin status, histopathologic subtype, and primary tumor size were not associated with DSS.



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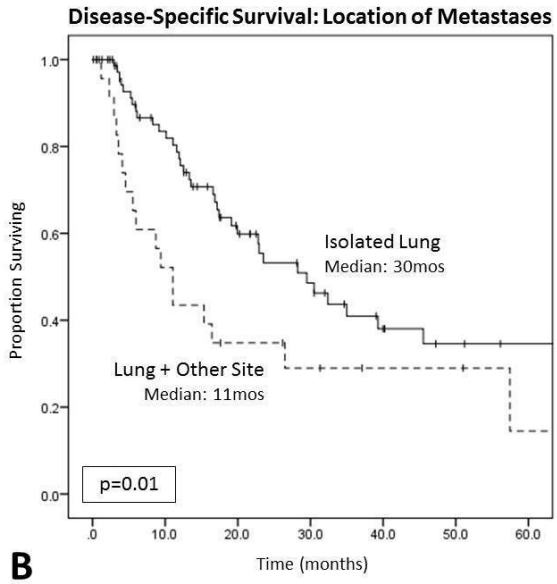

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Conclusion: Patients with metastatic disease comprise the minority of patients undergoing resection of STS. Despite their overall poor prognosis, complete removal of all sites of disease and the presence of isolated lung metastases are associated with improved survival after resection, even when accounting for grade, LN status, and receipt of other therapy. Histology specific analyses are needed to more accurately define those best suited for resection in the setting of metastatic disease.

Poster 230 #2798446

IMPACT OF OOPHORECTOMY ON SURVIVAL IN PATIENTS WITH UTERINE LEIOMYOSARCOMA (LMS)

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Objective: For localized uterine LMS hysterectomy is the primary modality of therapy. The NCCN uterine sarcoma guidelines are currently ambivalent with regard to the need for oophorectomy in women of reproductive age, suggesting that this decision should be individualized. Bilateral salpingo-oophorectomy (BSO) is generally recommended only for women who are peri/post-menopausal based on a SEER database analysis that did not demonstrate an improvement in survival in patients undergoing oophorectomy and to avoid subjecting younger women to early menopause. However, many physicians recommend a BSO in all women due to the concern that the estrogen may stimulate the risk of recurrence. Indeed, 40-80% of uterine LMS express estrogen receptors (ERs) and/or progesterone receptors (PRs) and targeted inhibition of this pathway through aromatase inhibition can achieve stability of disease in refractory patients. The purpose of this study is to determine the impact of oophorectomy on survival in patients with uterine LMS.

Methods: Patients who had a non-metastatic uterine LMS and underwent at least a hysterectomy for disease control between 2004 and 2014 were eligible. Chi-square tests and multivariate logistic regression were used to compare sociodemographic and tumor factors between the groups receiving and not receiving oophorectomy. All-cause mortality was analyzed using the Kaplan-Meier method and Cox proportional hazards regression. Stage was defined as 1: confined to uterus, 2: involving cervical stroma, 3: local or regional spread.

Results: 2,793 patient cases were identified and included in the analysis. 14.6% of patients did not receive oophorectomy. Year of diagnosis, facility location, higher stage and increased age and number of comorbidities were predictive for receipt of oophorectomy in the multivariate model. On unadjusted analysis, oophorectomy was predictive of worse survival, however, when adjusted for age, stage, comorbidities and other factors there was no difference in survival between the two groups (HR 1.13, 95% CI 0.91-1.39; P=0.2736). In addition to expected factors, race and insurance status also had an impact on survival in the multivariate model.

Conclusion: This large database analysis supports the notion that oophorectomy does not impact survival in patients with uterine LMS undergoing hysterectomy. Also, the decreases in survival for stages 2 and 3 (compared to stage 1) were similar, with race and insurance status also impacting survival.

Table 1. Multivariate predictors of overall survival in patients with uterine LMS

Variable	Hazard Ratio	95% CI	P value
Type of Surgery			
Removal of tube(s)/ovary(ies)	1.13	0.91-1.39	0.2736
Hysterectomy alone	ref		
Stage			
2	1.85	1.46-2.33	<0.001
3	1.87	1.53-2.28	<.0001
1	ref		
Comorbidities (Charlson/Deyo Score)			
1	1.09	0.91-1.30	0.3325
2	1.34	0.94-1.90	0.1062
0	ref		
Age at Diagnosis, y			
18-40	0.31	0.19-0.51	<0.0001
40-49	0.38	0.28-0.51	<0.0001
50-64	0.69	0.53-0.88	0.0038
65+	ref		
Race			
African American	1.25	1.07-1.46	0.0054
Other/Unknown	1.08	0.82-1.41	0.5866
White	ref		
Insurance Status			
Not insured	1.37	1.04-1.80	0.0235
Medicaid	1.43	1.10-1.85	0.0072
Medicare	1.00	0.78-1.29	0.9928
Other Governement Insurance	1.31	0.63-2.75	0.4713
Unknown	0.97	0.49-1.89	0.9163
Private/Managed Care	ref		

Poster 231 #2800984

ANTIBODY-DRUG CONJUGATE TARGETS FOR DRUG DEVELOPMENT IN SARCOMA: DIVING DEEPER INTO TCGA

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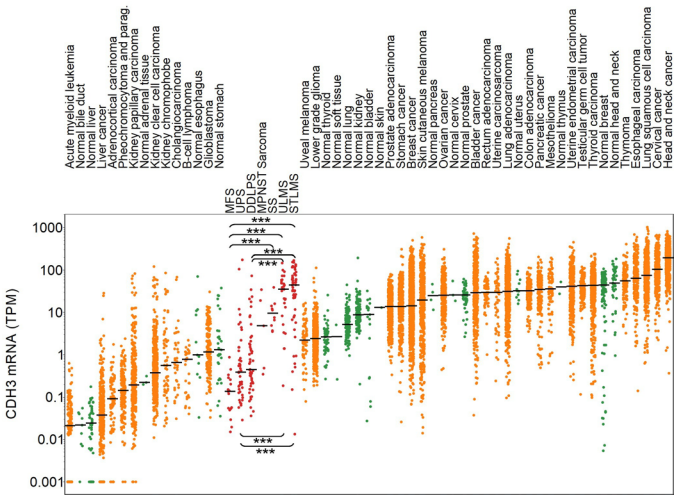
Objective: Antibody-drug conjugates (ADCs), which combine specific antibodies with cytotoxic payloads, have emerged as a promising strategy for targeted anti-cancer drug delivery. The efficacy of ADCs is highly dependent on the expression of the antibody target. We analyzed the expression of ADC targets currently in clinical trials in sarcoma subtypes for future ADC drug development.

Methods: We used RNA sequencing data from the Cancer Genome Atlas (TCGA) to analyze the expression of ADC targets (CD70, CDH3/6, ERBB2, F3, FOLR1, GPNMB, LRRC15, LYPD3, MSLN, PDGFRA, TNFRSF8) in sarcoma subtypes including dedifferentiated liposarcoma (DDLPS; n=50), uterine leiomyosarcoma (ULMS; n=27), soft tissue leiomyosarcoma (STLMS; n=53), undifferentiated pleomorphic sarcoma (UPS; n=44), myxofibrosarcoma (MFS; n=17), synovial sarcoma (SS; n=10), and malignant peripheral nerve sheath tumor (MPNST; n=5).

Results: CD70 expression was significantly higher in DDLPS (p<0.001), UPS (p<0.001), MFS (p<0.001), and MPNST (p<0.05) than in SS, and it was significantly higher in DDLPS (p<0.01), UPS (p<0.01), and MFS (p<0.05) than in STLMS. CDH3 expression was greater in STLMS and ULMS than in UPS (p<0.001), MFS (p<0.001), and DDLPS (p<0.001). It was also higher in SS than in MFS (p<0.001). ERBB2 expression was low in sarcoma, however, it was overexpressed in MPNST when compared with the expression in UPS (p<0.001), MFS (p<0.01), and ULMS (p<0.05). Furthermore, ERBB2 expression was higher in SS than in UPS (p<0.001), MFS (p<0.001), ULMS (p<0.01), and STLMS (p<0.05). GPNMB was highly expressed in most sarcomas, with the exception of SS, in which the expression was lower than in DDLPS (p<0.01), leiomyosarcomas (p<0.001), UPS (p<0.001), and MFS (p<0.001). LRRC15 also appeared to be a relevant target, especially in UPS, where its expression was significantly higher than in ULMS (p<0.001) and STLMS (p<0.01). MSLN expression was relatively low except in SS and MPNST, where it may be a relevant target. Interestingly, PDGFRA (target for olaratumab) was also highly expressed in most sarcomas with the exception of leiomyosarcoma. TNFRSF8 seems to be the most appropriate in DDLPS, where its expression was higher than in SS (p<0.001) and both leiomyosarcomas (p<0.001), as well as in MFS, where its expression was higher than in SS (p<0.05), ULMS (p<0.001), and STLMS (p<0.05).



Expression of P-cadherin (CDH3) in sarcoma. Clinical trials are ongoing with P-cadherin targeted Anti-body drug conjugates including a Radioimmunoconjugate with Y90. (Clinicaltrials.gov # NCT0265963, NCT02375958, NCT02454010)

Conclusion: Sarcoma subtypes express multiple ADC target genes, warranting further clinical validation and evaluation.

Poster 232 #2805171

NBTXR3 TREATMENT INDUCES ANTITUMORAL IMMUNE RESPONSE IN HUMAN SOFT TISSUE SARCOMA

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Objective: NBTXR3 is an aqueous suspension of functionalized hafnium oxide nanoparticles, undergoing seven clinical trials for enhancing radiation therapy (RT). They were designed for high dose energy absorption/deposition within the cancer cells when exposed to radiotherapy (NBTXR3 + RT), leading to tumor cell death and possible improved outcomes. In preclinical studies, NBTXR3 + RT also proved to cause immunogenic cell death and activate immune response. Here, we discuss the hypothesis that NBTXR3 + RT induces a specific adaptive immune response compared to RT alone in patients with STS.

Methods: Tumor tissues pre-(biopsy) and/or post-treatment (resection) were collected from patients (pts) with locally advanced STS, who received either NBTXR3 as intratumor injection and RT (14 pts) or RT alone (12 pts), as preoperative treatment (NCT02379845). Immunohistochemistry and Digital Pathology for immune biomarkers and for Immunoscore® (CD3/CD8) were analyzed. Gene expression profiling and pre-optimized immune-gene signatures called Immunosign® were also used.

Results: NBTXR3 + RT showed a significant increase of T cells (CD3/CD8) and a pronounced increase of CD103+ immune cell infiltration post vs pre-treatment (P<0.01), which were not seen for RT alone, and an increase in Immunoscore (CD3 + CD8 cell densities) compared to RT alone (P<0.07). Additionally, up-regulation of immune system gene expression, especially adaptive immunity genes expression, between pre- and post-treatment was marked for NBTXR3 + RT when compared to RT alone. Indeed, a functional analysis of genes up-regulated in NBTXR3 + RT demonstrated enhanced cytokine activity (IL7, IFNA, IL16, IL11, IFNG), adaptive immunity (RAG1, GZMA, TAP1, TAP2, TBX21, STAT4, IFNG, LCK, LTK, CD37, CD22) and T cell signaling pathway (CD28,

CTLA4, CD274, BTLA, TIGIT, CD40LG, CD5, CD3E, ZAP70).

Conclusion: NBTXR3 + RT triggers an enhanced adaptive immune response and contributes to transform “cold” tumor into “hot” tumor. These findings support the idea of NBTXR3 + RT being efficiently combined with immunotherapeutic agents, although further evaluations are needed to reinforce these results.

Poster 233 #2756283

PREOPERATIVE RADIOTHERAPY PRECLUDES THE USE OF EXISTING PROGNOSTIC NOMOGRAMS FOR PRIMARY RETROPERITONEAL SARCOMA (RPS)

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Objective: RPS site-specific nomograms have previously been created by several high volume centers with the intent of estimating risk of recurrence and death for the individual patient. However, only a small subset of patients treated at these centers received preoperative external beam radiation therapy (Pre-XRT). Our aim was to evaluate the predictive accuracy of these nomograms in patients who have undergone Pre-XRT and resection.

Methods: All patients who underwent curative treatment for primary RPS at Princess Margaret Cancer Centre/ Mount Sinai Hospital Toronto between1996-2015 were identified from a prospective database. The study cohort comprised patients who received Pre-XRT and resection. Exclusion criteria were: 1)distant metastases at presentation; and 2)postoperative RT (XRT and/or brachytherapy) for primary tumor.
We assessed each of four previously described nomograms [1-4] for validity in our patient cohort by measuring: i) extent of discrimination between the actual survival in relation to nomogram-predicted probabilities as quantified using Harrell’s concordance index; and ii) level of calibration quantified objectively as a summary of variance from the nomogram-predicted probabilities for all risk categories. Each of the previously formulated outcomes for each of the nomograms (Overall Survival (OS), Disease-Free Survival (DFS), Disease-Specific Death (DSD), Local Recurrence (LR), Distant Recurrence (DR), at the specified time points) was examined.

Results: 187 patients (89F, 98M) who underwent Pre-XRT and resection at our center met inclusion criteria. Median postoperative follow-up time was 58 mos (4-243), and 3-, 5-,and 10-yr OS estimated by the Kaplan Meier method were 85%, 75%, and 54%, respectively.

Results are summarized in Table 1. Comparing the actual outcomes with those predicted by each nomogram, the concordance index (c-index) ranged from 0.51-0.90. 7-yr DFS and 10-yr OS were notably underestimated by the nomograms, whereas 10-yr LR was overestimated. Level of calibration was also highly variable, and showed the greatest accuracy for 10-yr DR.

RPS-specific Nomogram	Outcome	Extent of discrimination (Concordance Index)	Level of calibration (Variance)
MD Anderson, Anaya et al. 2009 [1]	OS – 3 yr	0.64	0.0249
	OS – 5 yr	0.67	0.0273
Istituto Nazionale di Tumori, Milan, Ardoino et al. 2010 [2]	OS - 5 yr	0.61	0.0482
	OS - 10 yr	0.58	0.0508
Tri-Institution (MDA, Milan, UCLA), Gronchi et al. 2013 [3]	OS – 7 yr	0.64	0.0107
	DFS – 7 yr	0.58	0.0298
MSKCC, Tan et al. 2016 [4]	DSD – 10 yr	0.75	0.0229
	LR – 10 yr	0.51	0.0533
	DR – 10 yr	0.90	0.0078

Conclusion: Previous RPS site-specific nomograms under-predict survival in a cohort of 187 consecutive patients who received XRT prior to resection. The MSKCC nomogram c-index is accurate for DR, but LR was overestimated. One potential interpretation of these results is that Pre-XRT reduces LR. A distinct nomogram may be required for patients who have undergone Pre-XRT for primary RPS.

Poster 234 #2773296

PREDICTORS OF EXTENDED HOSPITAL STAY IN PATIENTS FOLLOWING SURGICAL RESECTION OF SOFT TISSUE SARCOMAS: ANALYSIS OF THE ACS-NSQIP DATABASE

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Objective: To identify factors affecting extended hospital stay in patients undergoing surgical resection of soft tissue sarcoma from a national cohort.

Methods: The American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database was used to identify patients who underwent surgical resection of a STS from 2005 to 2013. Primary malignant soft tissue neoplasms were identified. Patients treated with wide excision and amputation were recognized using the current procedural terminology codes. Prolonged operative time was defined as greater than 90th percentile of time required per procedure. A multivariable logistic regression model was used to determine associations between modifiable factors, non-modifiable patient factors and surgical factors with extended hospital stay following surgery.

Results: A total of 866 patients met our inclusion criteria. Among them, 539 had lower limb tumors, 210 patients had upper extremity lesions and 117 patients had pelvic masses. 90% of patients were amenable to limb salvage; the remainder received an ablative surgery. Model 1 included modifiable patient factors.and showed that bleeding disorder was independently predictive of increased length of hospital stay (LOS) by 5 fold (OR= 4.98, p=0.001). Malnourishment, as defined by an albumin of less than 3.5 g/dL was also predictive of prolonged LOS (p<0.001). Model 2 investigated the association of LOS with non-modifiable factors. We found that older age, pre-operative radiotherapy (OR=2.78, p=0.002), surgical site (OR=3.79, p<0.001) and patients treated with amputation (p<0.001) had significantly higher odds of a prolonged LOS. Model 3 focused on surgical factors, and demonstrated that prolonged operative time (OR=9.0, p<0.001), higher wound (OR=2.54, p<0.001), and ASA classes (OR=1.83, p=0.008) significantly predicted extended patient admission to hospital.

Conclusion: Quality metrics such as extended hospital stay following surgery can be understood by compartmentalizing risk factors into modifiable and non-modifiable patient factors, and surgical factors. This study demonstrates that patients who are malnourished, and hypercoagulable are at increased risk of extended hospital stay after soft tissue sarcoma excision, which may represent targets for future quality improvement initiatives. Similarly, risk factors for prolonged LOS include older patients, higher wound and ASA class, pelvic or lower extremity soft tissue malignancy, and treatment with pre-operative radiation or amputation.

Poster 235 #2732396

SAFETY AND EFFICACY OF TRABECTEDIN WHEN ADMINISTERED IN THE INPATIENT VS. OUTPATIENT SETTING IN A SUBSET ANALYSIS OF A PHASE III RANDOMIZED CLINICAL TRIAL

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Objective: Trabectedin (T) has been shown to improve progression free survival (PFS) (4.2 vs 1.5 months, HR 0.55, p < 0.0001) in comparison to dacarbazine (D) in patients (pts) with advanced leiomyosarcoma or liposarcoma following failure of prior chemotherapy. Pts randomized to T in this phase III trial (ET743-SAR 3007) received T as a 24 hr IV infusion in either an inpatient (InP) or outpatient (OP) setting, based upon site preference. Here we report the safety, efficacy, and patient reported outcomes (PROs) of pts based on first infusion site of care.

Methods: Pts were randomized 2:1 to receive T (1.5 mg/m2) or D (1 g/m2 over 20-120 min). Site of T infusion was based on institutional preference/standard of care. The site of T administration (InP vs OP) was collected for the first infusion with the assumption that site of care was unchanged for subsequent doses.

Results: Of 378 pts treated with T, 100 (27%) and 277 (73%) pts received T as InP or OP, respectively. No differences were observed in PFS or overall survival (OS) by site of care (InP vs OP): Median PFS of 4.1 vs 4.2 months; HR 0.90, p = 0.49 and median OS of 14.3 vs 13.7 months; HR 0.89, p = 0.40. No difference in other efficacy endpoints between InP vs OP were observed: disease control rate (CR+PR+(SD ≥ 18wks)) (38% vs 33%; Odds Ratio [OR] 1.22; p = 0.44) and Overall Response Rate (14% vs 8%; OR 1.76; p = 0.15)). Grade 3-4 adverse events (AEs) occurred in 87% InP vs 79% OP pts and grade 3-4 SAEs occurred in 43% InP vs 33% OP. The most common grade 3-4 AEs in both groups were increased ALT/AST, hematologic toxicity, nausea and fatigue. The incidence of grade 3-4 febrile neutropenia was similar in both groups at 5.0% InP vs 4.7% OP, as was increased blood creatine phosphokinase at 5.0% InP vs 6.1% OP, and catheter related complications of any grade at 16% InP vs 15% OP. No clinically meaningful differences were observed in PROs measured by MD Anderson Symptom Inventory scores.

Conclusion: The majority of patients randomized to the trabectedin arm of the ET743-SAR-3007 Phase III study received trabectedin in the OP setting. Treatment outcomes with trabectedin suggest equivalent efficacy and safety when administered in the InP or OP setting.

Poster 236 #2733032

RACIAL DISPARITIES IN PATIENTS WITH SOFT TISSUE SARCOMA OF THE EXTREMITIES

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Objective: In the United States, race and socioeconomic status are well known predictors of adverse outcomes in several different cancers. Existing evidence suggests

that race and socioeconomic status may impact survival in soft tissue sarcoma (STS). We investigated the National Cancer Database (NCDB), which contains several socioeconomic and medical variables and contains the largest sarcoma patient registry to date. Our goal was to determine the impact of race, ethnicity and socioeconomic status on outcomes in patients with soft tissue sarcoma of the extremities (STS-E).

Methods: We retrospectively analyzed 14,067 STS-E patients in the NCDB from 1998 through 2012. Patients were stratified based on race, ethnicity and socioeconomic status. Univariate and multivariate analyses were used to correlate specific outcomes measures with these factors. Then, long-term survival between groups was evaluated using the Kaplan-Meier (KM) method with comparisons based on the log-rank test. Multiple variables were analyzed between two groups.

Results: Of the 14,067 patients analyzed, 84.9% were white, 11% were black and 4.1% were Asian. Black patients were significantly more likely (7.18% vs 5.65% vs 4.47%) than white or Asian patients to receive amputation (p=0.027). Black patients were also less likely to have either an above-median education level or an above-median income level (p<0.001). In addition, black patients were more likely to be uninsured (p<0.001) and more likely to have a higher Charleson Comorbidity Score than white or Asian patients. Tumors were larger in size upon presentation in black patients than in white or Asian patients (p<0.001). Black patients had significantly poorer overall survival and a 20% higher likelihood of dying than did white or Asian patients (p<0.001) with a KM 5-year survival of 61.4% vs 66.9% and 69.9% respectively (Figure 1), even after multivariate analyses were carried out.

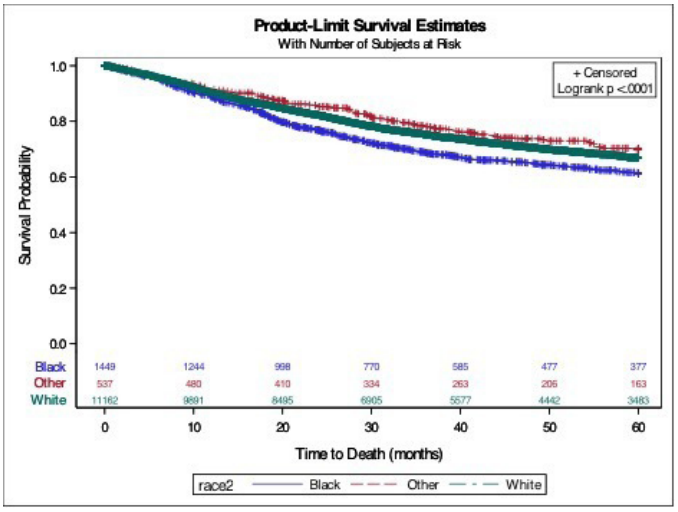

Figure 1. Kaplan Meier Survivorship Curve for Race

Conclusion: This large database review reveals concerning trends in black patients with STS-E. These include larger tumors, poorer resources, a greater likelihood of amputation, and poorer survival than white and Asian patients. Future studies are warranted to help ensure adequate access to effective treatment for all patients.

Poster 237 #2758399

SOFT TISSUE SARCOMA OF THE EXTREMITIES: THE VALUE OF TREATING AT HIGH-VOLUME CENTERS

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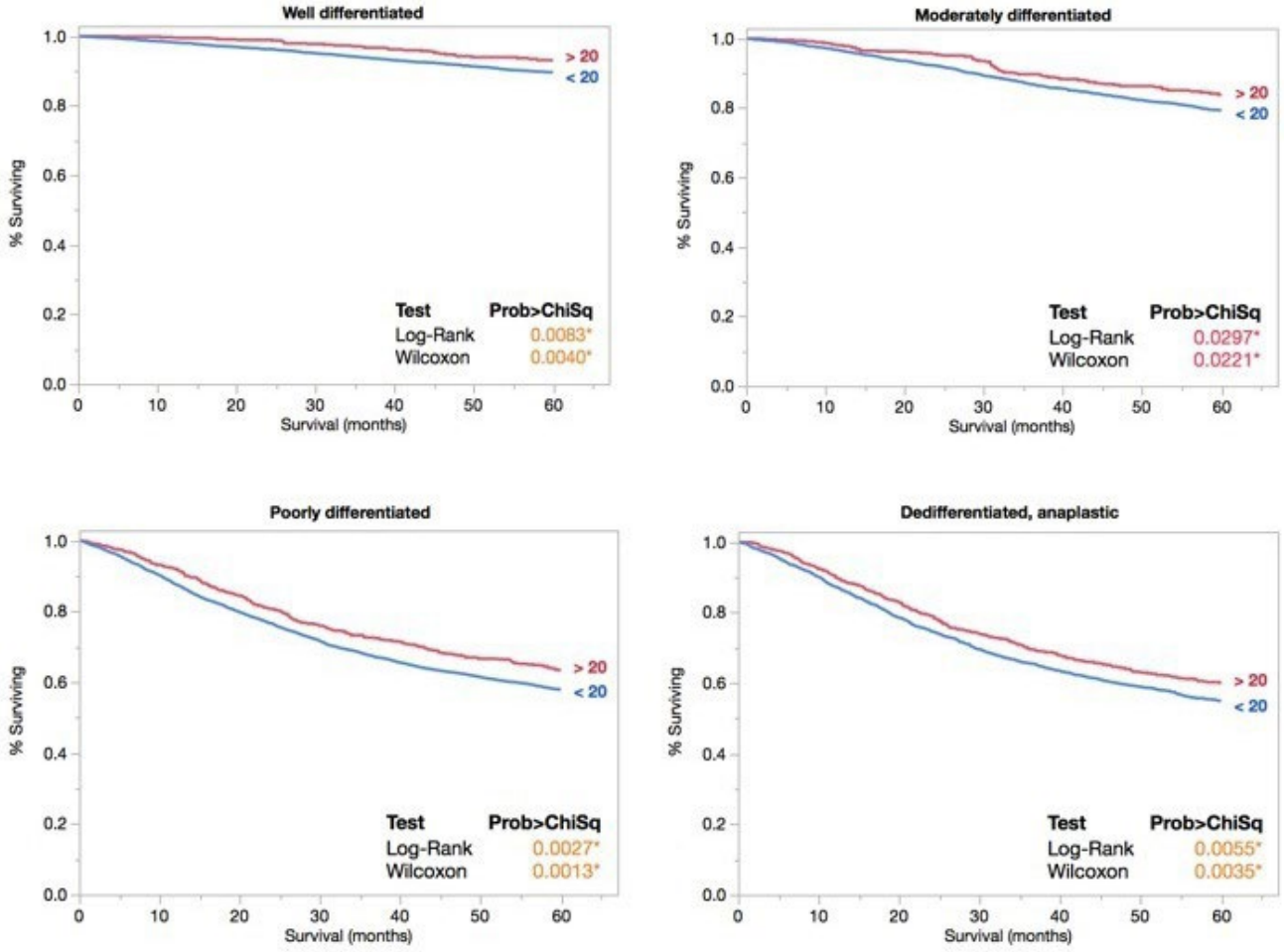
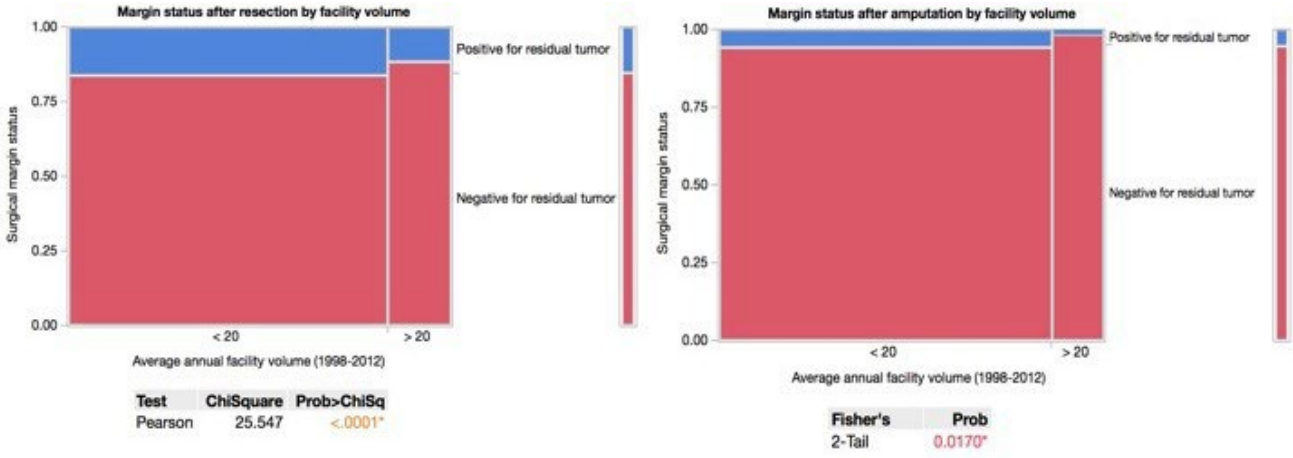
Objective: For many types of cancer, outcomes are improved when patients receive management at treatment centers that encounter high numbers of cases annually. This correlation has been suggested to be of even greater importance in the case of less common malignancies, such as sarcoma. Indeed, existing evidence suggests that facility case volume may impact survival in soft tissue sarcoma (STS). The largest sarcoma patient registry to date is contained within the National Cancer Database (NCDB). Our goal was to determine the impact of facility case volume on outcomes in patients with soft tissue sarcoma of the extremities (STS-E).

Methods: We retrospectively analyzed 25,434 STS-E patients in the NCDB from 1998 through 2012. Patients were stratified based on per year facility sarcoma volume. 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: Of the 25,434 patients analyzed, 3,310 were treated at high-volume centers (HVCs, >20 cases annually) and 22,096 were treated at low-volume centers (LVCs). Patient demographics were similar within both patient cohorts, though patients treated at HVCs were more likely to have larger and higher grade tumors (p<0.001). In a multivariate analysis, patients treated at HVCs had better outcomes across several domains. They had a lower risk of mortality overall than those treated at LVCs (risk ratio 0.792, p<0.001) with five-year survival rates that were superior in patients with high grade tumors treated at HVCs (60.1% five year survival) vs. LVCs (54.8% five year survival, p<0.001). Patients treated at HVCs were also less likely to have positive margins (p<0.001) and were less likely to receive an amputations for larger intermediate-grade tumors (p= 0.0031). The 90 day survival was poorer at LVCs (p<0.001), and there was an estimated average five-year survival benefit of +4.5% at HVCs relative to LVCs (p<0.0001).



5-Year KM curves comparing patient survival when treated at facilities with average annual case volume greater or less than 20 per year on average, by tumor grade. Log-Rank and Wilcoxon tests for survival difference were calculated for each set of KM curves.



Surgical margin status by total facility volume from 1998-2012.

Conclusion: With the largest patient cohort to date, this database review suggests that patients with STS-E should receive treatment at HVCs. Patients receiving treatment at HVCs had lower rates of margin positive surgery and improved survival. Further investigation is necessary to help improve the referral of appropriate patients to the high volume sarcoma centers.

Poster 238 #2761557

EPIRUBICIN AND IFOSFAMIDE WITH PREOPERATIVE RADIATION FOR HIGH-RISK SOFT TISSUE SARCOMAS (STS)

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Objective: While wide surgical resection is the cornerstone of treatment for high-risk extremity STS, the use and timing of chemotherapy varies among institutions as does the timing of radiation therapy. We previously reported results of a phase II study using a regimen of pre- and post-operative epirubicin and ifosfamide with preoperative hypofractionated radiation (Ryan CW, et al. Cancer 2008). We now report follow-up from these study subjects supplemented with data from a subsequent extensive institutional experience using this approach.

Methods: Seventy-seven patients total were included - 25 from the original phase II study and 52 from a retrospective chart review. Patients with localized, intermediate or high grade STS of the extremities or body wall measuring >5cm were treated with epirubicin 30mg/m2/day and ifosfamide 2.5g/m2/day on days 1-4 every 21 days for 3 preoperative and 3 postoperative cycles. During cycle 2 of preoperative therapy, epirubicin was omitted, and a total of 28 Gy of radiation (8 fractions) was delivered.

Results: The majority of tumors were located in the lower extremity (71%), the median tumor size was 10 cm, and the predominant histology was pleomorphic/NOS (48%). Median follow-up time was 3.6 years (range 2 months to 12 years) among all patients and 4.5 years (range 5 months to 12 years) among survivors. The 5-year rates for overall survival (OS), distant disease-free survival (DDFS), and freedom from local regional failure (LRF) were 72.9% (CI: 59.1% to 82.6%), 58.5% (CI: 45.0% to 69.7%), and 87.5% (CI: 73.2% to 94.4%) respectively. Tumor size >8 cm was associated with a lower 5-year OS rate (61.0% versus 95.7%, p=0.04). Pathologic response ≥90% was demonstrated in 39% of tumors (29/75) and was associated with a trend towards improved 5-year OS (82.9% versus 65.0%, p=0.27) and DDFS (68.6% versus 50.2%, p=0.29). Wound complications requiring surgical intervention occurred in 30% (23/77) of patients with infection accounting for the majority of cases (43%). Long term follow-up revealed two late deaths from suspected therapy-related myeloid neoplasms.

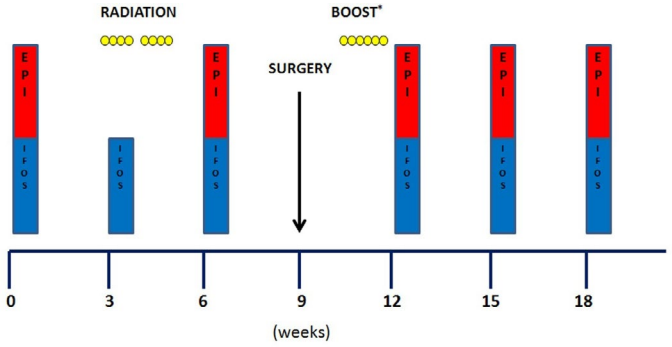

Figure 1: Treatment Schema. Diagram of therapeutic regimen, including chemotherapy, radiation therapy, and surgical resection. EPI indicates epirubicin; IFOS, ifosfamide; *boost was given to patients with positive margins only

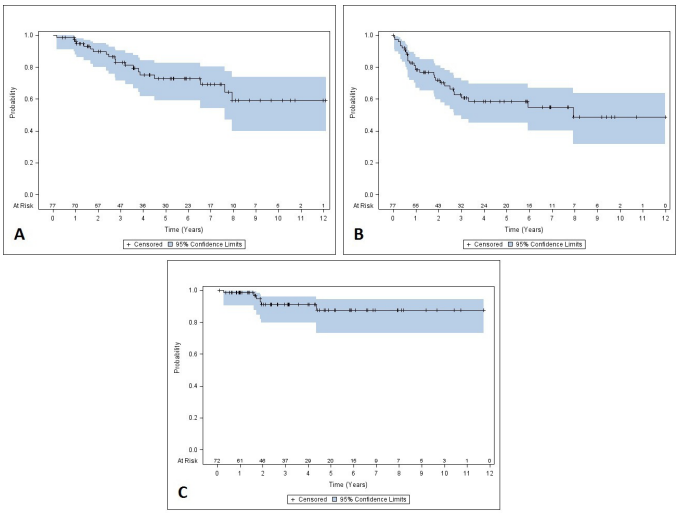

Figure 2: Kaplan-Meier curves of (A) Overall Survival, (B) Distant Disease-Free Survival, and (C) Freedom from Local Regional Failure (5 amputations excluded). Censored events are noted with crosses, with the number at risk detailed along the X-axis. 95% confidence intervals are shaded in blue.

Conclusion: Treatment with preoperative radiation and pre- and post-operative epirubicin and ifosfamide was associated with favorable clinical outcomes. Survival and recurrence rates were comparable to those reported with other preoperative chemotherapy regimens in high-risk extremity STS. We are currently studying the addition of sorafenib to this regimen.

Poster 239 #2767177

NEGATIVE PRESSURE WOUND THERAPY FOR SURGICAL SARCOMA WOUNDS - A CASE CONTROL TRIAL

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Objective: To compare negative pressure wound dressings with conventional absorbent dressings following sarcoma resection

Methods: This case controlled study evaluated patients with closed surgical wounds in which the cohorts consisted of an intervention group (NPWT) and a matched control group (absorbent dressings). Patients were matched in terms of age, gender, and site of tumour by an independent researcher. The primary outcome was wound complications and secondarily surgical drain volume. A t-test was performed for comparison of means and Z-testing for comparison of proportions using SPSS v23 (SPSS Inc, Chicago, Illinois).

Results: There were 9 consecutive patients who had a NPWT dressing applied as a routine measure immediately post op and 9 matches identifiend in our database.

The groups were well matched for demographics and tissue diagnosis. In the NPWT group, none of the patients developed wound infections in comparison to 3 patients in the controlled group which was statistically significant (p=0.0287). The control group showed a higher volume from the wound drains (525ml versus 338ml in the NPWT group). Although there was a trend to lower volume drains there was insufficient numbers to show a statistical difference (p=0.335).

Table showing the demographic of the study group

	NPWT	Control	p-value
Mean age (years) [SD]	56.11 (23.96)	57.25 (23.63)	0.75
Male:female ratio	2:1	2:1	1.00
Osteosarcoma (n)	2	2	1.00
Soft tissue sarcoma (n)	7	7	1.00
Mean duration of VAC (days)	5.4	-	N/A
Mean pre op albumin	36.8	36.9	0.61

Results

	NPWT	Control	p-value
Average volume in surgical drain (ml)	338	525	0.332
Post op infections (n)	0	3	0.028

Conclusion: Use of NPWT in surgical wounds after sarcoma resection had fewer wound complications, which could improve not just quality of life and patient care, but also may give rise to financial savings in the long term. A prospective randomised controlled trial within this cohort of sarcoma patients is now being undertaken for further evaluation (VACtrial@gmail.com).

Poster 240 #2767607

EN BLOC NEPHRECTOMY FOR PERIRENAL RETROPERITONEAL SARCOMA IS BENEFICIAL IN LOCAL CONTROL OF TUMOR AND ACCEPTABLE WITH RESIDUAL KIDNEY FUNCTION BASED ON RENAL ADAPTATION

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Objective: The purpose of this study was to evaluate the efficacy of en bloc nephrectomy for perirenal retroperitoneal sarcoma (RPS) with respect to postoperative kidney function and oncological benefits.

Methods: We performed a comparative study of 114 patients undergoing surgery for primary RPS, classifying cases as nephrectomy (NPX, N = 65) versus no nephrectomy (no-NPX, N = 49). The Δ and % change between preoperative and postoperative estimated glomerulus filtration rate (eGFR) were analyzed to compare renal function changes after surgery. Kaplan-Meier analysis was performed to verify the incidence of local relapse between the two groups

Results: During median follow up of 29 months, median postoperative eGFR of 65 patients in the NPX group decreased to 73.5% of preoperative eGFR. Although 38 patients (58%) of the NPX group experienced progression of CKD stage after nephrectomy, no patients progressed to end-stage renal disease (ESRD). In FNCLCC grade 2, the NPX group had statistically significant local control benefit, compared with the no-NPX group (P = 0.048).

Conclusion: Residual renal function after en bloc nephrectomy was stabilized without progression to ESRD. Moreover, en bloc nephrectomy for perirenal RPS might be considered to secure a complete resection margin for local tumor control.

Baseline Characteristics of Patients Undergoing Surgery With or Without Nephrectomy for Primary Retroperitoneal Sarcoma (RPS)

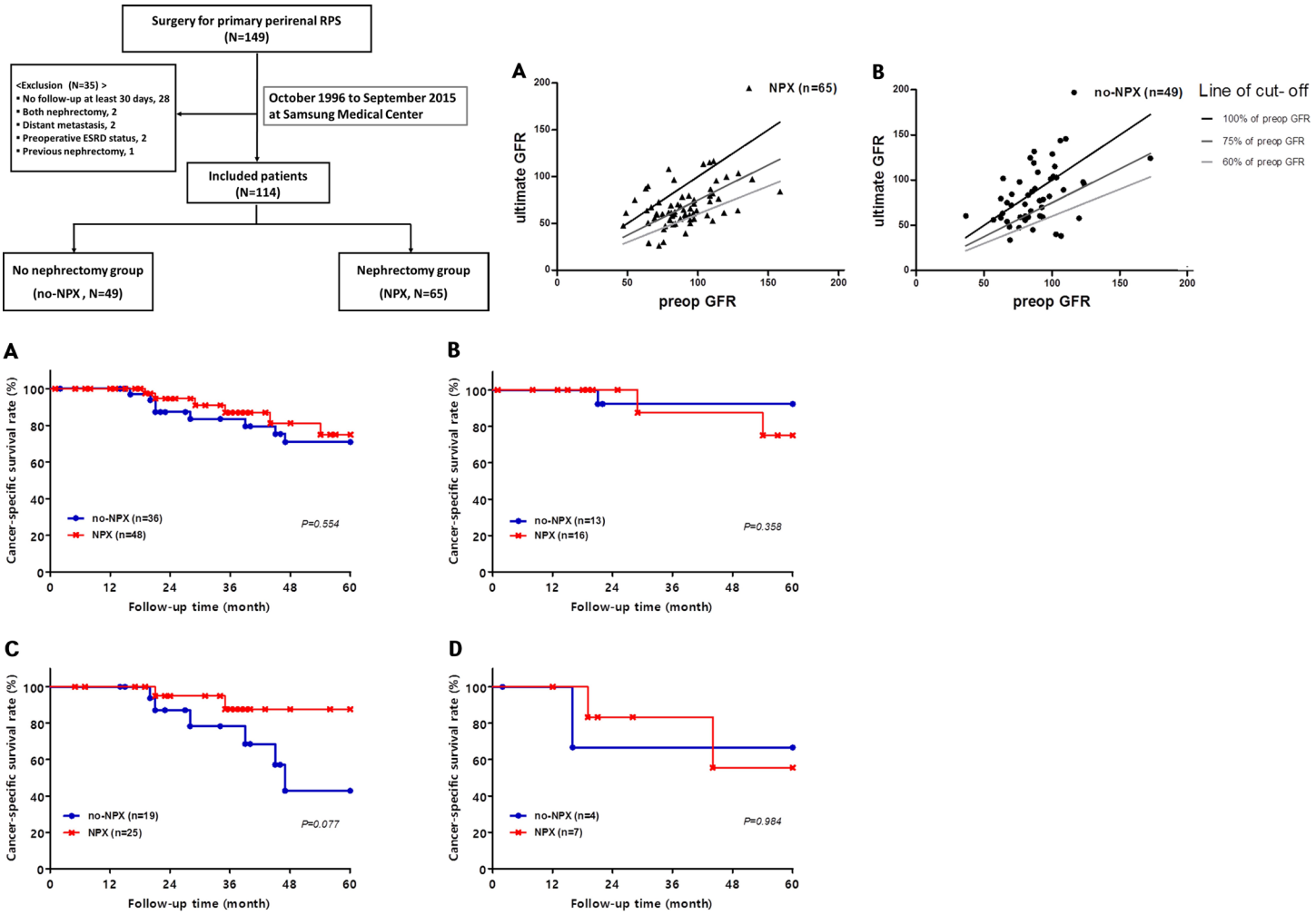
Characteristics	Total	No nephrectomy (N = 49)	Nephrectomy (N = 65)	P value
Age (years), median (IQR)	57 (49-64)	56 (49-63)	57 (48-65)	0.937
Gender, n (%)				
Male	57 (50%)	24 (49%)	33 (51%)	1.000
Female	57 (50%)	25 (51%)	32 (49%)	
BMI (kg/m2)	23.2 (20.8-25.2)	23.9 (20.9-26.1)	22.7 (20.4-24.7)	0.071
ASA score 1:2:3, n (%)	36:73:5 (32:64:4%)	16:30:3 (33:61:6%)	20:43:2 (31:66:3%)	0.751
Tumor size (cm), median (IQR)	18 (12-31)	12 (9-19)	26 (16-36)	<0.001
FNCLCC Grade, n (%)				
1	30 (27%)	13 (27%)	17 (26%)	
2	55 (48%)	26 (49%)	31 (48%)	
3	29 (25%)	12 (24%)	17 (26%)	
Histology, n (%)				
Liposarcoma	87 (77%)	28 (57%)	59 (89%)	
Leiomyosarcoma	15 (13%)	9 (19%)	6 (9%)	
UPS	5 (4%)	5 (10%)	0 (2%)	
Fibrosarcoma	2 (2%)	2 (4%)	0	
MPNST	5 (4%)	5 (10%)	0	
Macroscopic complete resection, n (%)				
Yes	84 (74%)	36 (74%)	48 (74%)	
No	30 (26%)	13 (26%)	18 (26%)	
Contiguous organ resection other than kidney, n (%)				
No	69 (61%)	38 (78%)	31 (47%)	
Yes	45 (39%)	11 (22%)	35 (53%)	
Radiation therapy,				
No	45 (40%)	26 (53%)	19 (29%)	
Neoadjuvant	3 (2%)	0 (0%)	3 (5%)	
Adjuvant	57 (50%)	18 (37%)	39 (61%)	
Palliative	8 (8%)	5 (10%)	3 (5%)	

BMI: Body mass index; ASA: American Society of Anesthesiologists; IQR: interquartile range; UPS: Undifferentiated pleomorphic sarcoma; MPNST: Malignant peripheral nerve sheath tumor

Detailed data of resected organ and microscopic pattern (invasion versus adhesion) of perirenal RPS between NPX and No-NPX groups.

Resected organ	Number		P value	Invasion type		Adhesion type		P value
	NPX (N = 65)	no-NPX (N = 49)		NPX	no-NPX	NPX	no-NPX	
Kidney	65 (100%)	0 (0%)	< 0.001	20 (31%)	0 (0%)	36 (55%)	0 (0%)	< 0.001
Ureter	65 (100%)	0 (0%)	< 0.001	3 (5%)	0 (0%)	5 (8%)	0 (0%)	0.033
Colon	24 (37%)	5 (10%)	0.002	4 (6%)	1 (2%)	15 (23%)	0 (0%)	< 0.001
Adrenal gland	12 (19%)	3 (6%)	0.091	2 (3%)	1 (2%)	5 (8%)	0 (0%)	0.132
Small bowel	9 (14%)	3 (6%)	0.228	4 (6%)	0 (0%)	4 (6%)	0 (0%)	0.028
Pancreas	9 (14%)	1 (2%)	0.042	2 (3%)	1 (2%)	7 (11%)	0 (0%)	0.038
Spleen	10 (15%)	0 (0%)	0.005	1 (2%)	0 (0%)	5 (8%)	0 (0%)	0.069
Total	129	12	N/A	36	3	77	0	N/A

BMI: Body mass index; ASA: American Society of Anesthesiologists; IQR: interquartile range; UPS: Undifferentiated pleomorphic sarcoma; MPNST: Malignant peripheral nerve sheath tumor



Poster 241 #2773490

PREDICTORS OF 30-DAY REOPERATION RATE IN PATIENTS TREATED WITH SURGICAL RESECTION OF SOFT TISSUE SARCOMA: ANALYSIS OF 866 PATIENTS FROM THE ACS-NSQIP DATABASE

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Objective: The rate of reoperation is often used as a surrogate for quality of care. The aim of our study was to identify factors affecting the 30-day reoperation rates in patients undergoing surgical resection of a soft tissue sarcoma of the extremity or trunk from a national cohort database.

Methods: We used the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database to identify patients who underwent surgical resection of a STS from 2005 to 2013. Primary malignant soft tissue neoplasms were identified. Patients treated with wide excision and amputation were identified using the current procedural terminology (CPT) codes. A total of 866 patients met the inclusion criteria; 539 (62%) had lower extremity tumors, 210 (24%) in the upper extremity, and 117 (14%) had pelvic lesions. Seven hundred and seventy-three patients (89%) underwent surgical excision; 93 (10 %) patients were managed with an amputation. Uni- and multivariable logistic regression models were used to explore the association between reoperation rates and modifiable and non-modifiable patient factors as well as surgical factors. Statistical analysis was carried out using Stata 14 (StataCorp. 2015).

Results: Among the modifiable patient factors, including body mas index (BMI), diabetes mellitus, dyspnea, smoking, hypertension and bleeding disorders, hypertension was identified as independently predictive of 30-day reoperation (OR=1.89, p=0.02).

Models based on non-modifiable factors such as age, sex, pre-operative radiotherapy, surgical site and surgery type identified age (OR=1.02, p=0.016) and wound site (OR=1.62, p=0.3) as statistically significant predictors of reoperation. Surgical factors were also modeled using length of operation, wound and ASA classification and presence of deep wound infection. Wound classification (OR=1.57, p=0.007), higher ASA class (OR=1.54, p=0.04) and deep wound infection (OR=7.42, p<0.001) were significantly predictive of reoperation. When con-

sidering all modifiable, non-modifiable and surgical factors together, wound classification (OR=1.59, p<0.01), deep wound infection (OR=6.8, p<0.001) and wound site (OR=1.58, p=0.04) were highly predictive of a patient requiring a second operation within 30-days of the index procedure.

Conclusion: A large national cohort demonstrates that age, hypertension, surgical site, wound and ASA class are predictive of 30-day reoperation among patients who undergo resection of an extremity or pelvic soft tissue malignancy.

Poster 242 #2777744

DOES THE MODIFIED GLASGOW PROGNOSTIC SCORE AID IN THE MANAGEMENT OF PATIENTS UNDERGOING SURGERY FOR A SOFT TISSUE SARCOMA?

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Objective: Background: The modified Glasgow Prognostic Score (mGPS) is a validated prognostic indicator in various carcinomas as demonstrated by several meta-analyses. The mGPS includes pre-operative CRP and albumin values and calculates a score from 0 to 2 that correlates with overall outcome. Scores of 2 are associated with poorer outcomes. To date this correlation has not been proven in the sarcoma patient group. Our aim was to assess if the mGPS is reliable as a prognostic indicator for patients with a soft tissue sarcoma (STS).

Methods: All patients with a STS diagnosis presenting during years 2010-2014 were included. We identified patients using our prospectively collected MSK oncology database. We performed a retrospective case note review examining demographics, preoperative blood results and outcomes (no recurrence, local recurrence, metastatic disease and death).

Results: There were 94 patients who met the inclusion criteria. Of these 56% were female and 53% were aged over 50 years. 91% of tumours were high grade (Trojani 2/3) and 73% were >5cm. 45 patients had an mGPS score of 0, 16 had a mGPS of 1 and 33 had an mGPS of 2. On univariate analysis, an mGPS of 0 or 2 was statically significant with regards to the prognosis and overall outcome, p=0.012 and p=0.005 respectively (table 2). In addition, on univariate analysis, we also found a statistically significant association between CRP, albumin, tumour size and neutrophil count to the development of metastasis and death.

Modified Glasgow Prognostic Score	
Biochemical Measurements	Score
CRP <10 mg/L and Albumin >35 g/L	0
CRP < 10mg/L and Albumin <35 g/L	0
CRP >10mg/L	1
CRP >10 mg/L and Albumin <35 g/L	2

Table 1 - mGPS scoring system

mGPS	Number of patients	No recurrence or metastasis	Metastasis	Local Recurrence	Death	P value
0	45	31	8	1	5	0.012
1	16	11	2	0	3	0.908
2	33	8	10	1	14	0.005

Table 2 – univariate analysis of mGPS and overall outcome

Conclusion: This study has shown that pre-treatment CRP and albumin level (mGPS) are important factors in predicting oncological outcome. The number of cases of local recurrence were too few for any association to be identified. A score of 0 relates to an improved prognosis whilst a score of 2 relates to an increased risk of developing metastatic disease and death. mGPS as a prognostic indicator was not affected by either the tumour size or grade. The group of patients with an mGPS score of 1 was not large enough for any statistically significant conclusions to be drawn. Although we did not find histological tumour grade to directly relate to the oncological outcome, this has been previously demonstrated.

We believe that a pre-operative mGPS should be calculated to help predict oncological outcome and in turn influence management. Further work is being undertaken with a larger cohort.

Poster 243 #2782904

FUSION IMAGING TO EVALUATE THE RADIOGRAPHIC ANATOMICAL RELATIONSHIP BETWEEN PRIMARY TUMORS AND LOCAL RECURRENCES IN RETROPERITONEAL SOFT TISSUE SARCOMA

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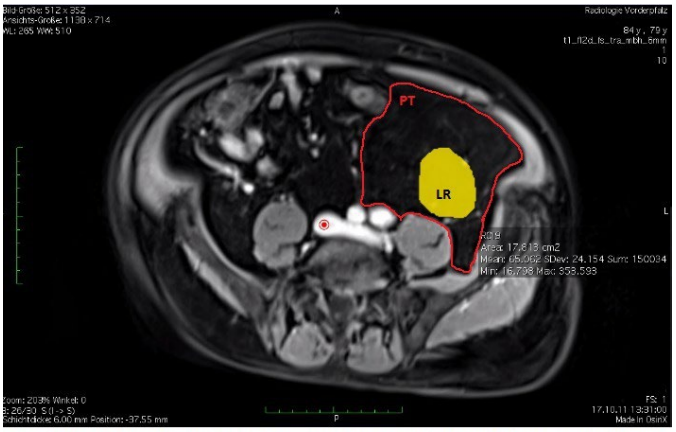
Objective: Local recurrence (LR) of retroperitoneal sarcoma (RPS) is a frequent event and occurs in up to 35% of all patients even after primary treatment in high volume expert centers. This study was designed to evaluate the feasibility of fusion imaging to detect the radiographic anatomical relationship of local recurrences and primary tumors to improve primary treatment of RPS.

Methods: From our local database we ex-

tracted 10 Patients with locally recurrent RPS who were primarily treated at our center and in whom the full scale imaging of imaging had been archived: preoperative and postoperative MRI/CT scans. By using the 3-point-converter of the OsiriX Pro system (v.3.9.4 64-bit) we converted and overlapped the imaging of primary tumors and local recurrences. Primary aim of the study was to evaluate the feasibility of fusion imaging in RPS.

Results: Fusion imaging was technically feasible in 7/10 cases. The most important technical limit of the overlapping process was anatomical distortion caused by the shifted anatomy due to very large primary tumors. In 5/7 cases, the local recurrence was located within the (previous) anatomical border of the primary tumor or immediately close to the resection margin (see image 1). Interpretation of fusion imaging required detailed knowledge of surgical and radiation oncology treatment strategies to distinguish local recurrences at primary tumor or distant intraabdominal sites.



Fusion of imaging of a patient with retroperitoneal Liposarcoma. The local recurrence (LR) within the anatomical borders of the primary tumor (PT).

Conclusion: Fusion imaging is feasible in most patients with local recurrences of RPS and anatomical distortion due to large primary tumor size appears to be the most important technical limit. Learning from the anatomical relationship between primary tumor and local recurrence might advise surgical oncologists where to use an absolutely radical approach and where it might be less important. It is necessary, to confirm these initial data in larger cohorts (e.g. using the TARPPS initiative).

Poster 244 #2783092

PHASE 1 STUDY OF OLARATUMAB PLUS DOXORUBICIN IN JAPANESE PATIENTS WITH ADVANCED SOFT TISSUE SARCOMA

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Objective: Olaratumab (olara) is a human IgG1 monoclonal antibody that selectively binds to platelet-derived growth factor receptor alpha. In a phase 1b/2 randomized study (Study JGDG, NCT01185964), olara plus doxorubicin (DOX) showed a significant improvement in overall survival (OS) over DOX alone in patients with advanced soft tissue sarcoma (STS). Based on exposure-response analysis of the study, trough serum olara level at the end of Cycle 1 (Cmin1) predicted the effect of olara on progression-free survival and OS. This multicenter, non-randomized, open-label phase 1 study (Study JGDK, NCT02377752) assessed the safety and pharmacokinetics (PK) of olara 15 mg/kg in combination with DOX 25 mg/m2 or 75 mg/m2 in Japanese patients with advanced STS. In addition, the safety and PK of a loading dose of olara 20 mg/kg plus DOX 75 mg/m2 was also assessed.

Methods: Patients were enrolled in 3 cohorts of 6 patients each. Cohort 1 (C1) and Cohort 2 (C2) received olara 15 mg/kg (Days 1, 8 of 21-day cycle); Cohort 3 (C3) received a loading dose of 20 mg/kg olara in Cycle 1 only (Days 1, 8), followed by 15 mg/kg in subsequent cycles. The dosages of DOX were 25 mg/m2 (Days 1, 2, 3; the most common dosing regimen in Japan) in C1, and 75 mg/m2 (Day 1) in C2 and C3. DOX was discontinued after completion of 6 cycles. No patients received the cardioprotective agent dexrazoxane. The primary objective was safety and tolerability. Secondary objectives included PK and antitumor activity.

Results: In total, 19 patients were enrolled. There were no dose-limiting toxicities (DLTs) in C1 or C3. In C1, one patient experienced a grade 4 infusion-related reaction during the first olara administration, which was not deemed a DLT. In C2, one patient had a DLT of grade 3 febrile neutropenia and another patient developed grade 3 left ventricular dysfunction after 6 cycles. More patients (5) in C3 (loading dose) achieved Cmin1 above the therapeutic target level identified in the exposure-response analysis of the phase 1b/2 study (>61 µg/mL) than in C1 (2) or C2 (3). Partial response was confirmed in 4 patients

(21.1%; C2: 2; C3: 2). Nine patients (47.4%; C1: 2; C2: 4; C3: 3) completed at least 6 cycles.

Conclusion: As anticipated, a loading dose of olara of 20 mg/kg achieved Cmin1 above the hypothesized therapeutic target level in most patients. The results showed an acceptable safety profile of the regimen (olara loading dose of 20 mg/kg and DOX 75 mg/m2) used in an ongoing phase 3 study in Japanese patients.

Poster 245 #2783491

GENOMIC CHARACTERIZATION OF UTERINE LEIOMYOSARCOMA PATIENTS TO DEFINE EXPLORATORY BIOMARKERS IN THE PHASE III RANDOMIZED TRIAL OF TRABECTEDIN VERSUS DACARBAZINE

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Objective: Understanding disease biology of soft tissue sarcomas (STS) is key to developing patient-specific treatments and improving outcomes in metastastic disease with median overall survival of approximately 1 year. A recent multicenter Phase 3 trial compared the activity of trabectedin to dacarbazine in the treatment of advanced liposaromas and leimoyosarcomas (Demetri et al. 2016, JCO); archival tumor samples were collected from the majority of 518 study participants. Analysis of these samples, in the context of associated clinical data, may identify candidate prognostic and predictive biomarkers to inform therapeutic decisions. In this pilot study, we evaluated 10 archival FFPE samples from uterine leiomyosarcoma (uLMS) patients to assess the feasibility of whole exome sequencing (WES) and RNA-seq platforms in characterizing genomic aberrations. Review of the submitted tumor samples suggests that 329 LMS and 127 LPS samples are available for analysis, along with peripheral blood cells from a subset of 346 patients.

Methods: DNA and RNA were extracted from FFPE tissues using Qiagen AllPrep kit. DNA sequencing was performed using Agilent WES (Exome Seq 51mb Kit) at 100X coverage. RNA sequencing was performed using TruSeq RNA Access method (Illumina). WES data was curated in COSMIC database to assess mutations in cancer-related genes. Differential gene expression was assessed using voom-limma method.

Results: In the pilot study, 60% of the RNA samples failed initial QC and RNA–seq QC metrics. Sequencing data confirmed the limitation of using RNA sequencing to evaluate these samples. In contrast, the DNA samples passed all the quality check assessments. Mutations were detected in genes previously implicated in STS, such as TP53, ATRX, RB1, MED12, PCLO, DNAH5, FSIP2, ABCA13 and ANKRD26.

Conclusion: Our pilot analyses suggest that WES analysis will be suitable for profiling the tumor samples collected from this trial and will allow for the correlation of genomic alterations with clinical outcomes. Analyses of archival tumor samples from the majority of study participants are in progress.

Poster 246 #2783910

EXOSOME-DERIVED MIR-25-3P AND MIR-92A-3P STIMULATE LIPOSARCOMA PROGRESSION

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Objective: The goal of this study was both to determine whether circulating miRNAs could serve as novel and specific potential biomarkers for LPS, and understand their functional significance in LPS progression.

Methods: Blood samples of LPS patients (n=24) were collected from OSU James Cancer Medical Center in Columbus. Extracellular vesicles derived from plasma samples were profiled for microRNAs (NanoString). We also assessed: macrophage infiltration, secretion of IL-6 from macrophages, TLR7/8 involvement, NF-kB pathway activation and cancer cell proliferation-migration-invasion, promoted by macrophage-secreted IL-6.

Results: MicroRNA profiling was performed on peripheral blood vesicles (PBVs) and total peripheral blood (PB) from LPS patients and healthy controls. A total of 26 miRNAs were significantly upregulated and 3 miRNAs were significantly down regulated. Validation of the miRNA panel in an independent cohort of LPS patients confirmed this signature. In particular, the expression of miR-25-3p and miR-92a-3p was demonstrated to be upregulated. Receiver-operating characteristic (ROC) curve analysis indicated that these miRNAs may be used as diagnostic biomarker with the ability to discriminate between the healthy cohort and patients with LPS. Furthermore,

in the in-vitro study phase, these miRNAs were found to be secreted in extracellular vesicles (EVs) from LPS cell lines, showing their tumor origin. Moreover, we showed that miR-25-3p and miR-92a-3p impact the surrounding microenvironment, as LPS-derived EVs stimulate the secretion of IL-6 from macrophages in a TLR7/8 dependent fashion. We also showed that IL-6 secretion occurs through the NF-κB pathway and finally we discovered that macrophage-secreted IL-6 promotes tumor proliferation, migration and invasion in a feedback loop.

Conclusion: In conclusion in this study we demonstrated that circulating miRNA-25-3p and miRNA-92a-3p can serve as novel potential biomarkers for LPS. Furthermore we showed that both miR-25-3p and miR-92a-3p have functional significance by promoting the secretion of pro-inflammatory cytokine IL-6 from tumor-associated macrophages (TAM) in a TLR7/8-dependent manner, which in turn leads to LPS progression, via this interaction with the surrounding microenvironment. Our study provides novel and previously unreported insight into LPS progression, identifying the importance of communication between LPS cells and their microenvironment as process critically involved in LPS progression.

Poster 247 #2785212

CLINICAL CHARACTERISTICS OF DESMOPLASTIC SMALL ROUND CELL TUMOR IN CHILDREN TEN YEARS OF AGE AND YOUNGER. AN MD ANDERSON CANCER CENTER (MDACC) SERIES

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Objective: Desmoplastic small round cell tumor (DSRCT) is a rare, aggressive soft tissue sarcoma that presents in adolescents and young adults as peritoneal sarcomatosis. Limited data exist regarding the clinical characteristics and outcomes of younger patients. Our goal was to describe the clinical characteristics of this population and determine potential factors contributing to overall survival.

Methods: We reviewed the records of DSRCT patients 10 years (y) of age and younger treated at MDACC from 1996 to 2017, on an institutional review board-approved study. Descriptive statistics and survival analysis were performed via multivariate analysis. All statistical analyses were performed using SAS 9.3 for Windows.

Results: Twenty-nine patients were identified. Median age at diagnosis was 8.1 years (range (R), 3.7 to 10.9). There was a male predominance 86.2%. Twenty-five patients (86.2%) had a positive EWSR1-WT1 mutation by PCR, one (3.4%) did not have the mutation and three (10.3%) had unknown mutation status. Thirteen patients (44.8%) had metastasis at diagnosis. The most common site of metastasis was liver (84.6%), followed by extraperitoneal lymph nodes (76.9%), lung (46.1%) and bone (23%). Fifteen patients (51.7%) received chemotherapy with vincristine, doxorubicin, cyclophosphamide alternating with etoposide and ifosfamide (VDC/IE) in compressed cycles, of which four patients (26.6%) had a complete response (CR), 10 (66.6%) had a partial response (PR) and one (6.7%) had stable disease (SD). Nineteen patients (65.5%) had complete cytoreduction, 19 patients (65.5%) received hyperthermic intraperitoneal chemotherapy (HIPEC) and 16 patients (55.1%) received whole abdominopelvic radiotherapy (WART). Fourteen patients (48.2%) had treatment failure, of which six (42.8%) had local recurrence, seven (50%) had liver disease upon recurrence, five (17.8%) had lymph node involvement and three (10.7%) had lung disease. Median time to recurrence from diagnosis was 17 months (R, 14-21). Ten patients (34.4%) were still alive with a median follow-up time of 31 months, 15 patients (51.7%) died due to disease progression and 4 patients (13.7%) were lost to follow up. Median OS was 29 months (R, 4-98) and median OS for patients who received HIPEC was 33 months.

Conclusion: Treatment failure remains a challenge in young patients with DSRCT. Improved systemic and local therapies are required to improve the overall survival.

Poster 248 #2785910

TREATMENT OUTCOMES OF EXTRASKELETAL MYXOID CHONDROSARCOMA; A RETROSPECTIVE MULTI-INSTITUTIONAL STUDY OF 35 CASES IN JAPAN

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Objective: Extraskeletal myxoid chondrosarcoma (EMC) is rare soft tissue sarcoma, which has characteristic of an indolent clinical course. Surgery with or without radiation is a mainstay of the treatment. We retrospectively investigated prognostic factors and treatment outcomes of EMC treated at 3 referral centers in Japan.

Methods: Between 1980 and 2015, 35 patients who had surgery and was histologically confirmed as EMC at 3 referral centers were enrolled in this study.

Results: The median age of patients at first visit was 55 years (range, 20-76 years), with a male-to-female ratio of 1.7:1. Tumors were mostly located in extremities (80 %), with the median size of the tumor 7 cm. The 5-year and 10-year disease specific survival rates were 87.3% and 78.3%, respectively. Eight patients (22.9 %) developed local recurrence after surgery, mostly due to inadequate wide resections. The 5-year local recurrence free survival rate was 78.4%. Eight patients had distant metastasis at diagnosis, and eleven developed later. Post-metastatic survival rate was 71% at 5 years and 62.1% at 10 years. The 5-year and 10-year metastasis free survival rates were 44.3% and 38.7%, respectively. In 16 patients (45.7 %), image diagnosis showed trans-fascial growth of the tumor. Large tumor size (more than 10 cm) was a significant prognostic factor of worse metastasis free survival ($p<0.001$). Tumor located in extremities, deep location and trans-fascial growth had tendency to develop distant metastasis, but those were not statistically significant. Nine patients received radiotherapy for local or distant disease, with one case of complete response and 2 cases of partial response. No significant chemotherapeutic responses were noted in patients with unresectable tumors (stable disease; 2 cases and progressive disease; 7 cases).

Conclusion: The tumor size was significantly correlated with metastasis frequency. A prolonged survival can be expected in EMC patients, in spite of a high rate of metastases during follow-up. Adequate wide excision of primary tumor is important for local control. Radiation therapy is useful to a certain extent as adjuvant or palliative setting.

Poster 249 #2786450

TERT PROMOTER MUTATION INFLUENCE THE PROGNOSIS OF SOLITARY FIBROUS TUMORS OF THE EXTREMITIES

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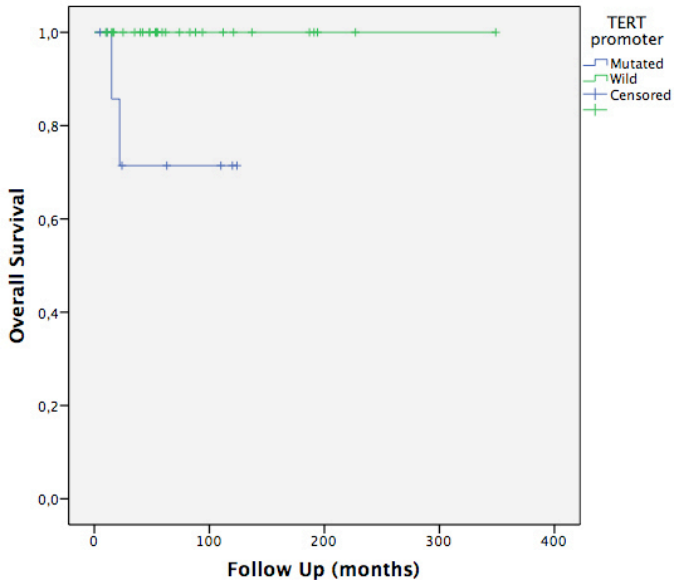
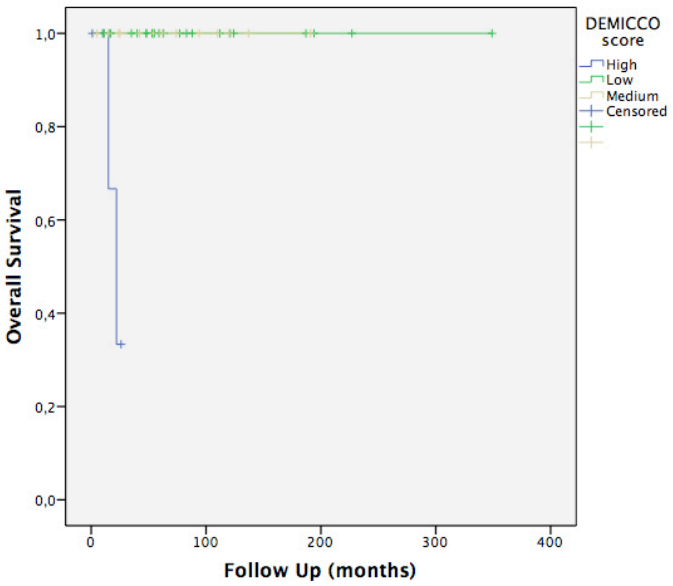
Objective: SFT is a rare mesenchymal tumor of fibroblastic differentiation affecting very rarely soft tissues of the extremities.Original criteria for malignancy are defined as hypercellularity,mitotic activity,pleomorphism and tumor necrosis.Recurrent somatic fusions of NAB2/STAT6 have been identified but its prognostic factor is still unclear. Telomerase reverse transcriptase (TERT) reactivation induced by promoter mutations was proposed as a potential molecular mechanism for aggressive clinical behavior. Aim of this study is to evaluate molecular prognostic factors in SFT of the extremities

Methods: Fourty-one primary SFT of the extremities were reviewed.Tumor size and depth were recorded.Risk stratification was assessed by Demicco's score (patient age, tumor size and mitotic rate).Tumors were scored for mitotic figures,cellularity,nuclear pleomorphism and presence of necrosis.Immunohistochemistry was performed and sections immunostained with CD34,STAT 6 and p53.A total of 24 NAB2-STAT6 fusion types were analyzed.The genetic status of C228T and C250T polymorphisms at the TERT promoter region was investigated from the 35 cases

Results: Metastasis-free survival was 89% at 10 years. Sarcoma specific survival was 94% at 10 years.None of the patients developed LR.Thirty seven SFT were highly cellular with foci of necrosis in 9 cases and high pleomorphism in 16.Mitotic figures ranged from 0 to 18;7 cases had a mitotic activity ≥4.STAT6 expression was present in all 41 cases,CD34 expression in all but one case.Nuclear expression p53 was ≥ 2+ in 13, 1+ in 14 and complete absence in the remaining 14.In 27 cases we detected one of the 24 NAB2-STAT6 fusion variants analyzed.TERT mutation (C228T) was signifanctly associated to histological aggressiveness criteria and Demicco score.Hypercellularity and p53 immunoreactivity did not influence OS.Both patients who died of the disease presented mutation of TERT promoter.A higher metastatic rate was observed in SFT with higher than 4 mitoses,necrosis and with TERT promoter mutation. No correlation between the NAB2-STAT6 fusion type and malignancy was found.



Correlation between TERT promoter mutation and patients' overall survival



Correlation between Demicco score and patients' overall survival

Conclusion: Overall, patients with surgically resected SFT have a relatively good prognosis with OS of 94% at 10 years. The strongest predictors of time to DM and OS were the number of mitosis,the presence of necrosis and the mutation of TERT promoter. We did not found any prognostic association between the different fusion genes NAB2-STAT 6 and p53 expression and patients' prognosis.

Poster 250 #2790185

EFFICACY OF SECOND-LINE TREATMENT BETWEEN PAZOPANIB AND GEMCITABINE/ DOCETAXEL IN PATIENTS WITH METASTATIC SOFT TISSUE SARCOMA

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Objective: We retrospectively reviewed outcomes of second-line of treatment with pazopanib, an oral multi-tyrosine kinase inhibitor, or gemcitabine/docetaxel, in patients with advanced soft tissue sarcoma(STS).

Methods: Between 1995 and 2015, 91 patients with advanced STS treated with pazopanib or gemcitabine/ docetaxel after one cytotoxic regimen.

Results: Among the 91 patients who previously treated at least one cytotoxic chemotherapy regimen, 46 patients received with pazopanib and 45 patients received with gemcitabine/docetaxel. In this study population. Common subtypes included leiomyosarcoma (n=22), angiosarcoma (n=11), MFH/UPS((n=14), synovial sarcoma (n=9), and liposarcoma (n=9). The median progression free survival(PFS) and overall survival(OS) were 4.5 months (95% CI 3.413-5.587) and 12.6 months (95% CI 7.225-17.45) in pazopanib group, compared with 3.0 months(95% CI 0.807-5.193, p=0.439) and 14.2 months(95% CI 4.228-24.172, p=0.362) in gemcitabine/docetaxel. PFS was longer in the patients with leiomyosarcoma, synovial sarcoma, ASPS(alveolar soft part sarcoma), MPNST(malignant peripheral nerve sheath tumor) and MFH/UPS (malignant fibrous histiocytoma/high-grade undifferentiated pleomorphic sarcoma) (7.7, 3.1,12.8, 5.6, and 5.8 months) in pazopanib treatment and angiosarcoma (3.0 months) in gemcitabine/docetaxel treatment. The overall response rate(ORR) was 6.5% in pazopanib, 26.7% in gemcitabine/ docetaxel. Difference in ORR between gemcitabine/ docetaxel and paclitaxel were significantly pronounced in subgroups which had over 50-year old patients (31.6% vs 2.9%, p=0.006), FNCLCC (French Rederation Nationale des Centres de Lutte Contre le Cancer) grade 1,2 (40.9% vs 0%, p=0.001) and SD(stable disease), PD(progression disease) of best response in previous treatment (23.3% vs 3.0%, p=0.022). Based on these results, the histologic subtype of STS was divided two groups: pazopanib-(synovial sarcoma) or gemcitabine/docetaxel-(leiomyosarcoma, MFH/UPS, angiosarcoma) favorable group.

Conclusion: Pazopanib and gemcitabine-docetaxel are well tolerated in patients with advanced soft tissue sarcoma and demonstrates the different efficacy according to subtypes.

Poster 251 #2793125

TRABECTEDIN INDUCED MONOCYTES REDUCTION: RESULTS FROM THE ANALYSIS OF A LARGE SERIES

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Objective: The antitumor activity of Trabectedin (T) appears to be related not only to a direct effects on cancer cells, but also on the tumor microenvironment. In fact, T has potent immunomodulatory effects, being selectively cytotoxic against monocytes and tumor-associated macrophages. In addition, T inhibits the production of proinflammatory and angiogenic mediators, inducing changes in the tumor microenvironment which ultimately contribute to its antitumor activity. The aim of the present study was to evaluate the modification in the number of circulating monocytes (M) during T administration in a large series of soft tissue sarcoma patients.

Methods: This retrospective analysis was conducted in three centers, extrapolating data from clinical charts or databases. Complete blood count was available for each patient before and after T administration for the first two

T courses. Patients were treated in cancer centers with T at the approved dose of 1.5 mg/m2, given as a 24-hour infusion every 3 weeks. All the patients included had metastatic or locally advanced inoperable soft tissue sarcomas, and had received at least one previous line of anthracycline-based treatments.

Results: 114 (59 female and 55 male, median age 54 ys) patients were included in this analysis. The most frequent hystotypes were: leiomyosarcoma (25 pts); dedifferentiated/well differentiated liposarcoma (21 pts) and mixoid liposarcoma (17 pts). Median reduction in the number of circulating M was 35% (95%CI: 22.5%-49.1%, P=0.03) and 41% (95%CI: 30.8%-63.7%; P=0.002) at day 7 and 14 respectively. The reduction was not statistically significant between day 0 and day 21. The modifications in M number were similar in the second course of T. 59 patients showed a reduction of at least 40% compared to M basal levels. The reduction of WBC and neutrophils was less pronounced, even though still statistically significant. Of interest, we also analysed the number of circulating M in a control group of 21 ovarian cancer patients treated with T as monotherapy, and we did not identify a statistically significant reduction in M number. This observation supports the hypothesis that T may play a role in the modulation of tumour microenvironment specifically in sarcoma patients.

Conclusion: Our data confirm the previous observation that T may induce a significant and reproducible reduction of M along the first two T courses. We are currently analysing whether there is a correlation between M reduction and clinical outcome.

Poster 252 #2794392

THE IMMUNOLOGIC MICROENVIROMENT OF UTERINE ADENOSARCOMAS

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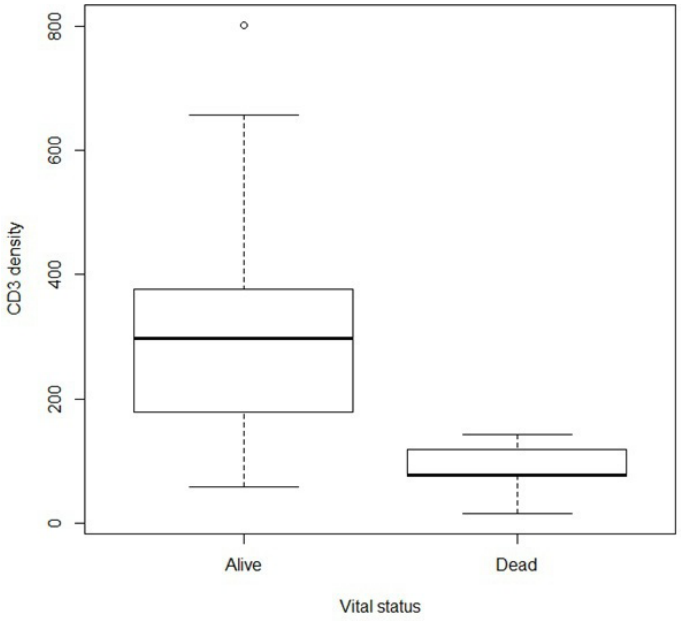
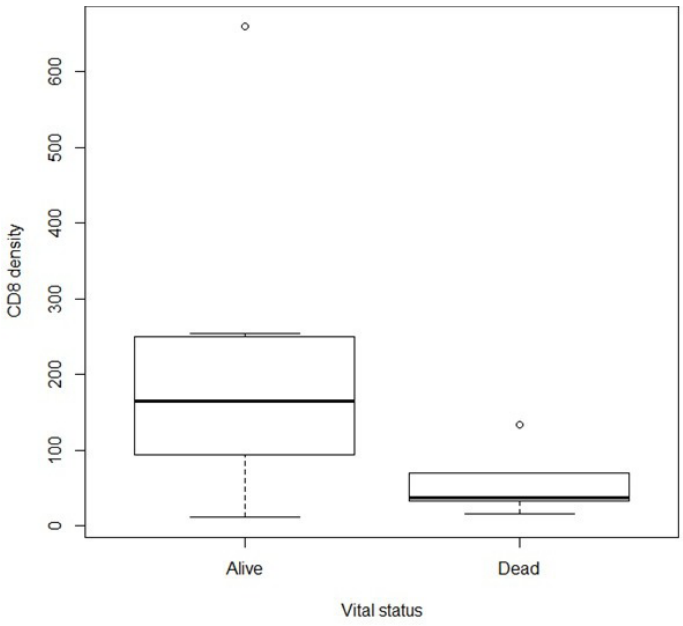
Objective: Uterine adenosarcoma is a rare with an age-adjusted incidence of 0.2 per 100,000 in the US population. Standard treatment involves surgical resection with hysterectomy and BSO, resulting in a 50-70% 5-yr overall survival (OS). There is no standard adjuvant therapy with radiation or surgery. It is important to understand the immunologic microenvironment of uterine adenosarcomas, to assess potential response to immunotherapy. The objective of this study was to examine the immune infiltrate and PD-1/PD-L1 expression in uterine adenosarcoma, and correlate this with OS status, disease-free survival status and clinical prognostic factors.

Methods: The institutional tumor registry identified 165 patients (pts) with uterine adenosarcoma seen in consultation between 1982 and 2014. Fifteen cases had tumor paraffin-embedded blocks available. Immunohistochemistry study for CD3, CD8, FOXP3, CD163, PD-1 and PD-L1 (clone 22C3) was performed and image analysis was used to assess the density (cells/mm2) except with PD-L1 where percentage of membranous staining on tumor cells was noted. Clinical and other prognostic pathological parameters were collected. The exact Wilcoxon rank sum test was used to compare the continuous variables between patient characteristics subgroups. The correlation between two continuous factors was measured by Spearman correlation.

Results: Of the 15 pts with available material, the median age of diagnosis was 48 (26-61) years. 14/15 cases were FIGO stage I, 10/15 had sarcomatous overgrowth and 9/15 had myometrial invasion. None had lymphovascular invasion. 4/15 tumors were negative for ER and PR. Immune infiltrate analysis median (range) density in cells/mm2 varied broadly: CD3 178 (15-802); CD8 117 (11-661); FoxP3 4.8 (0.2-82); CD163 791 (264-1861); and PD1 5 (1-65). 3 cases had rare (1%) PD-L1 tumoral membranous labeling. At last follow-up, 5 pts were dead, 6 had disease, and 5 had local recurrence. Pts who were alive or with no local recurrence had significant higher CD3 and CD8 median densities in tumors than those who were dead or with local recurrence (p=0.040; p=0.040). Pts with tumors negative for ER/ PR had significant higher CD163 median densities than tumors that were positive (p=0.040; p=0.040).





Conclusion: This is the first report characterizing the presence of immune infiltrate and PD-1/PD-L1 expression in uterine adenosarcomas. CD3+ CD8+ T-cells density may be prognostic and suggest these tumors might be amendable to immunotherapy. Further study is required.

Poster 253 #2796695

CHARACTERISTIC COPY NUMBER ALTERATIONS IN CIC-DUX4 GENE-FUSION AND EWING'S SARCOMAS USING TARGETED NEXT GENERATION SEQUENCING

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Objective: CIC-DUX4 gene-fusion sarcoma, once considered a variant of Ewing's sarcoma, is emerging as an independent molecular subset of small blue round cell tumors (SBRCT). We characterized CIC-DUX4 patients treated at the Dana-Farber Cancer Institute and compared tumor samples with Ewing's sarcoma using targeted next-generation sequencing (NGS) to identify mutations or copy number alteration which may be unique to this subset of tumors.

Methods: We queried the Dana-Farber Cancer Institute Oncology Data Retrieval Systems (OncDRS) to identify patients (pts) with CIC-DUX4 or Ewing's sarcoma who underwent targeted massively parallel sequencing of exonic DNA sequences of 300 cancer genes (OncoPanel). Gene rearrangements were confirmed by RT-PCR amplification or fluorescence in-situ hybridization.

Results: We identified 5 pts with CIC-DUX4 sarcoma (4 with NGS data) and 18 pts with Ewing's sarcoma (83.3% with ESWR1-FLI1 and 16.7% with ESWR1-ERG gene-rearrangements). Median age of CIC-DUX4 pts was 39 years and mean primary tumor size was 11.5 cm. Three pts with CIC-DUX4 sarcoma presented with localized disease and underwent surgical resection; two pts received standard-dose adjuvant Ewing's sarcoma chemotherapy regimen (cyclophosphamide, adriamycin, vincristine with etoposide and ifosfamide), however, both experienced disease relapse during treatment. One pt died of disease two months following disease recurrence and one pt is alive with disease 26 months following relapse. The third pt with localized disease received post-operative radiation and remains disease free at three years. Two pts presented with metastatic disease and died within eight months of diagnosis. Mutation analysis of CIC-DUX4 tumors identified 18 mutations across four samples. No driving or recurrent mutations were observed. Copy number analysis demonstrated recurrent loss of a portion of chromosome 1p in 3/4 (75%) of CIC-DUX4 samples, centered on the tumor suppressor ARID1A (1p36) across all samples. One CIC-DUX4 sample did not show any loss or deletions in chromosome 1p (pt #3, localized disease, no evidence of disease). In Ewing's sarcoma, none of the tumor samples (0/18) had any alterations in chromosome 1. Alternatively, 33% of Ewing's sarcoma samples showed low copy number gains of proto-oncogenes cyclin D1 (CCND1), cyclin dependent kinase 4 (CDK4) and MYC.

Conclusion: CIC-DUX4 sarcomas are highly aggressive tumors with rapid disease progression. Loss of tumor suppressor ARID1A expression correlates with poorer prognosis in other malignancies (e.g., gastric and breast cancer). ARID1A gene copy number loss, not observed in any of the Ewing's sarcoma tumor samples, may contribute to the aggressive nature and poor prognosis of this subset of SBRCT.

Table 1. Clinical and Tumor Characteristics, Patients with CIC-DUX4 sarcoma

Patients	#1	#2	#3	#4	#5
Age/Gender	39/Male	25/Female	27/Male	50/Male	69/Female
Primary Site	Kidney	Perineum	Abdominal Wall	Parascapular	Thigh
Size (cm)	13.5	4.5	25	7.2	7.3
Localized vs. Metastatic (at presentation)	Localized	Localized	Localized	Metastatic	Metastatic
Surgery	Yes	Yes	Yes	No	No
Adjuvant RT	No	Yes	Yes	No	No
Adjuvant CT	CAV/IE	CAV/IE	No	NA	NA
Relapse (months)	Yes (5)	Yes (9)	No	NA	NA
Metastatic Sites	Liver; Peritoneum	Lungs; Dura	No	Chest Wall	Lungs
CD99 Staining	Multifocal	Negative	Multifocal	Not Reported	Focal
WT-1 Staining	Positive	Positive^	Positive	Not Reported	Positive
Chromosome 1p Portion Loss	Yes	Yes	No	Yes	Not Reported
Treatment for Metastatic Disease	No	Reg (4m); Paz (3.5m); Trab (1.5m); Gem/Doc (10m+)	No	No	Dox (2m)
Outcome (m)	DOD (9)	AWD (36)	NED (36)	DOD (5)	DOD (8)

RT indicates Radiotherapy; CT, Chemotherapy; CAV/IE, Cyclophosphamide, Adriamycin, Vincristine/ Ifosfamide, Etoposide; NA, Not Applicable; Reg, Regorafenib; Paz, Pazopanib; Tra, Trabectedin; Gem/Doc, Gemcitabine/Docetaxel; Dox, Doxorubicin; DOD, Died of Disease; AWD, Alive with Disease; NED, No Evidence of Disease;
^ - Diffuse nuclear pattern

Table 2. DNA variants in CIC-DUX4 sarcoma tumor samples

	Gene	DNA sequence change	Amino acid change
Patient #1	PIK3CA	c.1357G>A	p.E453K
	ARID2	c.500C>A	p.S167Y
	EPHA5	c.2225T>G	p.V742G
Patient #2	AR	c.528C>A	p.S176R
	CSF1R	c.1420G>A	p.V474
	CUX1	c.2341C>A	p.P781T
	ERBB2	c.664G>A	p.G222S
	GATA3	c.527C>T	p.A176V
	REL	c.1133C>T	p.T378I
Patient #3	ARID2	c.1760G>T	p.S587I
	BAP1	c.796A>G	p.T266A
	CIITA	c.1643G>A	p.R548Q
	CREBBP	c.250C>A	p.P84T
	ERCC6	c.2875G>T	p.V959L
	JAK3	c.3275G>A	p.G1092D
	NTRK2	c.1717-4C>A	
Patient #4	ERCC4	c.736T>A	p.S246T
	MAP3K1	c.2948_2951TGTC>T	p.S984del

Poster 254 #2797054

PAZOPANIB IN ADVANCED DESMOPLASTIC SMALL ROUND CELL TUMOR: A RETROSPECTIVE ANALYSIS OF 29 PATIENTS

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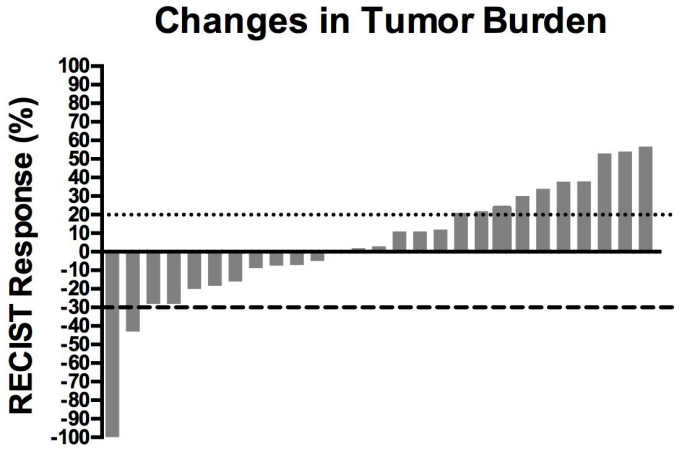
Objective: Desmoplastic small round cell tumor (DSRCT) is an aggressive, often fatal soft tissue sarcoma that lacks an optimal salvage regimen and is, in part, characterized by overexpression of vascular endothelial growth factor-A and its cognate receptor, VEGF receptor-2, which promotes tumor angiogenesis. Though pazopanib (a multi-targeted receptor tyrosine kinase inhibitor with anti-angiogenic properties) is FDA-approved for the treatment of soft tissue sarcomas (STS), few DSRCT patients were included in the STS studies that led to its FDA-approval and an accurate estimate of DSRCT response has not previously been reported.

Methods: To measure the antineoplastic effect of pazopanib in a group of heavily pre-treated DSRCT patients harboring wide-spread metastatic disease, we conducted a retrospective review of 29 DSRCT patients treated at MD Anderson Cancer Center from January 2012 to December 2016. Demographic and clinical characteristics were summarized and median progression-free survival (PFS) and overall survival (OS) from start of pazopanib treatment were estimated using the Kaplan-Meier method.

Results: The mean age at pazopanib treatment was 27.5 years (range, 5.2-47.8 years). According to RECIST 1.1 (Figure 1), best response for 16 patients was stable disease (55%), one had partial response (3%), one had complete response (3%), and best response for 11 patients was progressive disease (38%). Two patients whose best responses to-date was stable disease are still on pazopanib treatment after 22.3 and 6.7 months of follow-up. Estimated median PFS was 5.63 months (95% CI 3.23-7.47). Median OS was 15.7 (95% CI 10.3-32.4) months, with a median follow-up of 16.8 months (range, 3.8-30.1 months) for the 11 patients censored for OS. Doses of pazopanib between 400-800mg were included with tolerance profile; 23 patients continued pazopanib until progression or death, 4 discontinued because of side effects or other reasons, and 2 are still on pazopanib.



Conclusion: In the largest study conducted to date assessing pazopanib in DSRCT, 62% of patients achieved clinical benefit (e.g. CR, PR, or SD), which compares favorably to the overall clinical benefit rate reported in prior studies that enrolled patients diagnosed with diverse STS subtypes. Prospective multi-center validation is warranted and follow-up studies that seek to develop tissue-based biomarkers predictive of pazopanib response could eventually help enrich for good-responders.

Poster 255 #2797219

EPIDEMIOLOGY, INCIDENCE, AND SURVIVAL OF ALVEOLAR SOFT-PART SARCOMA: SEER DATABASE ANALYSIS

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Objective: Alveolar soft-part sarcoma (ASPS) is a rare and distinct histological soft tissue sarcoma subtype. The rarity and lack of primary literature studies available makes study of this disease very difficult. One approach is to use population based databases to study large numbers of these tumors. The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program of United States population-based data from 1973 to 2014 offers a unique opportunity to perform detailed analyses of incidence and survival of rare neoplasms. The purpose of this study was 1) to evaluate patient demographics, clinical behavior, incidence, and survival for alveolar soft-part sarcoma and 2) to determine if there were any variables that affected the rate of survival.

Methods: The SEER database was used to search for patients diagnosed with alveolar soft-part sarcoma between 1973 and 2014. Patient demographics, tumor characteristics, incidence, and survival trends were all analyzed. Differences in the epidemiology, overall survival,

5-year survival rate, and incidence were also analyzed using t-test statistical test, a Chi-squared analysis, and pairwise tests with correction of multiple factors with the Holm-Bonferroni procedure. Significant differences were based on a $p < 0.05$. In addition, univariate regression analysis was used to determine whether any variable had a significant effect on survival in these patients.

Results: There were a total of 267 patients identified in the SEER database. All patient demographic, clinical and tumor data can be found in Table 1. Survival and incidence data can be found in Table 2. The rate of metastasis at diagnosis was seen in 23.6% of patients. Of the variables in the predictive model, only metastasis and year of diagnosis (> 2004) were significant predictors of time until death and negatively affected survival ($p<0.05$).

Variable		Alveolar soft-part sarcoma (N=267)
Clinical Variables		
Median Age (years)		31.25
Gender		
	Males	116 (43.4 %)
	Females	151 (56.6 %)
	M:F	0.77:1
Race		
	Caucasian	157 (58.8 %)
	African American	60 (22.5 %)
	Asian	43 (16.1 %)
	Other	7 (2.6 %)
Neo-adjuvant Therapy		
	Radiation Therapy	127 (47.6 %)
	Non-radiation Therapy	140 (52.4 %)
Tumor Data		
	Average Size (cm)	8.1 cm
Background Tumor Grade		
	Grade I	4 (1.5 %)
	Grade II	6 (2.2 %)
	Grade III	46 (17.2 %)
	N/A	211 (79.1 %)
Metastasis (at presentation)		63 (23.6 %)

Table 1: Patient demographic, clinical, and tumor data.

Overall Survival (Months)	Rate of 5-year survival (%)	Rate of 10-year survival (%)	Incidence (per 100,000)
82.7	41.1 %	21.0 %	0.014

Table 2: Survival Data and Incidence

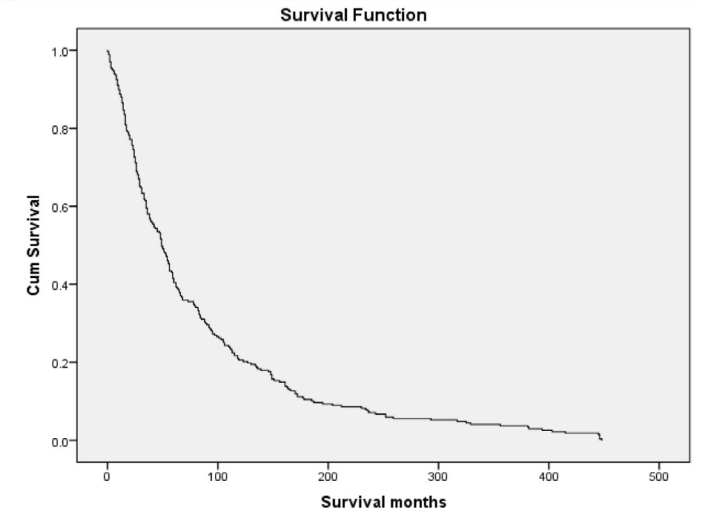

Figure 1: Kaplan-Meyer graph illustrating survival.

base study on alveolar soft-part sarcoma demonstrating that useful information can be gleaned from population database analysis for rare tumors. This study provides information on a very rare disease and helps create a historic perspective and a reference for survival to be compared to as new immunotherapy drugs are created to treat this disease. This type of study represents one method of gaining knowledge about rare tumors that would otherwise be difficult to gain in single or even multi-center studies. Further study will be needed to clarify the exact implications of the findings presented.

Poster 256 #2803416

AN INTERNATIONAL MULTI-INSTITUTIONAL RETROSPECTIVE REVIEW OF PRIMARY CARDIAC SARCOMAS (PCS)

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Objective: PCS is a rare but often fatal disease. The current study aimed to analyze the impact of baseline demographics, local and systemic therapies in a contemporary cohort.

Methods: Clinical records of PCS across 5 institutions in 3 continents were reviewed and collected. Kaplan-Meier method was used to estimate survival. Cox proportional hazard model was used to associate variables to progression free survival (PFS) or overall survival (OS)

Results: A total of 47 pts with PCS were identified over a 10-year period (1996-2016) with a median follow-up time of 12.9 months (mths). The median age at diagnosis was 41 (range 18-79), and 43% (n=20) had metastatic disease on presentation. Tumor equally originated from right- (n=23) and left-heart (n=23). The common histologies were angiosarcoma (n=18, 38%), intimal sarcoma (n=8, 17%), and sarcoma NOS (n=10, 21%). 66% (n=31) had surgical (S) treatment for PCS, and only 4 (13%) pts had R0 resection. The median primary lesion size was 49 mm (20-84 mm). 53% (n=24) pts received multi-modality

treatment (45% S + chemotherapy (C), 4% S + XRT, 4% S + C + XRT[JL1] [TC2]). 70% (n=33) pts received adjuvant or palliative C. The median OS was 17.7 ms (95% CI 12.4-21.8 mths). For all pts, age ≥ 65 was the only significant negative prognostic factor (Table 1). 29 advanced pts received palliative C (52% combination, 48% single agent). The median PFS for first-line C was 3.8 ms (95% CI 1.5-6.9 mths). The best response for first-line C was PR 10 (35%), SD 4 (14%), PD 12 (41%). 60% (6/10) of pts with PR were angiosarcoma (n=5) or intimal sarcoma (n=1) pts treated with anthracycline. For localized PCS, angiosarcoma histology was a significant factor for worse PFS (HR 3.05, p = 0.04), and a trend for worse OS (HR 2.56, p=0.11)(Table 2). No significant improvement in OS was identified in pts presenting throughout the 20 year period of this review (pre- vs post 2012; HR 1.1, p = 0.81).

Table 1:
Prognostic factors for all pts (n = 47)

Variable	HR (95% CI)	P-value
Age ≥ 65	7.43 (2.54-21.72)	0.0002**
Metastatic disease at diagnosis	1.87 (0.90 – 3.88)	0.09
Multi-modality treatment	0.64 (0.32-1.27)	0.20
Angiosarcoma histology	1.58 (0.72-3.47)	0.26

** P<0.05

Table 2:
Prognostic factors in pts with localized disease (n=27)

Variable	HR (95% CI)	P value
Age ≥ 65	10.23 (2.46-42.66)	0.0014**
Intimal sarcoma	0.23 (0.05-1.09)	0.064
Left heart origin	0.33 (0.1-1.07)	0.065
Multi-modality treatment	1.09 (0.43-2.77)	0.86

** P<0.05

Conclusion: The prognosis of PCS remains poor. There has been no significant improvement in OS compared to historically reported cohorts. Further research is required for this rare entity.

Poster 257 #2803624

A COMPLETE RESPONDER TO PAZOPANIB IN HIGH-GRADE SOFT TISSUE SARCOMAS

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Objective: Soft tissue sarcomas (STS) are rare malignant tumor. Recently, the FDA approved pazopanib, an oral multi-target tyrosine kinase inhibitor (TKI) and targeting VEGFR, FGFR, PDGFR and c-kit, to treat patients with advanced STS. However, to our best knowledge so far, there are no reports revealed STS cases indicated complete response (CR) to pazopanib. In this study, we described the clinico-pathological features of extremely rare case that an advanced STS had CR to pazopanib for only one-month treatment. Furthermore, to elucidate factors of high sensitive response to pazopanib, integrative analyses were performed using surgical samples of the case.

Methods: Whole genome sequencing and transcriptome sequencing were carried out using matched tumor and normal sample by HiSeq2500 (Illumina). Phospho-RTK array analysis was performed with the matched samples. Focus formation assay regarding identified gene mutations were performed using 3T3 cells. Confirmation analyses of our findings, especially frequency rate, were verified by cBioPortal with published huge data of clinical sequencing (MSK-IMPACT database: Zehir A et al. Nat Med 2017).

Results: A 70-year-old female was diagnosed with advanced STS and started oral pazobanib 400 mg daily. Her first control scan after one month showed CR with pazopanib for multiple metastases. After few months treatment of pazopanib, she had hepatic adverse events and the treatment of pazopanib was terminated. After cessation of the pazopanib, she died with disease progression. With respect to integrative analyses, three somatic mutations were identified in kinase genes by sequencing as well as three phospho-protein had significant high expression in the tumor was found by phospho-RTK-arrays. In focus formation assays, overexpression of identified kinase

genes demonstrated transformation potentials in 3T3 cells. In analyses of copy number alteration and mRNA expression, these results were consistent with the phosho-protein expressions of phospho-RTK-arrays.

Conclusion: We treated an extremely rare case (super-responder) that an advanced STS had CR to pazopanib for one-month treatment. We also performed integrative analyses using tumor samples and we found several factors that might be associated with high sensitive response to pazopanib.

Poster 258 #2803941

PRIMARY PLEOMORPHIC SARCOMA (PS) AND LEIOMYOSARCOMA (LMS) OF BONE: RETROSPECTIVE AND MOLECULAR ANALYSIS OF AN ORIGINAL SERIES

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Objective: To describe the clinico-pathological features of 23 patients (pts) affected by primary PS and LMS of bone, confirm the diagnosis by molecular analysis, excluding cases of dedifferentiated chondrosarcoma, evaluate the clinical outcome and explore the prognostic impact of these features on disease-free (DFS) and overall survival (OS).

Methods: Primary PS and LMS of bone surgically treated from 2004 to 2015 were retrospectively reviewed. For each patient we retrieved the clinical charts, the available imaging and histopathological slides and we assessed age, sex, stage, histotype, histological-grade as well as surgical and/or medical therapy. IDH1 mutational status was evaluated and immunohistochemical staining was performed for smooth muscle actin and desmin. The histological material of 20 pts was available for molecular analysis, and tumour DNA was extracted from freshly cut FFPE sections by GeneRead™ DNA FFPE (Quiagen). ddPCR (Bio-rad) was used to determine the presence of IDH1 p.R132H and p.R132C mutations.
DFS and OS rates were calculated according to the Kaplan-Meier method. The differentiation (myogenic, MD, versus non myogenic, NMD) was correlated with the outcome using Kaplan-Meier method.

Results: 23 cases with primary PS or LMS of bone were included in the study. Median age was 49 years (range 13-90), male/female 14/9, 18 had localised disease and 5 metastatic disease, 17 received surgery, 14 received adjuvant therapy, 1 received neoadjuvant chemotherapy and 5 received up-front chemotherapy for advanced disease. All cases were histologically and radiologically reviewed: 17 PS and 6 LMS were identified. All cases were high-grade (FNCLCC grading system). 5-year OS of the whole series was 60% (95% CI; 3,1 – NE) and 5-year DFS was 50% (95% CI; 1,6 – 12,2). Pts with advanced disease were 13: 5-year OS in this subgroup was 38% (95% CI; 2,5 – NE). We identified MD in 11 cases. There were no significant differences between the MD and NMD groups in terms of DFS (logrank p-value=0,6788) and OS (logrank p-value=0,7389). DNA for molecular analysis was available for 15 out 20 pts and no IDH-1 mutation was detected (allele frequencies were 0.33% to 1.45 % for p.R132H and 0.30% to 1.07% for p.R132C). We are also currently evaluating the status of the IDH-2 gene.

Conclusion: These primary malignant bone tumours are very rare and carry a poor prognosis after relapse or when radical surgery is not feasible. MD did not predict a worse outcome than NMD in terms of OS and DFS.

Poster 259 #2804233

SOFT TISSUE SARCOMA AND TIME TO TREATMENT: AN ANALYSIS OF THE NATIONAL CANCER DATABASE

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Objective: To determine the current national standard in the United States for time to treatment interval (TTI), defined as the period from diagnosis to first definitive treatment, in soft tissue sarcoma, and to identify the characteristics associated with TTI variability.

Methods: An analysis of the National Cancer Database identified 46,274 patients with soft tissue sarcoma diagnosed from 2004-2013. Patient exclusions included pediatric patients <18 years old (not available from this database), patients that did not receive definitive treatment (n = 4,695) in the form of surgery, systemic therapy or radiotherapy, and outliers with a TTI > 365 days (n =47). Final analysis included 41,529 patients. Kruskall-Wallis tests identified differences between covariates regarding TTI. A negative binomial regression model identified the variables that were independent risk factors for delayed TTI.

Results: The median TTI was 22 days. Approximately 57% of patients were definitively treated in the same center where the diagnosis was made. The most common initiating treatment modality was surgery (68%), followed by radiotherapy (16%) and systemic therapy

(15%). Longer TTI was correlated with the following factors: having a transition in care (Incidence rate ratio [IRR]=1.76; P<0.001), receiving radiotherapy (IRR=1.42; P<0.001) or systemic therapy (IRR=1.24; P<0.001) as index treatment, seeking care at an academic center (IRR=1.22; P<0.001), Medicaid insurer (IRR=1.20; P<0.001), being uninsured (IRR=1.15; P<0.001), Medicare insurer (IRR=1.07; P<0.001), spindle cell sarcoma (IR=1.08; P=0.006), upper extremity tumor site (IRR=1.06; P=0.010), non-white race (IR= 1.06; P=0.003), lower extremity tumor site (IRR=1.05; P=0.002), and female gender (IRR=1.03; P=0.031). Shorter TTI was correlated with the following factors: having surgery (IR=0.68; P<0.001) as index treatment, receiving treatment at a comprehensive cancer center (IR=0.87; P<0.001), tumor size >8 cm (IR=0.91; P<0.001), age >30 years (IR=0.92; P=0.002), private insurer (IR=0.92; P<0.001), liposarcoma (IR=0.94; P=0.028), higher grade (IR=0.94; P<0.001), trunk tumor site (IR=0.96; P=0.004), and median income >$48,000 (IR=0.97; P=0.020).

Conclusion: Delays in TTI in STS are associated with socio-economic, healthcare, and tumor characteristics. Transitions in care between institutions are responsible for the greatest delays in STS TTI. Physicians need to be aware of the causes of delay, as we work to improve national delays in diagnosis and treatment initiation.

Table 1. Time to Treatment Initiation and Patient Demographics

	Number of Patients (%)	Median TTI, days (IQR)	P-Value
Total Number of Patients	41529	22 (0 - 42)	
Age, years			0.001
Median, [range]	60 [18-90]		
18-30	3632 (9)	21 (1, 42)	
31-50	9577 (23)	22 (0, 41)	
51-70	15583 (38)	23 (2, 42)	
71+	12737 (31)	23 (0, 43)	
Sex			0.645
Male	23183 (56)	22 (0, 42)	
Female	18346 (44)	22 (0, 42)	
Race			0.444
White	34935 (84)	22 (0, 42)	
Black	4463 (11)	23 (0, 44)	
Other/Unknown	2131 (5)	22 (0, 43)	
Charlson/Deyo Score			0.611
0	34258 (83)	22 (0, 42)	
1	5780 (14)	23 (0, 43)	
≥ 2	1491 (4)	21 (0, 42)	
Histology			<0.001
Spindle Cell Sarcoma	2888 (7)	26 (7, 48)	
Undifferentiated Pleomorphic Sarcoma (MFH)	10589 (26)	23 (3, 40)	
Liposarcoma	6507 (16)	21 (0, 40)	
Other	21545 (52)	22 (0, 43)	
Facility Type			<0.001
Community Cancer Program	2495 (6)	16 (0, 36)	
Comprehensive Community Cancer Program	11644 (28)	18 (0, 36)	
Academic Center	18132 (44)	28 (10, 47)	
Integrated Network Cancer Program	2210 (5)	21 (0, 39)	
Other/Unknown	7048 (17)	21 (0, 42)	
Insurance			<0.001
Uninsured	1759 (4)	22 (0, 45)	
Private Insurance	19147 (46)	22 (0, 40)	
Medicaid	2737 (7)	24 (2, 48)	
Medicare	16044 (39)	23 (0, 42)	
Other/Unknown	1842 (4)	29 (9, 50)	
Income			0.001
< $38,000	6889 (17)	22 (0, 43)	
$38,000 - $47,999	9460 (23)	23 (0, 43)	
$48,000 - $62,999	10888 (26)	23 (0, 42)	
$63,000+	13542 (33)	22 (0, 40)	
Unknown	750 (2)	21 (0, 42)	
Distance from Facility			<0.001
< 21 miles	24555 (59)	21 (0, 40)	
21-50 miles	7380 (18)	25 (5, 43)	
51-100 miles	4055 (10)	26 (8, 46)	
>100 miles	4302 (10)	28 (11, 48)	
Unknown	1237 (3)	23 (0, 43)	
Transition in Care			<0.001
Yes	18042 (43)	33 (17, 53)	
No	23487 (57)	14 (0, 32)	
Year of Diagnosis			<0.001
2004	3591 (9)	20 (0, 39)	
2005	3760 (9)	20 (0, 40)	
2006	3768 (9)	21 (0, 40)	
2007	3991 (10)	22 (0, 42)	
2008	4078 (10)	22 (0, 42)	
2009	4235 (10)	22 (0, 42)	
2010	4396 (11)	23 (0, 43)	
2011	4360 (11)	24 (1, 42)	
2012	4637 (11)	25 (3, 44)	
2013	4713 (11)	26 (5, 44)	
Primary Tumor Site			<0.001
Head/Neck	3467 (8)	23 (0, 46)	
Upper Extremity/Shoulder	6038 (15)	25 (0, 45)	
Lower Extremity/Hip	16540 (40)	24 (8, 42)	
Trunk	13383 (32)	21 (0, 42)	
Other	2101 (5)	14 (0, 36)	
Tumor Size			<0.001
≤ 5.0 cm	11741 (28)	22 (0, 44)	
> 5.0 cm	29788 (72)	22 (3, 41)	

Table 1. Continued

Grade			<0.001
1, Well Differentiated	3525 (9)	20 (0, 43)	
2, Moderately Differentiated	4701 (11)	24 (0, 44)	
3, Poorly Differentiated	12574 (30)	22 (3, 41)	
4, Undifferentiated	9468 (23)	23 (7, 42)	
Unknown	11261 (27)	22 (0, 43)	
Clinical Staging			0.033
Stage I	1859 (5)	22 (0, 43)	
Stage II	1373 (3)	23 (0, 42)	
Stage III	8082 (20)	25 (12, 42)	
Stage IV	4601 (11)	24 (9, 42)	
Unknown	25614 (62)	22 (0, 43)	
First-Line Treatment Modality			<0.001
Surgery	28307 (68)	16 (0, 39)	
Radiation	6556 (16)	32 (21, 48)	
Systemic	6068 (15)	28 (17, 44)	
Other	55 (0.1)	24 (9, 37)	
Multi-modal	543 (1)	31 (17, 48)	

Table 2. Multivariable Model

	Incidence Rate Ratio on TTI (95% CI)	P-Value
Age (>30 years)	0.92 (0.87, 0.97)	0.002
Sex (Female)	1.03 (1.00, 1.06)	0.031
Minority Race	1.06 (1.02, 1.11)	0.003
Deyo Score ≥ 1	1.03 (0.99, 1.07)	0.141
Histology		
Spindle Cell vs all other diagnoses	1.08 (1.02, 1.14)	0.006
UPS (MFH) vs all other diagnoses	0.98 (0.93, 1.03)	0.505
Liposarcoma vs all other diagnoses	0.94 (0.89, 0.99)	0.028
Facility Type		
Academic Center vs any other institution	1.22 (1.19, 1.26)	<0.001
Comprehensive Cancer Center vs others	0.87 (0.84, 0.90)	<0.001
Insurance		
Uninsured vs Private Insurance	1.15 (1.07, 1.23)	<0.001
Private Insurance vs all others	0.92 (0.90, 0.95)	<0.001
Medicaid vs Private Insurance	1.20 (1.13, 1.28)	<0.001
Medicare vs Private Insurance	1.07 (1.03, 1.10)	<0.001
Income > $48,000	0.97 (0.94, 0.99)	0.020
Distance to facility ≥21 miles	0.97 (0.94, 1.01)	0.101
Transition in Care	1.76 (1.71, 1.81)	<0.001
Primary Tumor Site		
Head	1.02 (0.97, 1.07)	0.502
Upper Extremity	1.06 (1.01, 1.10)	0.010
Lower Extremity	1.05 (1.02, 1.08)	0.002
Trunk	0.96 (0.93, 0.99)	0.004
Tumor Size		
> 8.0 cm	0.91 (0.88, 0.94)	<0.001
Grade		
Overall grade	0.99 (0.98, 1.00)	0.024
Grade 3 or 4	0.94 (0.91, 0.97)	<0.001
Clinical Staging		
Stage overall	1.00 (1.00, 1.01)	0.429
Stage II or III	1.00 (0.93, 1.07)	0.905
First-Line Treatment Modality		
Surgery vs other tx	0.68 (0.66, 0.70)	<0.001
Radiation vs other tx	1.42 (1.36, 1.48)	<0.001
Systemic vs other tx	1.24 (1.19, 1.29)	<0.001

****Incidence Rate Ratio means for every 1 point increase in the independent variable, the rate of time to treatment initiated (in days) would change by a factor of that value while holding all of the other variables in the model constant.**

Poster 260 #2804237

LONGER TIME TO TREATMENT IN SOFT TISSUE SARCOMA IS NOT ASSOCIATED WITH WORSE SURVIVAL: AN ANALYSIS OF THE NATIONAL CANCER DATABASE

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Objective: To determine if time to treatment interval (TTI), defined as the period from diagnosis to first definitive treatment, influences the survival of patients diagnosed with soft tissue sarcoma (STS).

Methods: A retrospective analysis of the National Cancer Database identified 46,274 patients with STS diagnosed between 2004-2013. Patient exclusions included pediatric patients <18 years old (not available from this database), patients that did not receive definitive treatment (n = 4,695) in the form of surgery, systemic therapy or radiotherapy, patients without follow-up data (n = 4,837), and outliers with a TTI > 365 days (n = 47). Final analysis included 36,692 patients who were separated into 3 groups based on TTI. Groups included TTI < 31 days (Group 1), 31-60 days (group 2), and >60 days (group 3). $\chi 2$ -tests identified differences among covariates. Survival was estimated with Kaplan-Meier models and compared with log-rank tests. A Cox proportional hazards model adjusted for all covariates.

Results: Median TTI was 22 days. Approximately 62% of patients were in Group 1, 25% of patients were in Group 2, and 13% of patients were in Group 3. At five years, survival for Groups 1, 2 and 3 was 52%, 54%, and 54%, respectively. At 10 years, survival for Groups 1, 2 and 3 was 38%, 40% and 38 %, respectively. Longer TTI did not worsen survival. Group 2 (HR=0.82; P<0.001) and Group 3 (HR=0.83; P<0.001) had increased adjusted survival compared to Group 1. Shorter survival was significantly associated (P<0.05) with stage III and IV disease (HR=1.26 and 3.82), grade 2, 3 and 4 tumors (HR=1.37, 2.39 and 2.48), age 51-70 years and >71 years (HR=1.26 and 2.11), Charlson score of 1 or ≥2 (HR=1.21 and 1.69), tumor size >5 cm (HR= 1.64), systemic or radiation therapy as index treat-

ment (HR=1.49 and 1.44), and black race (HR=1.08). Longer survival was significantly associated (P<0.05) with liposarcoma or undifferentiated pleomorphic sarcoma (HR=0.60 and 0.77), an upper or lower extremity tumor site (HR=0.61 and 0.64), private insurer (HR=0.74), income of $48,000-62,999 or >$63,000 (HR=0.91 and 0.83), treatment at an academic center or comprehensive community cancer program (HR=0.87 and 0.91), transitioning care (HR=0.89), female gender (HR=0.91), and being > 100 miles from the facility (HR=0.91).

Conclusion: Longer TTI is not associated with a survival disadvantage. This is important in counseling patients, who may delay treatment to receive a second opinion or seek care at a tertiary sarcoma center.

Figure 1. Kaplan-Meier survival curve comparing TTI; log-rank test P<0.001

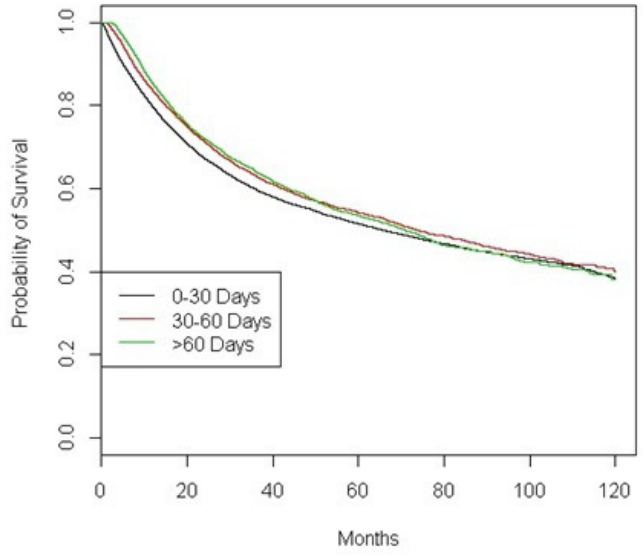

Table 2. Cox proportional hazard model

	Hazard Ratio (95% CI)	P-Value
TTI		
Group 1, (0-30 days)	Reference	
Group 2, (31-60 days)	0.82 (0.79-0.85)	<0.001
Group 3, (>60 days)	0.83 (0.79-0.87)	<0.001
Age		
18-30	Reference	
31-50	1.06 (0.97-1.16)	0.172
51-70	1.26 (1.14-1.4)	<0.001
71+	2.11 (1.89-2.35)	<0.001
Sex		
Male	Reference	
Female	0.91 (0.88-0.94)	<0.001
Race		
White	Reference	
Black	1.08 (1.02-1.14)	0.005
Other/Unknown	0.91 (0.84-0.98)	0.013
Charlson/Deyo Score		
0	Reference	
1	1.21 (1.16-1.27)	<0.001
≥ 2	1.69 (1.58-1.82)	<0.001
Histology		
Spindle Cell Sarcoma	Reference	
Undifferentiated Pleomorphic Sarcoma (MFH)	0.77 (0.73-0.82)	<0.001
Liposarcoma	0.60 (0.55-0.64)	<0.001
Other	0.98 (0.92-1.04)	0.485
Facility Type		
Community Cancer Program	Reference	
Comprehensive Community Cancer Program	0.91 (0.86-0.97)	0.006
Academic Center	0.87 (0.82-0.93)	<0.001
Integrated Network Cancer Program	0.97 (0.89-1.06)	0.486
Other/Unknown	0.80 (0.72-0.88)	<0.001
Insurance		
Uninsured	Reference	
Private Insurance	0.79 (0.73-0.86)	<0.001
Medicaid	1.08 (0.98-1.19)	0.137
Medicare	1.05 (0.96-1.15)	0.314
Other/Unknown	0.91 (0.82-1.02)	0.105
Income		
< $38,000	Reference	
$38,000 - $47,999	0.96 (0.91-1.00)	0.067
$48,000 - $62,999	0.91 (0.86-0.95)	<0.001
$63,000+	0.83 (0.79-0.87)	<0.001
Unknown	1.62 (1.39-1.88)	<0.001
Distance from Facility		
< 21 miles	Reference	
21-50 miles	1.00 (0.96-1.05)	0.877
51-100 miles	1.00 (0.94-1.06)	0.96
>100 miles	0.91 (0.86-0.97)	0.002

Table 2. Continued

Unknown	1.07 (0.94-1.22)	0.3
Transition in Care		
Yes	0.89 (0.86-0.92)	<0.001
No	Reference	
Year of Diagnosis	0.99 (0.98-0.99)	<0.001
Primary Tumor Site		
Head/Neck	Reference	
Upper Extremity/Shoulder	0.61 (0.57-0.65)	<0.001
Lower Extremity/Hip	0.64 (0.61-0.68)	<0.001
Trunk	0.96 (0.91-1.02)	0.203
Other	1.27 (1.18-1.37)	<0.001
Tumor Size		
≤ 5.0 cm	Reference	
> 5.0 cm	1.64 (1.58-1.71)	<0.001
Grade		
1, Well Differentiated	Reference	
2, Moderately Differentiated	1.37 (1.24-1.51)	<0.001
3, Poorly Differentiated	2.39 (2.20-2.61)	<0.001
4, Undifferentiated	2.48 (2.27-2.70)	<0.001
Unknown	2.16 (1.98-2.36)	<0.001
Clinical Staging		
Stage I	Reference	
Stage II	0.99 (0.88-1.12)	0.861
Stage III	1.26 (1.15-1.39)	<0.001
Stage IV	3.82 (3.47-4.21)	<0.001
Unknown	1.17 (1.07-1.28)	<0.001
First-Line Treatment Modality		
Surgery	Reference	
Radiation	1.44 (1.38-1.50)	<0.001
Systemic	1.49 (1.42-1.56)	<0.001
Other	2.20 (1.58-3.06)	<0.001
Multi-modal	1.27 (1.11-1.45)	<0.001

Poster 261 #2804312

A PROFOUND TRANSCRIPTIONAL REPROGRAMMING AND A RESETTING OF THE IMMUNOLOGICAL CONTEXTURE SUSTAIN THE RHABDOMYOBLASTIC HETEROLOGOUS DEDIFFERENTATION OF RETROPERITONEAL LIPOSARCOMAS

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Objective: Rhabdomyoblastic dedifferentiation was shown to be associated to a significant aggressive course in WD/DD retroperitoneal liposarcoma (RLPS), with a risk of distant spread of 90%. What are the molecular events that underlie this aggressive behaviour is still largely unknown. Aim of this study was to understand whether the dedifferentiation towards a myogenic (M) or rhabdomyoblastic (R) lineage heralds a different transcriptional profile and to dissect the molecular mechanisms behind RLPS aggressive transformation.

Methods: Nine patients with primary untreated RLPS with R and nine with M dedifferentation who underwent surgery at our Istitution (2008-2016) were selected. The presence of R or M dedifferentiation was confirmed by an expert sarcoma pathologist. Non neoplastic, WD and DD areas were selected for the analyses. Matched WD areas were macrodissected from 7 M-DD and 5 R-DD. RNA was extracted from FFPE WD and DD areas and profiled by RNA-seq (ave 50 million reads per sample) on an Illumina Hiseq1000 platform. STAR, HTseqcount and DESEQ2 were used for reads mapping, quantification and differential expression analysis, respectively. Gene enrichment, functional annotations and pathways analysis were performed by using WebGestalt, GSEA and IPA.

Results: Principal component analysis (PCA) of the transcriptional profile of WD and DD tumors highlighted two major clusters: M-DD and WD (irrespective of whether associated to M-DD or R-DD) vs R-DD. Increased cell proliferation and reduced differentiation strongly marked the transition from WD to DD. Activation of genes related to muscle development and suppression of genes related to inflammation and vasculature development was observed in R-DD vs WD.

The comparison between the R-DD and M-DD highlighted an enrichment in genes related to skeletal muscle development in the R-DD and a marked augment of genes related to immune and inflammatory response in the M-DD. Immunostaining with CD4, CD34, CD163 and CD209 confirmed a reduced representation of immune cells, particularly of the myelomonocytic lineage, in R-DD compared to M-DD.

Conclusion: The results of this analysis suggest that R dedifferentiation in RLPS is associated with a profound transcriptional reprogramming towards the skeletal muscular lineage. Moreover, the reduced immune infiltration observed in R-DD might suggest a less inflammatory tumor microenvironment in the more aggressive forms of RLPS. Further studies (including in vivo models) are ongoing to validate these data.

Poster 262 #2804318

OPTIMIZED THERMOSENSITIVE DOXORUBICIN LIPOSOMES FOR NEOADJUVANT TREATMENT OF LOCALLY ADVANCED SOFT TISSUE SARCOMA (STS) – A PROOF OF CONCEPT STUDY IN SPONTANEOUS FELINE FIBROSARCOMA

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Objective: Neoadjuvant anthracycline and ifosfamide based chemotherapy in patients with high-risk STS has shown to improve overall survival. However, response to doxorubicin (DOX) and ifosfamide combination chemotherapy is limited to less than 30% for most STS subtypes. One important shortcoming of standard drug application is the limited drug penetration. This can be overcome with intravascular release of DOX from thermosensitve liposomes (TSL) based on phosphatidyldiglycerol (DPPG2) showing an improved pharmacokinetic profile.

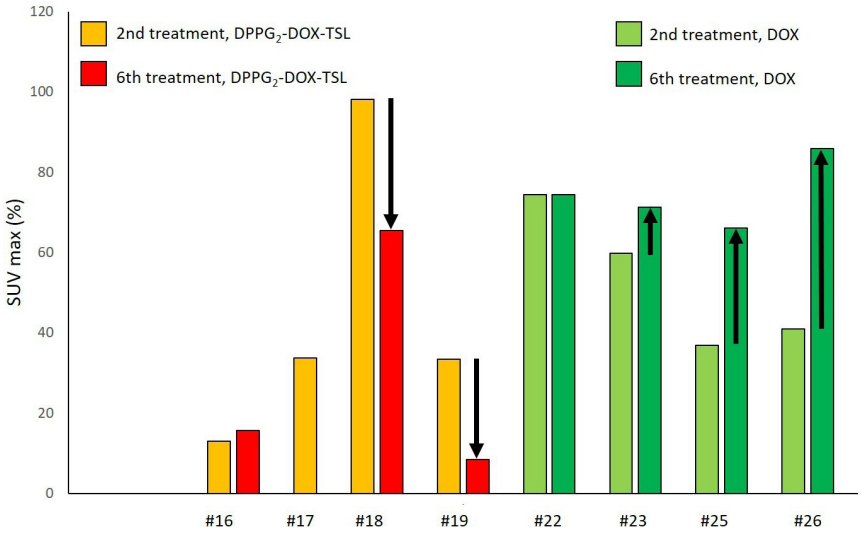
Methods: Twenty-two client-owned cats with advanced STS were enrolled. Intraindividual dose escalation was allowed in the first group receiving DPPG2-TSL-DOX (N=5, 0.1–0.4 mg/kg DOX). Constant dose levels of DPPG2-TSL-DOX were applied in the other groups with

DOX 0.4 mg/kg (N=3), 0.6 mg/kg (N=3), 0.8 mg/kg (N=3) and 1.0 mg/kg (N=4). respectively. The control group received free DOX at 1.0 mg/kg (N=4). Regional hyperthermia (RHT) with a target temperature of 41.5 °C was started 15 min before i.v. drug application and continued for a total of 60 min. Six RHT treatments were applied every other week. Tumor growth was monitored by MRI and for dose levels ≥ 0.6 mg/kg DOX also with 18F-FDG PET. Histopathologic response was assessed in resected tumors. Blood analysis, echocardiography and clinical investigations have been routinely performed.

Results: Dose escalation of DPPG2-DOX-TSL + RHT up to 1.0 mg/kg DOX q 14 days for 6 cycles was feasible without reaching dose-limiting toxicity. Tumor responses were dose dependent and most pronounced in the highest dose level. Here, all cats treated with DPPG2-DOX-TSL + RHT (4/4) showed a metabolic partial response (MPR, >30% decrease in SUVmax) whereas for cats treated with free DOX + RHT, only one cat showed a MPR (1/4). Regarding tumor volumetry, from the DPPG2-DOX-TSL group 2/4 showed SD, 1 PR, 1 PD whereas all cats treated with free DOX+ RHT (4/4) showed PD after 6 cycles of treatment. The pattern of response was also different with a continuing metabolic response for the DPPG2-DOX-TSL group whereas for the free DOX group an initial response was seen after 2 cycles with further progression after 6 cycles.

Treatment group	No.	Tumor volume (cm^3)			Metabolic tumor response according to PERCIST			Response evaluation	
		Initial	After treatment	Change (%)	Initial SUV_{max}	SUV_{max} after treatment	Change (%)	Volume	PERCIST SUV_{max}
$DPPG_2$-TSL-DOX	# 16	23.0	19.7	- 14	16.1	2.5	- 84	SD	PR
	# 17*	14.1	19.7	+ 40	7.1	2.4	- 66	SD	PR
	# 18	8.2	29.1	+ 253	5.8	3.8	- 35	PD	PR
	# 19	10.2	4.4	- 57	8.6	0.7	- 92	PR	PR
DOX	# 22	15.2	43.2	+ 185	3.9	2.9	-26	PD	SD
	#23	16.9	34.0	+ 101	9.0	6.4	-22	PD	SD
	#25	21.9	31.5	+44	15.0	9.9	-34	PD	PR
	#26	4.7	8.9	+89	3.5	3.0	-14	PD	SD

Response evaluation according to MRI and PET measurements



Metabolic response according to treatment duration

Conclusion: DOX-loaded DPPG2-TSL demonstrate a significant improved antitumor efficacy in feline STS as compared to free DOX. The change in pattern of response suggests a more effective drug delivery by DPPG2-TSL. This offers a new treatment option for the neoadjuvant treatment of high-risk STS potentially also in humans.

Poster 263 #2804336

HIGH THROUGHPUT GENOME STUDY TO IDENTIFY PREDICTORS OF AGGRESSIVENESS IN PATIENTS WITH SPORADIC DESMOID TUMOR WHO UNDERGO A WAIT AND SEE APPROACH

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Objective: Wait and see approach for desmoid-type fibromatosis (DF) patients has become part of the routine treatment strategy. Two parallel European prospective studies have been conducted to validate this approach. However, predictive factors to select the risk of progressive disease in the individual patient are still lacking.
A translational project was run in order to identify genomic signatures associated to specific behaviors in patients enrolled within the Italian prospective observational study.

Methods: DF fresh frozen samples from enrolled patients who have been biopsied at our Institution were collected for translational studies. Whole exome sequencing was performed on DNA extracted from 12 fresh frozen biopsies using Nextseq500 (Illumina, CA) sequencer. Deep sequencing of CTNNB1, APC and LAMTOR2 was performed on additional 12 FFPE cases of WT DF using Truseq custom amplicon low input kit (illumina) for library preparation and sequenced on MiSeq instrument (illumina).

Results: Twelve fresh frozen biopsies were analyzed through exome sequencing. Using Sanger sequencing 10 mutated DF (8 T41A and 2 S45F) and 2 WT were identified. In WT cases, two genes were found to be mutated: APC in one case (p.D1696N and p.D1670H) and LAMTOR2 (p.V92M) in the other. Globally, DF exhibited low somatic sequence mutation rate (mean 0.36 mutations per megabase), and in the CTNNB1-mutated group no other recurrent mutational event was identified.

Overall, in this group, only 2/12 patients (17%) were shifted from an observational approach to a specific treatment for progressive disease.

In order to enlarge the study on WT DF subtype and identified new potential mutations, high deep sequencing of CTNNB1, APC and LAMTOR2 was conducted on a retrospective series of 12 additional WT DF. No other mutation of LAMTOR2 was detected. APC mutation was detected in one case, while low-frequencies CTNNB1 mutations were found in 6 samples (50%) (mean of 16% reads). However, 5 cases (42%) remained WT for CTNNB1 or APC mutations. Further analyses are ongoing in this subgroup to identify other potential molecular events determining tumorigenesis.

Conclusion: DF is characterized by a low load of mutational events, which do not seem to be associated to the clinical course of the disease. A minority of DF is wild type for either CTNNB1, APC or any other gene involved in the WNT pathway. The clinical and molecular meanings of these findings need further investigation.

Poster 264 #2804345

THE RISK OF LOCAL RECURRENCE IN CASE OF UNPLANNED EXCISION WITHOUT ADDITIONAL WIDE EXCISION

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Objective: Unplanned excision of soft tissue sarcomas is an inevitable problem in the management of sarcoma. An intralesional procedure is often performed without considering the possibility of malignancy, because sarcomas are rare. In these cases, additional wide excision should be performed at an early stage. However, in cases of patients declining an additional operation or were left untreated for a long period of time from the initial excision, observation without additional surgery may be selected. The purpose of this study was to investigate the risk of local recurrence for patients with inappropriate excision and no local residual tumor without additional wide excision.

Methods: We surveyed cases in which unplanned excision was performed at previous hospitals for which follow up was possible. The subjects were 13 cases where additional wide excision and chemotherapy were not performed for some reason after the first visit. The average age at first visit was 44.4 ± 5.7 years. Survival rates were estimated by using Kaplan-Meier methods with the local recurrence of the tumor as the endpoint. We evaluated differences in survival curves in terms of gender, the type of sarcoma, tumor size at the initial surgery, methods of anesthesia at the initial surgery with log rank test ($p<0.05$ was considered significant).

Results: The mean follow-up period was 113.8 ± 22.0 months (26 to 232 months), local recurrence was observed in 11 cases among 13 cases, and the 1-year and 3-year survival rates were 46.2% and 23.1% , respectively. The time to recurrence was 13.1 ± 5.0 months (1.0 to 57.9 months). They included malignant fibrous histiocytoma in 7 cases, synovial sarcoma in 2 cases, others in 4 cases. There were 6 cases with the largest diameter of less than 30 mm and 8 cases were performed under local anesthesia. None of these cases showed a significant difference in the survival curve ($p = 0.20$, $p = 0.53$, 0.50)

Conclusion: The local recurrence rate after unplanned excision in this study was obviously higher than the reported recurrence rates after planned excision. In cases where there was no clear local residual tumor on imaging studies after unplanned excision, regardless of the type and size of the tumor and the anesthesia method, the risk of recurrence was high. Prompt and wide excision is desirable in cases of unplanned excision.

Poster 265 #2804349

EVERY OTHER WEEK DOSING OF TRC105 (ENDOGLIN ANTIBODY) IN COMBINATION WITH PAZOPANIB IN PATIENTS WITH ADVANCED SOFT TISSUE SARCOMA

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Objective: The endoglin antibody TRC105 is being studied in the pivotal Phase 3 TAPPAS trial with pazopanib (P) in patients with angiosarcoma (AS) as a weekly infusion at 10 mg/kg. Weekly dosing of TRC105 in combination with P was well tolerated in 94 soft tissue sarcoma (STS) patients treated in a Phase 1b/2 study. Every other week dosing with TRC105 has been proposed to decrease the frequency of infusions and for patient convenience.

Methods: Six patients (2 male, 4 female, mean age = 64.5 years) with advanced STS were treated with a hybrid dosing scheme of TRC105 10 mg/kg weekly for four doses followed by every other week dosing at 15 mg/kg starting on Cycle 2 Day 1 of recurring 4 week cycles. TRC105 was given concurrently with P, starting at 800 mg/day.

Results: Serum levels of TRC105 exceeded the target concentration of 20 µg/mL following four weekly doses of TRC105 at 10 mg/kg. The mean trough concentration pre-Cycle 2 Day 1 dose (prior to initiation of every other week dosing) was 124 µg/ml, range 81-174, and was maintained following every other week dosing at 15 mg/kg in every patient (mean trough concentration following the first and second every other weekly dose was 86 µg/ml, range 62-144 and 91 µg/mL, range 73-121, respectively). Trough concentrations exceeding the target concentration were maintained in every patient for the duration of treatment (up to 8 four week cycles). The most common TRC105 related AEs included grade (G) ≤ 2 telangiectasia (with epistaxis and gingival bleeding) and G≤3 anemia and G1 headache; most common P related AEs included G≤3 fatigue, diarrhea, and hypertension, which were similar in frequency to those observed using continuous weekly dosing of TRC105 at 10 mg/kg.

Conclusion: TRC105 was well tolerated when combined with P using a hybrid dosing scheme of 10 mg/kg weekly for four doses followed by every other weekly dosing at 15 mg/kg. Serum trough TRC105 levels were achieved in every patient following initial weekly dosing and were maintained using every other week dosing. This dosing scheme is currently being examined in patients with AS in an expansion cohort of the ongoing phase 1b/2 study.

Poster 266 #2804447

CHEMOTHERAPY IN ADVANCED MALIGNANT PHYLLODES TUMOR (PT) OF THE BREAST: A RETROSPECTIVE CASE-SERIES ANALISYS FROM THE ITALIAN RARE CANCER NETWORK

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Objective: To report on the activity and efficacy of chemotherapy in locally advanced/metastatic malignant PT of the breast. Data on chemo-sensitivity are lacking on these tumors.

Methods: We retrospectively reviewed cases of advanced malignant PT of the breast treated with chemotherapy at Fondazione IRCCS Istituto Nazionale dei Tumori in Milan and/or within the Italian Rare Cancer Network in the last 15 years. Responses are reported according to RECIST criteria.

Results: From 2002, 22 female patients were identified (one with locally advanced disease and 21 with metastatic disease). Median age was 50 years (range: 37-64 years). Most used chemotherapy regimens included: antracycline +/- ifosfamide (AI), gemcitabine +/- docetaxel (GD) and high-dose ifosfamide given as a continuous infusion for 14 days (HD-IFX). In particular, 17 patients received AI (all but one received the combination of the two drugs, all but one as first-line), 12 patients received GD (as first-line in 4 cases) and 11 patients received HD-IFX (as first-line only in 2 cases). Best responses according to RECIST were: 7 (41.2%) PR, 5 (29.4%) SD, 4 (23.5%) PD with AI (with 1 patient not evaluable); 3 (25%) SD, 9 (75%) PD with GD; 1 (9.1%) PR, 3 (27.3%) SD, 7 (63.6%) PD with HD-IFX. Median progression-free survival were: 6.3 months (CI 95% 2.5-8.8 months) with AI, 2.8 months (CI 95% 0.8-6 months) with gemcitabine-based chemotherapy; 2.5 months (CI 95% 1.0-7.3 months) with HD-IFX. Overall survival from the start of first-line chemotherapy was 19.6 months (CI 95% 13.9-31 months).

Conclusion: In this series, antracycline +/- ifosfamide demonstrated to be active in malignant PT of the breast, though with a limited progression-free survival. Gemcitabine +/- docetaxel and HD-IFX were apparently poorly active.

Poster 267 #2804592

TRAVELING TO HIGH-VOLUME CENTERS FOR TREATMENT OF RETROPERITONEAL SARCOMAS IS ASSOCIATED WITH IMPROVED SURVIVAL

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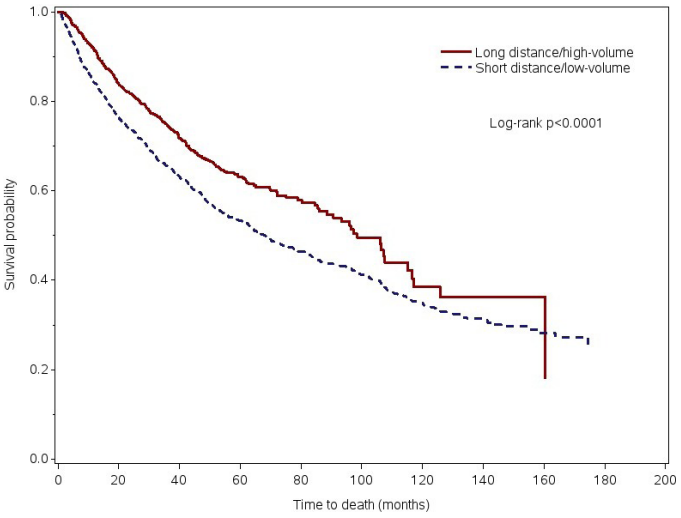
Objective: Guidelines recommend treatment of retroperitoneal sarcomas (RPS) at high-volume centers given the complexity of the disease. However, high-volume centers may not be accessible locally, with concerns about travel burden. This national study compared outcomes from treatment of RPS at local low-volume centers with treatment at distant high-volume centers.

Methods: Patients treated for RPS were identified from the National Cancer Database (1998-2012). Travel distance to treatment centers and annual hospital volume were divided into quartiles. Overlaying the upper and lower quartiles of travel distance with hospital volume status was employed to identify 2 groups: (1) short patient travel to low-volume hospitals (ST/LV), (2) long patient travel to high-volume hospitals (LT/HV). Outcomes were compared after adjustment for clinical, tumor, and neoadjuvant/surgical/adjuvant therapy.

Results: A total of 2599 patients were included; ST/LV group included 1309 patients who traveled a short distance (median=4 miles) to low-volume hospitals (performed a median of 1 RPS case/yr). LT/HV group included 1250 patients who traveled a long distance (median=56 miles) to high-volume hospitals (median=10 RPS cases/yr). Compared with ST/LV, LT/HV group were younger and often White (p<0.01); however, annual income and insurance status were similar between groups. LT/HV group had more comorbidities, higher tumor grade, and often received radical resection and radiotherapy (all p<0.01). Thirty-day mortality was significantly lower in the LT/HV (1.2% vs 2.8%, p=0.003). Ten-year survival was better in the LT/HV (39% vs 35%, p=0.0004) [Figure]. After adjustment, the LT/HV had a 27% improvement in survival (HR 0.73, p=0.0009).



Conclusion: This nationwide study suggests that traveling to high-volume centers for treatment of RPS confers a significant short-term and long-term survival advantage and support national treatment guidelines in advocating for the necessity of centralized surgical care for RPS.

Poster 268 #2804623

COMPARING OUTCOMES IN UPPER AND LOWER EXTREMITY SOFT TISSUE SARCOMAS

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Objective: Soft tissue sarcomas (STS) of the upper extremities have similar tumor characteristics to STS of the lower extremities, however they often present different treatment challenges. Due to anatomic differences, STS of the upper extremities often lie in closer proximity to critical limb structures, making limb-sparing, margin-negative surgical resection challenging. In contrast, lower extremity STS can present later or due to asymptomatic growth in the relatively larger compartments of the leg and thigh. The purpose of this study was to determine the impact of primary tumor location on survival outcomes for patients with STS of the upper and lower extremities using data from the largest sarcoma patient registry available, the National Cancer Database (NCDB).

Methods: We retrospectively analyzed 25,434 patients with STS of the extremities in the NCDB from 1998 through 2012. Patients were stratified based on primary tumor site of the upper or lower extremities. Univariate and multivariate analyses were used to compare tumor site with other tumor and patient characteristics. Long-term survival between groups was evaluated using the Kaplan-Meier (KM) method, with statistical comparisons made by Log-Rank tests.

Results: We identified 6452 patients with STS of the upper extremities and 18982 patients with STS of the lower extremities. Patients with STS of the lower extremities presented on average with larger tumors (median 8.0 vs 5.0 cm, p<0.0001) and were more likely to have metastatic disease regardless of tumor grade (5.0% vs 3.2%, p<0.0001). Overall, 5-year survival was higher for upper than for lower extremity STS (72.7% vs. 69.2%, p<0.0001); however, this advantage did not persist when patients were stratified by tumor size. For tumors <5cm there was no survival difference between sites (83.4% vs. 82.0%, p=0.1190), but in tumors >5cm a survival advantage was conferred to STS of the lower extremities (64.5 vs. 60.9%, p=0.0031). While upper and lower extremity STS had equal rates of resection vs. amputation, upper extremity STS was associated with a higher likelihood of positive margin status in tumors larger than 5 cm (23.4% vs. 19.7%, p<0.0001). The proportion of patients receiving adjuvant radiation therapy was comparable between tumor sites.

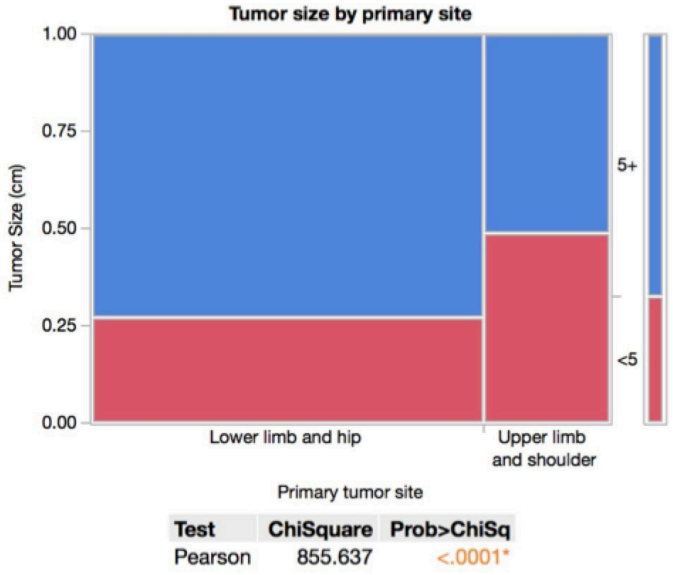

Fig 1 - Tumor size. STS of the lower extremities are larger on average than STS of upper extremities (median 8.0 vs 5.0 cm, p<0.0001).

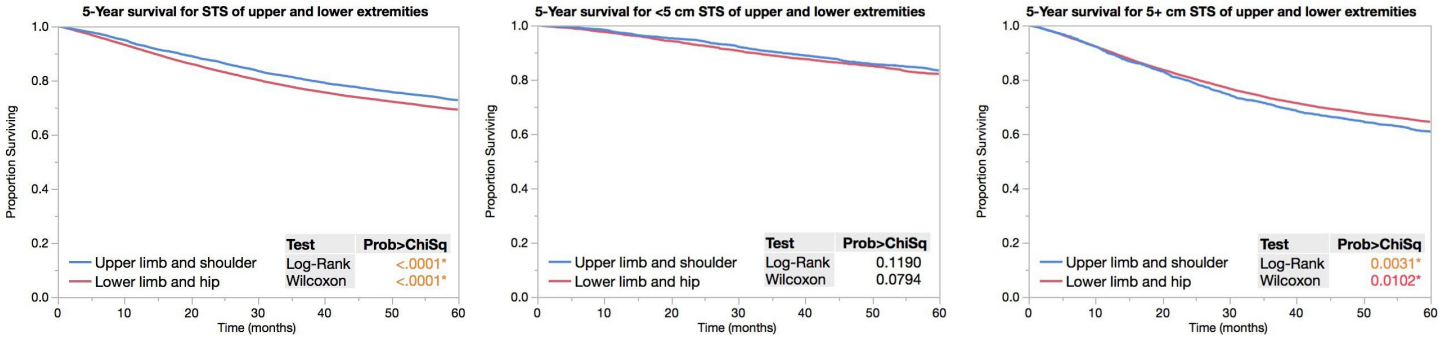

Fig 2 – The 5-year overall survival is higher in upper vs lower extremity STS. However, when stratified by tumor size, survival benefit is not present in <5cm tumors, and benefit is reversed in >5cm tumors, where survival is improved in lower extremity STS compared to upper (p=0.0031).

Conclusion: This database review suggests that, while treatment characteristics may be similar between the two locations, STS of the lower extremity may be associated with later presentation and worse overall outcomes, and for STS of the upper extremity, early treatment should be emphasized as negative margins may be more difficult to achieve in patients with larger tumors. For STS of both upper and lower extremities, further investigation is necessary to identify means to improve the early detection and adequate resection of these tumors.

Poster 269 #2804717

LOCALIZED, INTERMEDIATE AND HIGH GRADE SOFT TISSUE SARCOMA OF THE EXTREMITY AND TRUNK: THE ROLE OF CHEMOTHERAPY

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Objective: Soft tissue sarcomas (STS) are rare and heterogeneous tumors with different responses to systemic chemotherapy. Systemic chemotherapy in the adjuvant or neoadjuvant setting remains controversial in this disease though is often considered for patients with high risk of relapse. The goal of this study was to compare the outcomes of patients with intermediate to high-grade STS of the extremities and trunk that received surgery +/- radiation with the response of those that received surgery +/- radiation combined with neoadjuvant and/or adjuvant chemotherapy.

Methods: A retrospective chart review was performed to identify patients with localized soft tissue sarcoma of the extremity and trunk treated with definitive surgical management at our tertiary referral center from 2011 to 2016 that would be potentially considered candidates for adjuvant therapy. Inclusion criteria were: intermediate to high-grade histology, tumor size > 5 cm, and age at diagnosis > 40 years old. Patients who received adjuvant and/or neoadjuvant systemic therapy were compared to those that did not. Groups were compared for rate of relapse, and progression free survival (PFS) and overall survival (OS) using the Kaplan Meier (KM) method.

Results: 136 patients were identified as meeting study criteria. The cohort was separated into two categories based on treatment course. Group A (108 patients, 79.4%) received surgery +/- radiation and group B (28 patients, 20.6%) received surgery +/- radiation and chemotherapy. In the systemic therapy group, 24 patients received neoadjuvant chemotherapy, 3 patients received adjuvant chemotherapy, and 1 patient received both. The most common chemotherapy regimens were MAI (Mesna, Adriamycin, Ifosfamide) and Doxorubicin/Dacarbazine. Number of cycles ranged from 1-4.

Rate of relapse was numerically lower in the group that received chemotherapy, though this result was not statistically different (35.7% vs 39.6%, p=0.83). By KM method, there was a clear visual trend towards improved PFS and OS in the group receiving chemotherapy (Figure 1A/B), but these results did not reach statistical significance (p=0.36 and p=0.20, respectively). As an example, 2 year PFS (78.0% vs. 63.0%) and 2 year OS (92.7% vs. 78.5%) were both higher in the chemotherapy group by clinically meaningful amounts. Although these findings are not statistically significant, it does trend towards some benefit in the group that received chemotherapy. Both median PFS and median OS were not reached in either group.

Figure 1A. *Progression Free Survival stratified by with chemo vs. without chemo*

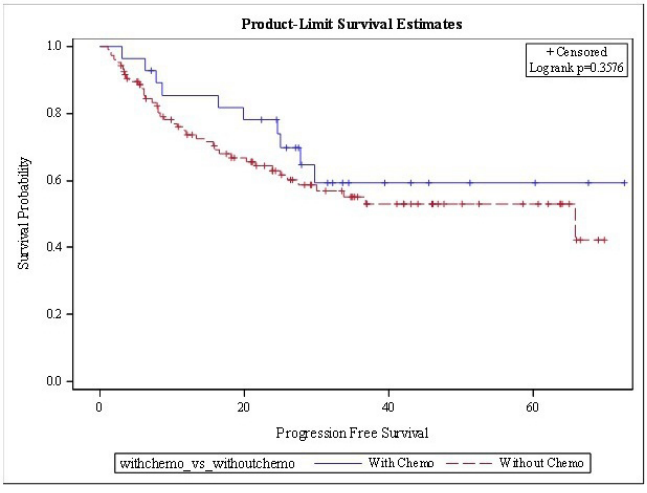
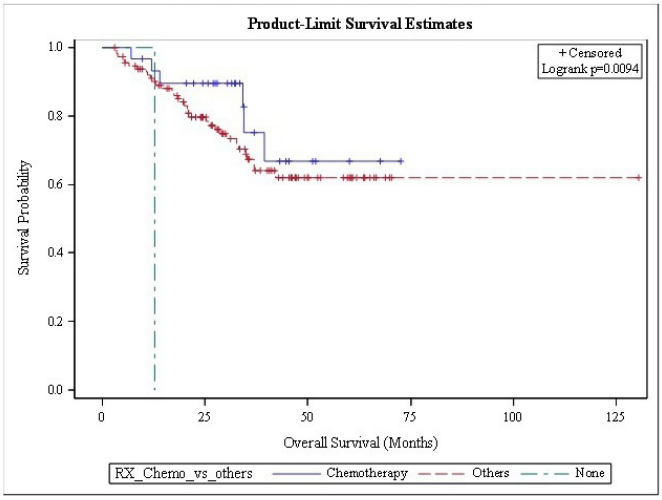


Figure 1B. *OS stratified by with chemo vs. without chemo*



Conclusion: In our retrospective analysis of localized extremity/trunk STS patients treated with definitive surgery, there was no statistical difference in outcomes between groups treated with neoadjuvant/adjuvant systemic therapy and those that did not. However, there was a consistent trend towards improved PFS, OS, and rate of relapse all favoring the group that received chemotherapy. The absolute values of these differences between groups would be considered clinically meaningful. The ability to detect statistically significant differences was limited by cohort size.

These findings are being further investigated with a larger cohort of patients. We are currently collecting comprehensive clinical and outcome data on a group of 523 patients diagnosed between 1/1/1998-12/31/2016, of whom 372 patients have received chemotherapy in their first course of treatment. Our plan is to fully analyze this larger cohort and incorporate these results into our final report.

Poster 270 #2804721

IMPROVING THE PRIMARY-SECONDARY CARE REFERRAL INTERFACE FOR SUSPECTED SOFT TISSUE SARCOMA: THE GOLF BALL PROJECT

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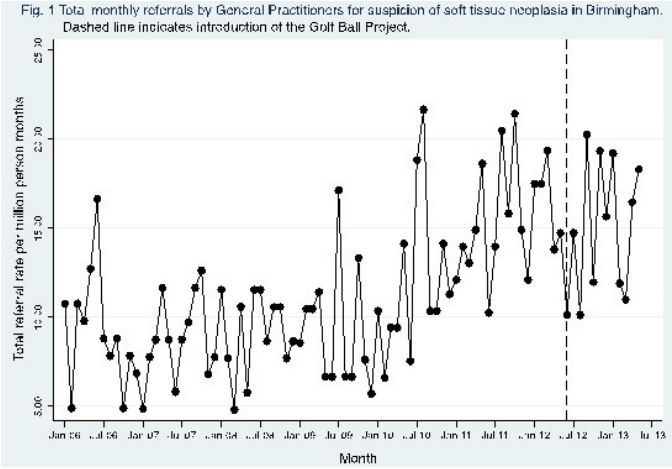
Objective: Delays in soft tissue sarcoma (STS) referral have a detrimental impact on patient survival and function. The primary study objective was to determine if exposure of General Practitioners to a passive educational intervention would increase the rates of referrals for suspected soft tissue malignancy, and the proportion of malignant referrals. The secondary study objective was to identify demographic factors associated with a change in these referral patterns.

Methods: 736 GPs practicing in the greater Birmingham area were mailed a package including golf ball keychain inscribed with “Is it sarcoma?”, a visual cue that 4.3 cm is a size of concern for suspected STS and should prompt referral. Monthly aggregates of new diagnoses of any malignancy, STS and other (non-STS) soft tissue malignancies were extracted from a prospectively collected institutional database, and population-adjusted referral rates were calculated. Poisson regression was used to compare the intervention rates over time. Logistic regression was used to compare the proportion of malignant referrals over time and to identify predictive factors for malignancy. Qualitative interviews were carried out with GPs to assess recall of the intervention, perception of guidance material and expected outcomes on referral patterns.

Results: A total of 89 months of follow-up available (77 months pre-intervention and 12 months post-intervention) yielded 97,722 patient-months of data and 1,087 new referrals for suspected soft tissue neoplasia. There were significantly fewer referrals in 2006-2010 (IRR of 0.62; 95% CI: 0.54-0.70; p<0.0001) as compared to the immediate pre-intervention period (2010-2012), but no significant change after initiation of the intervention (p=0.64). Nor was there a significant difference in the proportion of referrals that identified malignancies pre- and post-intervention. The adjusted multivariable logistic regression model demonstrates that tumour size, shorter duration of symptoms, older age, and male gender are significant predictors of a malignant referral. Patients presenting with tumours larger than a golf ball have 2.5 increased odds of malignancy (p<0.0001).



Conclusion: Population-adjusted referral rates for suspicion of soft tissue neoplasia have increased from 2006 to present, however, the Golf Ball project did not have a significant impact on referral rates or the proportion of malignant referrals. Patients with tumours bigger than the size of a golf ball are a significantly increased risk of malignancy.

Impact of Golf Ball Project on referral rates for the population of Birmingham due to suspicion of soft tissue neoplasia. Comparison of 3 time trends (January 1, 2006 to May 31, 2010; June 1, 2010 to May 31, 2012; after June 1, 2012).

Type of referral	IR (95% CI)	IRR	95% CI	p-value
Total referral	9.18 (8.41, 9.95)	0.54, 0.70	0.54, 0.70	<0.0001
January 1, 2006 to May 31, 2010	14.95 (13.34, 16.57)		0.88, 1.24	
June 1, 2010 to May 31, 2012*	14.93 (12.5, 17.36)	0.88, 1.24		0.641
June 2, 2012 to May 31, 2013^				
Any malignancy	1.33 (0.89, 1.77)	0.52	0.37, 0.73	<0.0001
January 1, 2006 to May 31, 2010	2.22 (0.96, 3.48)	1	0.48, 1.23	
June 1, 2010 to May 31, 2012*	1.76 (0.61, 2.91)	0.78		0.303
June 2, 2012 to May 31, 2013^				
STS	0.85 (0.52, 1.17)	0.62	0.40, 0.98	0.042
January 1, 2006 to May 31, 2010	1.10 (0.02, 2.18)	1	0.56, 1.89	
June 1, 2010 to May 31, 2012*	1.15 (0.25, 2.05)	1.03		0.931
June 2, 2012 to May 31, 2013^				
Other soft tissue malignancy	0.49 (0.28, 0.69)	0.40	0.24, 0.68	0.001
January 1, 2006 to May 31, 2010	1.12 (0.63, 1.61)	1	0.22, 1.15	
June 1, 2010 to May 31, 2012*	0.61 (0.23, 0.99)	0.51		0.106
June 2, 2012 to May 31, 2013^				

IRR estimated using the mid-year population estimate as the exposure.
IR = incidence rate per million person years; IRR = incidence rate ratio; CI = confidence interval; GB, Golf Ball.
*Timeframe immediately pre-GB project used as the reference.
^Timeframe for the post-Golf Ball project.

Poster 271 #2804819

THERAPY OF ADVANCED SOFT TISSUE SARCOMA (STS) USING OLARATUMAB/DOXORUBICIN (OD) VERSUS DOXORUBICIN/IFOSFAMIDE (DI): A NETWORK META-ANALYSIS (NMA)

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Objective: In therapy of advanced STS, doxorubicin (DOX) monotherapy has been effectively standard. DI-based multi-agent regimens have been advocated, but have not demonstrated improved overall survival (OS), despite improved overall response rate (ORR) and progression-free survival (PFS; Judson, 2014. Lancet Oncol 15:415). Recently OD was approved in the US for STS based on a randomized trial demonstrating improved OS vs DOX (Tap, 2016. Lancet 388:488). There was no improvement in ORR or PFS. DI has been advocated in situations where its improved ORR might be advantageous. No formal comparison of DI vs. OD has been reported.

Methods: A systematic review and NMA compared OD and DI regimens. We identified prospective, randomized trials in advanced STS of DOX-based regimens. All studies required comparator arms administering DOX monotherapy at ≥75 mg/m2. Treatment arms administered either OD or DI (Ifosfamide at ≥7 g/m2 per cycle) concurrently. Outcomes of interest included ORR, 6-m PFS and 1-y OS. Information regarding outcomes was either derived directly from the report, or through digitization of Kaplan-Meier curves with linear regression to allow extraction of parametric PFS/OS functions. NMA ranked the outcomes of interest.

Results: Our literature review identified 4 clinical trials meeting inclusion criteria (1-OD, 3-DI). For one study, 6-m PFS could not be determined. For all three outcome parameters, inconsistency of effects were not identified, allowing consistent effects models to be used. For ORR, OD and DI were ranked similarly to one another and superiorly to DOX. For both 6-m PFS and 1-y OS, the regimens were ranked in a similar order: OD>DI>DOX. The only statistically significant different was in 1-yr survival, where OD was superior to DOX. All other two-way comparisons were not statistically different.

Conclusion: OD therapy in advanced STS likely yields superior 6-m PFS and 1-y OS vs DI, while ORR of the two regimens is similar. Both regimens appear superior to DOX by all three measures of effect. We suggest that OD may be a suitable, less toxic replacement for DI in advanced STS therapy. While a randomized comparison of OD and DI is unlikely, results from ongoing trials may further clarify these findings.

Poster 272 #2804863

RADIATION ASSOCIATED AND NEUROFIBROMATOSIS ASSOCIATED MPNST HAVE WORSE OUTCOMES THAN SPONTANEOUS MPNST

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Objective: In an IRB approved protocol, we reviewed the clinical characteristics and outcomes of patients treated for malignant peripheral nerve sheath tumor (MPNST) at our institution and sought to characterize the impact of association with clinicopathologic features and treatment modalities on clinical outcomes.

Methods: We identified 275 patients with MPNST treated at our institution between 1960 and 2015 and collected the clinical information. Overall survival (OS), local control (LC) 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: With a median follow-up of 43.2 mo (range: 0.5-464.3), the median OS was 68.2 mo (95% CI: 45.7-90.6). There were 134 men and 141 women with a median age of 41 y (range: 3-95). Patients were classified as having either radiation-associated MPNST (raMPNST, n=19), neurofibromatosis-associated MPNST (nfMPNST, n=75), or spontaneous MPNST (sMPNST, n=181). The median time to development of raMPNST from prior radiation was 15 y (range: 6-50). Prior diseases in patients developing raMPNST included Hodgkin disease (8), testicular cancer (4), Wilms disease (2), benign disease (2), lung cancer (1), nasopharyngeal cancer (1), and ALL (1) at a median age of 21 y (range: 1-53). Compared with sMPNST, nfMPNST occurred relatively early in age (median: 31 y in nfMPNST, 36 y in raMPNST, 46 y in sMPNST, p<0.001). The rate of metastatic disease on presentation was similar (10.5% raMPNST vs 10.7% nfMPNST vs 10.5% sMPNST). No significant difference was found in surgery or chemotherapy (p=NS), although fewer patients with raMAPNST received radiation therapy (52.6% raMPNST vs 80% nfMPNST vs 64.1% sMPNST, p=0.016).

On univariate analysis, both raMPNST and nfMPNST showed worse OS (median: 16.2 mo, 35.5 mo vs 102.4 mo, p<0.001), LC (13.3 mo, 75.1 mo vs 223.9 mo, p=0.047), and MFS (14.8 mo, 42.6 mo vs median not reached, p<0.001) than sMPNST, although the differences between raMPNST and nfMPNST were not significant. On multivariate analysis, older age (HR=1.015, 95% CI: 1.006-1.025, p=0.002), raMPNST (HR=2.358, 95% CI: 1.310-4.243, p=0.004), nfMPNST (HR=1.942, 95% CI: 1.305-2.891, p=0.001), trunk (HR=1.739, 95% CI: 1.205-2.509, p=0.003), tumor size > 5 cm (HR=1.705, 95% CI: 1.119-2.599, p=0.013), positive lymph node (HR=3.204, 95% CI: 1.254-8.186, p=0.015), metastatic disease at diagnosis (HR=1.978, 95% CI: 1.220-3.206, p=0.006), and positive margin (HR=1.928, 95% CI: 1.327-2.799, p=0.001) were related with worse OS, whereas radiation therapy (HR=0.577, 95% CI: 0.405-0.822, p=0.002) and surgery (HR=0.264, 95% CI: 0.125-0.555, p<0.001) was associated with improved OS.

Among the 246 patients without metastatic disease at diagnosis, nfMPNST (HR=2.100, 95% CI: 1.316-3.350, p=0.002), primary disease in head/neck (HR=2.004, 95% CI: 1.158-3.467, p=0.013) or trunk (HR=2.279, 95% CI: 1.391-3.736, p=0.001), and positive margin (HR=4.573, 95% CI: 2.807-7.452, p<0.001) were related with worse LC, whereas radiation therapy (HR=0.359, 95% CI: 0.231-0.558, p<0.001) was correlated with improved LC. raMPNST (HR=2.353, 95% CI: 1.131-4.897, p=0.022), nfMPNST (HR=2.090, 95% CI: 1.339-3.263, p=0.001), and tumor size > 5 cm (HR=2.518, 95% CI: 1.368-4.636, p=0.003) were correlated with worse MFS.

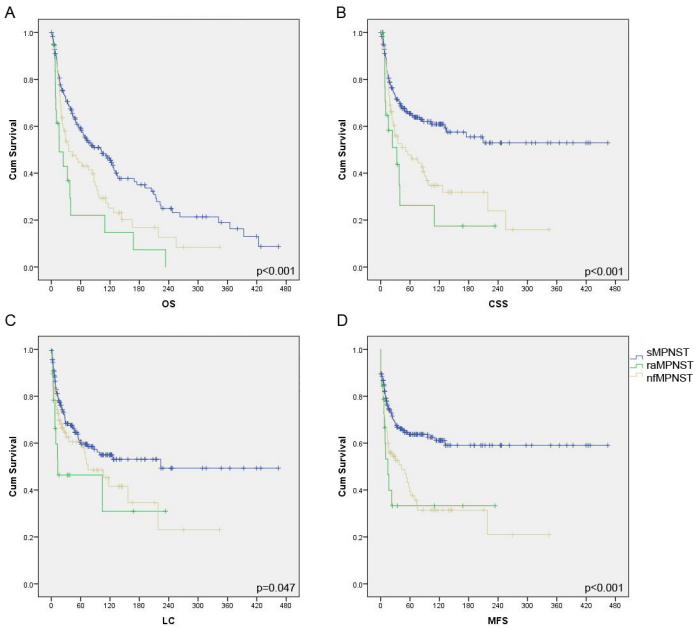

Fig 1. Kaplan-Meier curves of overall survival (A), cause-specific survival (B), local control (C) and metastasis-free survival (D).

Conclusion: Both radiation-associated and neurofibromatosis-associated MPNSTs have poorer prognosis than spontaneous MPNSTs, and warrant further characterization to determine optimal treatment.

WITHDRAWN

Poster 274 #2790532

PROGNOSTIC IMPLICATIONS OF SOFT TISSUE SARCOMA REEXCISION: A COMPARATIVE STUDY ON PLANNED EXCISION AND DELAYED REEXCISION

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Objective: Unplanned excision of soft tissue sarcoma (STS) is a source of concern due to possible tumor contamination of the surgical bed. This may subsequently lead to increased local recurrence and poor survival. We investigated whether timely performed reexcision has any prognostic implication on oncological outcomes compared with planned primary excision and delayed reexcision.

Methods: 412 patients with primary non-metastatic STS who were surgically treated at our institution between 2004 and 2016 were identified. After applying exclusion criteria, 153 reexcisions, 152 planned primary excisions, and 25 delayed reexcisions (more than 5 months) were included for analysis. We aimed to investigate the prognostic implications of reexcision in terms of local recurrence free survival (LRFS), metastasis free survival (MFS), and disease specific survival (DSS). Propensity score weighted regression was performed to adjust the effect of confounding factors and to compare oncological outcomes among three groups. The median follow-up period was 44 months.

Results: The 5-year LRFS, MFS, and DSS rate of the entire cohort was 89.9%, 78.3%, and 87.2%, respectively. After propensity score weighting, planned primary excision group showed significantly poor LRFS (hazard ratio

[HR] 3.303, p = 0.0086), MFS (HR 2.831, p = 0.0003), and DSS (HR 5.067, p = 0.0005) compared to reexcision group. Delayed reexcision group tended to have similar oncological outcomes with planned primary excision group; however, there was no statistically significant difference between delayed reexcision group and timely performed reexcision group. In the timely reexcision group, presence of residual disease was identified in 40.1%, and it was a significant prognostic factor for MFS in both univariate and multivariate analysis.

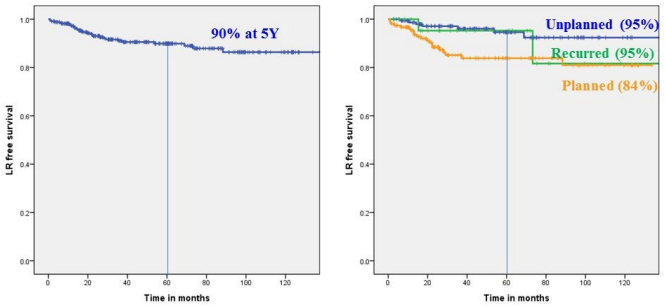

Figure 1. Acturial local recurrence free survival for patients undergoing reexcision, palnned primary excision, and delayed reexcision.

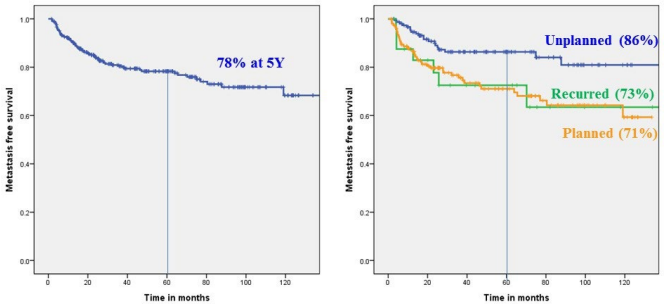

Figure 2. Acturial metastasis free survival for patients undergoing reexcision, palnned primary excision, and delayed reexcision.

Disease specific survival

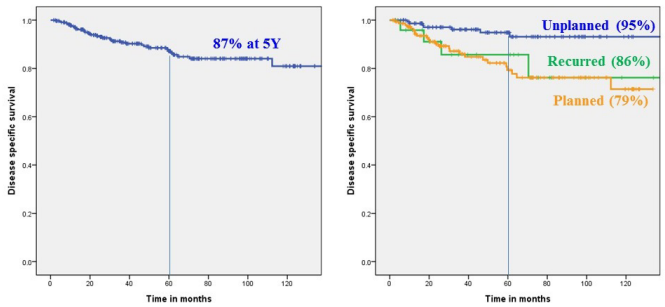

Figure 3. Acturial disease-specific survival for patients undergoing reexcision, palnned primary excision, and delayed reexcision.

Conclusion: The current study shows that compared to planned excision, timely and adequately performed re-excision can improve local control while not resulting in poor survival. The importance of timely referral to musculoskeletal tumor center and a prompt reexcision after unplanned excision should be emphasized in primary non-metastatic STS.

Poster 275 #2804644

PRECLINICAL RATIONAL FOR THE COMBINATION OF ADI-PEG20 WITH GEMCITABINE AND DOCETAXEL IN SOFT TISSUE SARCOMA

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Objective: Alterations in metabolic programming allow cancer cells to produce the biomass that is needed for rapid cell division. We have demonstrated that the loss of expression of argininosuccinate synthetase 1 (ASS1) occurs in ~90% of soft tissue sarcomas regardless of sarcoma histology. To identify strategies to optimize the therapeutic potential of ADI-PEG20 treatment, we employed an unbiased metabolomic strategy. This observation suggests that sarcomas may be sensitive to arginine deprivation therapy, an approach that is readily testable by administration of pegylated arginine deiminase (ADI-PEG20), an arginine – depleting enzyme that is already in clinical trials in other tumors.

Methods: To model the long term effects of arginine starvation, we derived Long Term ADI-PEG20-Treated (LTAT) cell lines by continuously culturing the ASS1-deficient cells with ADI-PEG20. These cell lines gained resistance to the growth inhibition caused by arginine starvation by re-expressing ASS1 after demethylating the promoter. We performed glucose carbon tracings, We explored the gemcitabine pathway by immunoblotting. In addition, we performed cell death assays examining the combinations of ADI-PEG20 with gemcitabine, docetaxel or the combination.

Results: Using Carbon 13 (C13) glucose labeled at all six positions, we identified that glucose was not being metabolized to lactate, citrate, or adenosine, but was directed into serine biosynthesis. gemcitibine was found to make cell lines, such as SKLMS1, that were resistant to gemcitibine sensitive. The sensitivity to gemcitibine and docetael was improved with the addition of ADI-PEG20.

Conclusion: ASS1 is a common metabolic defect in most sarcomas across histologies, making it the most common defect in sarcomas. ADI-PEG20 induces a metabolic reprogramming in ASS1-deficient sarcomas. Glucose is diverted to the serine/folate biosynthetic pathway for pyrimidine synthesis. Combination therapy driven by a biomarker using metabolism can lead to promising synergistic therapeutic combinations for the treatment of ASS1 deficient soft tissue sarcomas.

Poster 276 #2739128

BREAST CANCER HISTORY IS STRONGLY ASSOCIATED TO ANGIOSARCOMA OF THE BREAST -A POPULATION BASED STUDY IN SWEDEN 1993-2013

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Objective: To analyze the incidence of angiosarcoma in the breast in the Swedish population 1993-2013 and the relationship to previous cancer history

Methods: A database with gathered information from the Swedish cancer register, the cause of death register and the Swedish population register was used to identify cases of sarcoma. We used a combination of site coding according to ICD 7 and morphological coding according to SNOMED to find cases of sarcoma of the breast during the period 1993 to 2013. A total of 461 cases were identified of which 46 where angiosarcoma. (Table 1) Each case was matched to 10 controls by age and gender. Cancer history was recorded for cases and controls.

Results: We identified 46 cases of angiosarcoma, and 33 of these had a history of breast cancer. 24 were ipsilateral and 2 where contralateral. For 7 cases no data on laterality was available. This study shows a very clear risk association between angiosarcoma of the breast and previous breast cancer (Table 2). This highest risk occurs 5-10 years after breast cancer, OR 166.697 (35.147-790.619). We find no association between other types of sarcoma in the breast and previous breast cancer, with the exception of sarcoma NOS 5-10 years after breast cancer. Nor does his study does not show increased risk of later development of sarcoma in the breast after having other malignant tumors than breast cancer. Thus the risk association between angiosarcoma and previous breast cancer is a true attributable risk.

Conclusion: We show a very strong risk association between angiosarcoma of the breast and previous breast cancer. We also show an increasing incidence of this rare tumor over time. These findings may be caused by increasing use of radiotherapy in the treatment of breast cancer.

Group	Histology	SNOMED	n	Age at index Mean (min-max)	History of breast cancer n	History of breast cancer rate	History of other cancer n	History of other cancer rate
Angiosarcoma	Hemangiosarcoma	91203	44	69,8 (26-91)	32	72,7%	4	9,1%
	Lymphangiosarcoma	91703	2	62,0 (61-63)	1	50,0%	1	50,0%
Phyllodes	Phyllodes benign	90200	117	50,7 (19-89)	2	1,7%	5	4,3%
	Phyllodes border	90201	67	52,4 (17-84)	1	1,5%	2	3,0%
	Phyllodes malign	90203	177	57,7 (18-89)	5	2,8%	10	5,6%
Other	Spindle cell sarcoma	88013	6	70,7 (48-92)	0	0,0%	0	0,0%
	Giant cell sarcoma	88023	1	60,0	0	0,0%	0	0,0%
	Fibrosarcoma NOS	88103	5	71,8 (58-89)	3	60,0%	1	20,0%
	Aggressive fibromatosis	88211	1	35,0	0	0,0%	0	0,0%
	Malignant fibrous histiocytoma	88303	3	82,0 (74-88)	0	0,0%	0	0,0%
	Liposarcoma NOS	88503	3	61,7 (52-72)	0	0,0%	0	0,0%
	Leiomyosarcoma NOS	88903	7	62,4 (18-98)	0	0,0%	0	0,0%
	Endometrial stromal sarcoma	89303	2	53,5 (52-55)	0	0,0%	0	0,0%
	Osteosarcoma NOS	91803	1	77,0	0	0,0%	0	0,0%
	MPNST	95403	1	32,0	0	0,0%	0	0,0%
Sarcoma NOS		88003	24	68,8 (19-98)	5	20,8%	2	8,3%

	Breast cancer history (years)	OR	95 % CI	p	Other cancer history (years)	OR	95 % CI	p
Angiosarcoma	0-5	0.863	(0.009-78.552)	0.949	0-5	0.448	(0.005-38.618)	0.724
	5-10	166.697	(35.147-790.619)	0.000	5-10	0.000	(0.000-)	0.988
	>10	28.584	(7.711-105.954)	0.000	>10	3.279	(0.535-20.078)	0.199
Phyllodes benign	0-5	0.718	(0.093-5.523)	0.751	0-5	10.275	(1.408-74.952)	0.022
	5-10	2.377	(0.269-20.970)	0.436	5-10	2.959	(0.589-14.857)	0.589
	>10	0.000	(0.000-)	0.968	>10	0.988	(0.122-8.003)	0.991
Phyllodes borderline	0-5	0.000	(0.000-)	0.986	0-5	0.000	(0.000-)	0.985
	5-10	0.000	(0.000-)	0.990	5-10	1.180	(0.145-9.589)	0.877
	>10	1.292	(0.154-10.858)	0.813	>10	1.179	(0.145-9.595)	0.878
Phyllodes malignant	0-5	0.894	(0.206-3.875)	0.881	0-5	1.870	(0.618-5.657)	0.268
	5-10	0.947	(0.122-7.374)	0.959	5-10	1.575	(0.458-5.423)	0.471
	>10	0.905	(0.210-3.907)	0.894	>10	1.017	(0.358-2.894)	0.974
Other sarcoma	0-5	0.000	(0.000-)	0.991	0-5	0.852	(0.053-13.659)	0.910
	5-10	14.817	(0.603-364.199)	0.099	5-10	0.000	(0.000-)	0.987
	>10	6.398	(1.026-39.914)	0.047	>10	0.000	(0.000-)	0.988
Sarcoma NOS	0-5	4.451	(0.789-25.121)	0.091	0-5	0.000	(0.000-)	0.990
	5-10	11.118	(1.372-90.072)	0.024	5-10	0.000	(0.000-)	0.990
	>10	0.849	(0.063-11.422)	0.902	>10	2.348	(0.417-13.230)	0.333

Poster 277 #2756215

EFFICACY AND SAFETY OF PATIENTS TREATED LONG-TERM WITH TRABECTEDIN (T) ON THE EXPANDED ACCESS PROGRAM: A RETROSPECTIVE ANALYSIS

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Objective: Treatment of soft tissue sarcoma (STS) with long-term systemic therapy can be limited by cumulative toxicity. Treatment with T for prolonged courses without the cumulative toxicity has been previously described from clinical trials. Here we report the efficacy and safety for patients (pts) treated long term (≥6) months in a real world setting in the T Expanded Access Program from 2005-2010.

Methods: In this retrospective analysis of pts with pre–treated, relapsed/refractory STS of multiple histologies treated ≥6 mo with T (1.5 mg/m^2 iv q3wk), we compared pts treated 6-12 mo and >12 mo.

Results: Of 1853 pts, 401 (21.6%) remained on treatment ≥6 mos; 268 (14.5%) for 6-12 mo and 133 (7.2%) >12 mo. Demographics did not differ. Leiomyosarcoma or liposarcoma were the most common histologies. The mOS (mo) was 18.1 and 47.0, ORR was 7.8% and 6.8%, and clinical benefit rate (CR+PR+SD) (95%CI) was 47.4% (41.3;53.6) and 38.3% (30.1;47.2) in the 6-12 mo and >12 mo groups, respectively. The incidence of adverse events (AE)s and serious adverse events (SAE)s were similar in both groups (Table). The most common grade 3/4 AEs occurring in ≥5% were neutropenia, thrombocytopenia, anemia, ALT/AST increase, fatigue and nausea. A majority received dose reduction or delay; the primary reason for treatment discontinuation was disease progression. The longest observed duration of treatment was 55 mo (64 cycles; synovial sarcoma) and 54 mo (73 cycles; uterine leiomyosarcoma).

Conclusion: T can be safely administered and well tolerated in pts who receive a prolonged duration (≥ 6 mo) of therapy. Improved mOS may be achieved in pts who experience prolonged disease stabilization following T but adjustments in dose or schedule is frequently required.

Safety and Efficacy		
	6-12 Months (N=268)	>12 Months (N=133)
Median Treatment Duration (mo), range	8.4(6-12)	16.3 (12-55)
Treatment Response		
Complete response, n (%)	1 (0.4)	3 (2.3)
Partial response, n (%)	20 (7.5)	6 (4.5)
Stable disease, n (%)	106 (39.6)	42 (31.6)
Progressive disease, n (%)	20 (7.5)	12 (9.0)
Not available, n (%)	121 (45.1)	70 (52.6)
Treatment–emergent adverse events (TEAEs)	225 (84.0)	119 (89.5)
Serious TEAEs	88 (32.9)	47 (35.3)
Treatment discontinued	255 (95.1)	103 (77.4)
Due to disease progression	192 (71.6)	72 (54.1)
Due to adverse event	10 (3.7)	2 (1.5)
Patients with cycle delay	154 (57.5)	82 (61.7)
Patients with dose reduction	172 (64.2)	104 (78.2)

Poster 278 #2768809

SURGICAL MARGINS CORRELATE WITH LONG-TERM SURVIVAL (>10 YEARS) IN PATIENTS WITH PRIMARY PLEOMORPHIC LIPOSARCOMA

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Objective: Pleomorphic liposarcoma is an aggressive soft tissue sarcoma. Although surgery remains the only potentially curative therapy, there is ongoing debate about the significance of surgical margins on survival. Prior studies, including the largest to date (37 patients, median follow-up 38 months), have not shown a correlation between microscopic tumor after resection and overall survival. The aim of this study was to determine if surgical resection margins correlates with long-term survival.

Methods: From 1995 to 2015, 35 patients with pleomorphic liposarcoma were treated at the UCLA Sarcoma Program. The prospectively maintained UCLA Sarcoma Database was used to identify histologically-confirmed pleomorphic liposarcomas and long-term follow-up was

obtained. Clinical, pathologic and treatment variables were analyzed for survival. Overall survival (OS) was calculated from date of surgery to death or last follow-up.

Results: Median follow-up time for all patients was 8.52 years. The median survival for patients with an R0 resection was 10.14 years compared to 4.27 years for patients with an R1 resection (HR 2.95, CI 1.04 to 8.35) (Figure 1). Median age was 63 years (range 26-90 years). Tumor location included: 69% extremity (lower 43%, upper 26%), trunk (20%), and retroperitoneum (11%). Median tumor size was 10 cm (range 1.5 to 25 cm). Tumors greater than 10 cm were associated with poor prognosis (HR 5.12, CI 1.684-15.58) and patients treated with chemotherapy did not demonstrate improved survival (HR 1.97, CI 0.59-6.54).

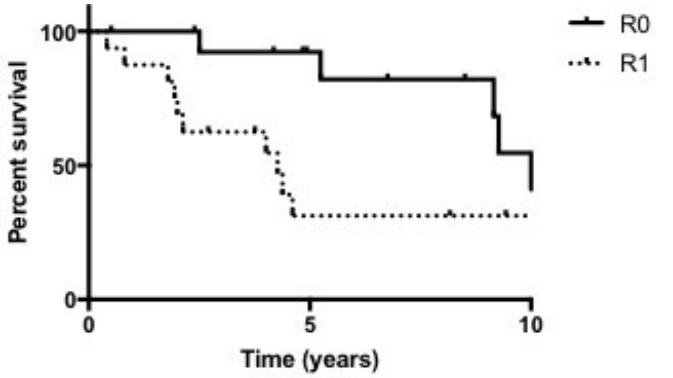

Figure 1. Patient survival stratified by surgical margins (R0 vs. R1) of primary tumor in patients with pleomorphic liposarcoma (Gehan-Breslow-Wilcoxon test p value = 0.0079; HR 2.95, CI 1.04 to 8.35)

Conclusion: Negative surgical margins correlate with improved long-term (>10 year) survival in patients with primary pleomorphic liposarcoma. This underscores the importance proper sarcoma surgery in the setting of the primary disease in this rare histologic subtype.

Poster 279 #2772598

PREDICTORS OF POST-PROGRESSION SURVIVAL AMONG PATIENTS WITH ADVANCED OR RECURRENT SOFT TISSUE SARCOMA THAT IS REFRACTORY TO FIRST-LINE DOXORUBICIN

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Objective: Doxorubicin (DXR) monotherapy is a standard, albeit low-efficacy, treatment for metastatic or recurrent soft tissue sarcoma (STS). Treatment options are limited in cases that are refractory to DXR therapy, and the efficacies of novel anticancer agents (e.g., pazopanib, eribulin, and trabectedin) are dependent on the STS pathological subtype. There are few non-histological predictors of post-progression survival among patients with STS. This study aimed to identify predictors of survival among patients with STS that was resistant to first-line DXR therapy.

Methods: We retrospectively examined data from patients with STS who had received first-line DXR treatment at our hospital between January 2010 and June 2016. Associations of chemotherapy efficacy and survival with patient characteristics and radiological findings were evaluated. Computed tomography was used to evaluate radiological disease progression (PD) during or after DXR treatment based on the Response Evaluation Criteria in Solid Tumors version 1.1. Post-progression survival was defined as the time from PD during or after DXR treatment to death.

Results: Among 255 patients with sarcoma, 57 patients with STS received first-line DXR treatment. Seven patients (12%) responded to treatment and 32 patients (58%) achieved disease control. Fifty-five patients exhibited radiologically confirmed PD during or after DXR treatment (Table). The PD patterns were progression without new lesions (33 patients) or the appearance of new lesions (22 patients). New metastatic lesions were observed in the lungs (13 patients), liver (5 patients), bone (3 patients), and muscle (1 patient). After failure of the DXR monotherapy, 35 patients received subsequent chemotherapy, including investigational agents, and 20 patients received best supportive care. The median overall and post-progression survivals were 26.9 months and 13.1 months, respectively. Post-progression survival was significantly shorter in patients with a performance status of ≥ 2 at the PD (1.4 months vs. 11.3 months, $p < 0.0001$) or with new lung metastasis (6.8 months vs. 11.8 months, $p = 0.01$). In multivariate analysis, these factors were independently associated with poor post-progression survival (hazard ratio: 7.91, $p = 0.05$; hazard ratio: 2.33, $p = 0.05$, respectively).

Conclusion: Among patients with STS who were refractory to DXR treatment, poor performance status and new lung metastasis were associated with shorter post-progression survival.

Patient characteristics	
	n=55
Age	53 (17-75)
Sex Male/Female	21/34
ECOG PS at PD	---
0	24
1	20
2	7
3	3
4	1
Histological type of STS	---
Leiomyosarcoma	20
Liposarcoma	14
Others	21
Site of primary disease	---
Abdomen	27
Thorax	9
Uterus	9
Others	10
Prior surgery Yes/None	42/13
Response to DXR PR/SD/PD	7/25/23
Pattern of PD	---
Progression of TLs/NTLs	33
Appearance of new lesions	22
Subsequent treatment	---
Dacarbazine	10
Pazopanib	7
Eribulin	6
Investigational agents	6
Others	6
Best supportive care	20

ECOG, Eastern Cooperative Oncology Group; PS, performance status; PD, progression disease; PR, partial response; SD, stable disease; TL, target lesion; NTL, non-target lesion. * Abdomen includes intra-abdominal, pelvic and retroperitoneal sites.

Poster 280 #2778996

AN OPEN-LABEL PHASE 1B, AND A RANDOMIZED, DOUBLE-BLIND PHASE 2 STUDY OF OLARATUMAB WITH GEMCITABINE PLUS DOCETAXEL IN THE TREATMENT OF PATIENTS WITH ADVANCED SOFT TISSUE SARCOMA (STS)

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Objective: While doxorubicin alone or in combination has been the mainstay of treatment for metastatic STS for decades, more recently gemcitabine plus docetaxel has shown efficacy. In a randomized phase 2 study (NCT01185964), olaratumab, a platelet-derived growth factor receptor alpha (PDGFR α) antibody, in combination with doxorubicin demonstrated a significant improvement of overall survival over doxorubicin alone in patients with advanced STS. Since some patients may not be appropriate candidates for doxorubicin-based regimens, or have received prior anthracycline treatment, we are exploring the efficacy and safety of olaratumab with gemcitabine plus docetaxel in patients with advanced STS.

Methods: ANNOUNCE 2 (NCT02659020) is a multicenter global phase 1b/2 study of olaratumab in combination with gemcitabine and docetaxel in patients with advanced or metastatic STS (age ≥16 years; ECOG 0-1; not amenable to curative treatment with surgery or radiotherapy; ≤2 prior lines of systemic therapy for advanced or metastatic disease, and have not received gemcitabine, docetaxel or olaratumab). Phase 1b consists of an open-label, single-arm, dose-escalation assessment of the safety and tolerability of olaratumab administered on days 1 and 8 at 15 mg/kg (Cohort 1) or 20 mg/kg (Cohort 2) with gemcitabine (900 mg/m2 Days 1 and 8) and docetaxel (75 mg/m2 Day 8) on a 21-day cycle. The primary objective is to determine the phase 2 dose of olaratumab with gemcitabine and docetaxel. Secondary objectives include safety, toxicity, pharmacokinetics, and immunogenicity of olaratumab in combination with gemcitabine and docetaxel. The randomized, double-blind, placebo-controlled phase 2 study will begin after the optimal dose of olaratumab has been determined. Patients will be randomized 1:1 to olaratumab plus gemcitabine and docetaxel or placebo plus gemcitabine and docetaxel with overall survival as the primary objective. Key secondary objectives include PFS, safety, PK, immunogenicity and patient reported outcomes. The study began in March 2016; planned enrollment for the 1b phase is approximately 50 patients.

Results: NA

Conclusion: NA

Poster 281 #2782565

EFFICACY OF TREATMENT IN PATIENTS WITH METASTASISED SOFT TISSUE SARCOMA.

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Objective: Patients with metastasised soft tissue sarcoma (STS) have a relatively poor prognosis. Therapeutic management may include chemotherapy (CTX), radiotherapy (RTX), surgery or a combination of these modalities.

Methods: Eighty-nine patients with metastatic disease, originally treated for localised G2/3 STS (G2: n=20, G3: n=69) between 1998 and 2016 at one institution were retrospectively included (m: 57, f: 38; mean age: 63 years). Demographic, tumour and treatment-related parameters were assessed (e.g. histology, ECOG performance status, albumin levels).
Kaplan-Meier survivorship curves and Cox-regression models were used to estimate overall survival (OS) and post-metastasis survival (PMS).

Results: Metastases developed after a median of 11.5 months (IQR: 4 months – 1.7 years). Median PMS was 1.1 years. 62 patients had lung metastases (69.7%), followed by soft tissue/lymph nodes in 16 patients (18.0%), four bone metastases (4.5%), three skip lesions (3.4%) and three abdominal metastases (3.4%). Singular metastasis was present in 37 patients (41.6%) and multiple metastases in 52 (58.4%).

Administration of postoperative RTX to the primary operation field was the only independent factor delaying time to onset of metastasis, irrespective of age, gender, tumour size and grade, use of adjuvant CTX and resection margin status (hazard ratio [HR]: 0.442; 95% confidence interval [CI]: 0.212-0.923, p=0.03). Two- and 5-year PMS was 39.8% and 22.5%, with 14 patients surviving > 4 years with metastatic disease. Resection of metastasis was the only independent factor significantly associated with an improved PMS, irrespective of age, gender, time to onset of 1st metastasis, ECOG performance status, number of metastases and haemoglobin- and albumin-levels at time of diagnosis (HR: 0.102, 95%CI: 0.019-0.539, p=0.007).

Conclusion: The treatment of STS-patients with metastatic disease is complex and should be tailored individually to each patient. Resection of metastases seems to prolong post-metastasis survival, irrespective of the time to onset of as well as number of metastases, the patient's general condition (reflected by ECOG performance status, albumin- and haemoglobin-levels), age and gender. Risks and benefits have to be weighed carefully against each other. However, a more aggressive therapeutic approach may control the disease for a reasonable time period.

Poster 282 #2782906

ATYPICAL LIPOMATOUS TUMORS OF THE EXTREMITIES: DOES OUR INCONSISTENT TERMINOLOGY HAVE PATIENT REPERCUSSIONS?

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Objective: Review all prior literature related to Atypical Lipomatous Tumors (ALTs) to assess local recurrence and metastasis risk using a well-powered composite sample size. Findings are intended to assess a local and remote recurrence rate for ALTs, identify risks factors for dedifferentiation, and confirm its lack of metastatic potential.

Methods: A systematic review was conducted following the guidelines published by the Cochrane Handbook and PRISMA. An electronic database search was performed for studies that report on the local recurrence rate and metastasis after ALT of the extremity in living human subjects. Data extracted from the studies included demographic variables. site and type of tumor, type of excision performed, local recurrence, timing of recurrence, incidence and location of metastases, incidence of dedifferentiation, and length of follow-up. Comparison of local recurrence rates after marginal and wide excisions was performed using an Odds Ratio, with $p < .05$ defined as significant. All values are expressed as mean ± standard deviation.

Results: Of 16 studies that included patients diagnosed with ALT, nine included ALT of the extremity (Table 1, 2). Regardless of mode of excision (marginal vs. wide), no metastatic disease was observed. Overall local recurrence rate was 15.1%. Local recurrence was more common after a marginal excision (Odds Ratio 9.98, 95% CI 2 to 50.9). Dedifferentiation was only noted after marginal excision, all within recurrent disease. Overall rate of dedifferentiation was 2.0% after all incidences of ALT, but 13.3% among all patients with recurrent disease. Dedifferentiation was more likely in patients with multiple local recurrences, with an average of 2.5 ± 1.4 recurrences noted prior to the histologic detection of dedifferentiation.

Conclusion: Based upon the findings of this meta-analysis, we make the following recommendations regarding the management of ALTs, based on both anatomy and prognosis:

1. The term "atypical lipomatous tumor" should be used for all extremity lesions meeting these histopathologic criteria, with "well differentiated" or "low grade" liposarcoma being reserved for retroperitoneal lesions.
2. Marginal excision is acceptable for ALTs.
3. Recurrent ALTs should be treated as having more aggressive biology, and consideration of a wide margin should be given as these lesions have a risk of further recurrence, dedifferentiation, and/or metastasis.
4. Lesions managed expectantly should be radiographically monitored for evidence of progression.

Involved Studies and Cited ALT Recurrence, Dedifferentiation and Metastasis Rate

Authors	Year Study Published	Country of Origin	# Patients	Marginal Excision	Wide Excision	Local Recurrence	Dedifferentiation	Metastasis	Mean Follow-Up Period (Years)
Chang et al.	2016	Taiwan	41	10	31	17.8% (7/41)	0	0%	7.0
Errani et al.	2016	Greece	43	43	0	13.9% (6/43)	1	0%	4.3
Kalimuthu et al.	2015	United Kingdom	88	88	0	8.9% (8/90)	1	0%	9.3
Kito et al.	2015	Japan	41	30	11	17.1% (7/41)	1	0%	8
Mavrogenis et al.	2011	Italy	44	36	8	10.6% (5/47)	1	0%	6.8
Mussi et al.	2014	Italy	151	151	0	9.4% (16/171)	0	0%	4.2
Rozental et al.	2001	USA	29	29	0	51.6% (16/31)	4	0%	7
Sommerville et al.	2005	United Kingdom	61	61	0	8.2% (5/61)	0	0%	4.2
Weiss et al.	1992	USA	46	46	0	43.5% (20/46)	3	0%	9

Composite ALT Management and Outcomes

Total Number of Patients	544
Marginal Excision	494
Wide Excision	50
Local Recurrence Rate	83 / 544 (15.3%)
Dedifferentiation	11 / 544 (2.0%)
Metastasis	0 / 544 (0%)
Follow-Up Period (Years)	6.6 ± 2.0

Poster 283 #2783404

SAFETY AND EFFICACY OF PAZOPANIB IN THE TREATMENT OF PATIENTS WITH ADVANCED SOFT TISSUE SARCOMAS- REAL LIFE DATA

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Objective: Pazopanib is a multikinase inhibitor registered for treatment of patients diagnosed with metastatic/locally advanced soft tissue sarcomas (STS). Clinical trials showed prolongation of progression free survival (PFS) compared to placebo, when used after failure of multiple previous lines of systemic treatment. The aim of the study was to assess the outcomes of STS patients treated with pazopanib in routine practice in reference sarcoma center.

Methods: From November 2012 to August 2016 102 patients have been treated with pazopanib at initial dose 800mg/day. Histological subtypes were: 28% – synovial sarcoma, 25%-pleomorphic sarcoma, 22% - leiomyosarcoma, 25%- other subtypes. Median age at treatment start was 44.5 years (range 18-87). All, but 4, patients received previously chemotherapy based on doxorubicin. The majority of patient received pazopanib as 3rd or 4th line of therapy (65%). In 57% metastatic disease was limited to the lungs only, Responses to treatment were assessed according to RECIST 1.1 criteria every three months.

Results: 11 patients (11%) had partial response to therapy, in 45 (45%) the disease was stable as the best response, and 44% cases had progressive disease at first assessment. Median PFS was 4 months. Median overall survival was 8 months. Median OS calculated from the diagnosis of metastatic disease was 30 months. In multivariable analyses factors having significant impact on PFS were age and neutrophil to lymphocyte count (as continuous variable). In multivariable analyses factors having negative impact on OS were hemoglobin level, neutrophil to lymphocyte count (as continuous variable) and male gender. The treatment was rather well tolerated. 50 patients (49%) had any treatment toxicity - usually it was grade 1 or 2 toxicity, that did not require an dose reductions. In 22 patients the drug dose was reduced because of toxicity. None of the patient had permanently stopped the treatment because of adverse events. There were also cases of rare adverse events of pazopanib such as pneumothorax, TIA or decreased left ventricular ejection fraction.

Conclusion: Our analyses confirmed efficacy and safety of pazopanib in a large group of STS patients treated outside clinical trials after failure of previous lines of therapy.

Poster 284 #2786869

FIFTY SHADES OF YELLOW: NOT ALL WELL DIFFERENTIATED LIPOSARCOMA (WDLPS) ARE CREATED EQUAL - THE CLINICAL BEHAVIOR OF WDLPS CAN BE EXTREMELY VARIABLE

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Objective: The pathogenesis of well differentiated liposarcoma (WDLPS) is poorly understood and pathologic characterization is often challenging. “Qualifying” terms are frequently included in the pathologic description of WDLPS and include terms such as adipocytic/lipoma-like, sclerosing, inflammatory, and spindle cell. Pathologic interpretation may be difficult when fibrous or myxoid areas with increased cellularity or an increased mitotic rate is present. The clinical implication of such pathologic qualifiers on patient outcome is unknown.

Methods: Patients with primary WDLPS of the retroperitoneum who underwent surgical resection at our institution between May 1996 and December 2011 were identified. Pathology reports of primary surgical resection specimens were reviewed and descriptive qualifiers to the final pathologic WDLPS diagnosis were noted.

Results: We identified 62 patients with primary WDLPS of the retroperitoneum. Descriptive qualifiers added to the pathologic diagnosis were associated with 36 cases (58%) (Figure). There were no differences in median age at diagnosis, gender, ethnicity, or surgical resection margin status between cases of WDLPS with and without associated pathologic qualifiers (Table). However, WDLPS with pathologic qualifiers were more likely to be larger (median size 32 vs 25.5cm, p=0.01) and multifocal (13 vs 7.7%, p=0.03) at diagnosis, require organ resection at time of surgery (50 vs 23.1%, p=0.01), and have higher incidence of local and distant recurrence (LR 83.3 vs 38.5%, p<0.01; DR 13.9 vs 0%, p=0.05). There was a trend towards shorter recurrence-free survival (RFS) and overall survival (OS) among patients with WDLPS associated with pathologic qualifiers (median RFS 1.6 vs 3.4 yrs, p=0.09; 5-yr RFS 10 vs 50%;

Pathologic qualifiers associated with the diagnosis of well differentiated liposarcoma at primary presentation

Pathologic qualifier	Number of cases with qualifier on pathologic evaluation (% of cases with any pathologic qualifier)
No pathologic qualifier	26
Any pathologic qualifier*	36
Focal areas of increased cellularity	12 (33.3%)
Necrosis	12 (33.3%)
Myxoid background	9 (25%)
Hyalinization, fibrosis, sclerotic pattern	7 (19.4%)
Focal area of dedifferentiation, incipient dedifferentiation	4 (11.1%)
Increased mitotic activity	2 (5.5%)
Inflammation	2 (5.5%)
Hemorrhage	2 (5.5%)
Spindle cells exhibiting fibro-histiocytic features	1 (2.7%)
Marked cytologic atypia of adipocytes	1 (2.7%)
Increased pleomorphism	1 (2.7%)
Bizarre cells	1 (2.7%)

*Some cases may have had more than one pathologic qualifier

Clinicopathologic characteristics and outcomes of patients with well differentiated liposarcoma at primary presentation

	Total (n=62)	Without pathologic qualifier (n=26)	With pathologic qualifier (n=36)	p value
Median age at diagnosis, yrs (range)	56.5 (32-80)	57 (39-80)	54 (32-76)	0.30
Age >55				
No Yes	29 (46.8%) 33 (53.2%)	11 (42.3%) 15 (57.5%)	18 (50%) 18 (50%)	0.56
Gender				
Male Female	35 (56.5%) 37 (43.5%)	15 (57.7%) 11 (42.3%)	20 (55.6%) 16 (44.4%)	0.80
Ethnicity				
White Hispanic African-American Other	49 (79%) 9 (14.5%) 3 (4.8%) 1 (1.6%)	20 (76.9%) 4 (15.4%) 1 (3.8%) 1 (3.8%)	29 (80.6%) 5 (13.9%) 2 (5.6%) 0 (0%)	0.69
Median tumor size, cm (range)	30 (8.5-100)	25.5 (9-100)	32 (8.5-78)	***0.01***
Tumor size >30cm				
No Yes	25 (40.3%) 37 (59.7%)	15 (57.7%) 11 (42.3%)	10 (27.8%) 26 (72.2%)	***0.02***
Surgical resection margins				
R0 R1 R2 Missing	10 (16.1%) 7 (11.3%) 5 (8.1%) 40 (62.5%)	8 (30.8%) 5 (19.2%) 2 (7.7%) 11 (42.3%)	2 (5.6%) 2 (5.6%) 3 (8.3%) 29 (80.5%)	0.32
Organ resection at time of primary tumor resection				
No Yes	38 (61.3%) 24 (38.7%)	20 (76.9%) 6 (23.1%)	18 (50%) 18 (50%)	***0.03***
Multifocal disease				
No Yes	47 (75.8%) 15 (24.2%)	24 (92.3%) 2 (7.7%)	23 (63.9%) 13 (36.1%)	***0.01***
Local recurrence				
No Yes Progression (R2 resection)	17 (27.4%) 40 (64.5%) 5 (8.1%)	15 (57.7%) 10 (38.5%) 1 (3.8%)	2 (5.6%) 30 (83.3%) 4 (11.1%)	***<0.01***
Distant recurrence				
No Yes Missing	53 (85.5%) 5 (8.1%) 4 (6.5%)	24 (92.3%) 0 (0%) 2 (7.7%)	29 (80.6%) 5 (13.9%) 2 (5.6%)	***0.05***
Histology on first recurrence				
WDLPS DDLPS Missing	23 (57.5%) 10 (25%) 7 (17.5%)	7 (53.8%) 3 (23.1%) 3 (23.1%)	16 (59.2%) 7 (25.9%) 4 (14.8%)	0.98
Last known status				
Alive Deceased	37 (59.7%) 25 (40.3%)	17 (65.4%) 9 (34.6%)	20 (55.6%) 16 (44.5%)	0.87

DDLPS: dedifferentiated liposarcoma; DRFS: distant recurrence-free survival; OS: overall survival; RFS: recurrence-free survival; R0: complete gross resection with negative margins; R1: complete gross resection with positive margins; R2: incomplete gross resection; WDLPS: well differentiated liposarcoma

Conclusion: WDLPS tumors characterized by pathologic qualifiers appear to behave more aggressively than their more typical WDLPS counterparts and may be associated with worse RFS and OS. There is a need for identification of better pathologic characteristics of WDLPS for reporting in order to provide more personalized treatment and potentially impact patient outcome.

Poster 285 #2787583

SOFT TISSUE SARCOMA OF THE EXTREMITY: DEFINING DELAY IN DIAGNOSIS

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Objective: The aim of this study was to investigate how duration of delay in diagnosis was related to survival.

Methods: Patients treated for extremity soft tissue sarcomas between 2006 and 2015 at a comprehensive cancer center were stratified based on various definitions of delay in diagnosis: at least two, six and twelve months between symptom onset and diagnosis. Descriptive statistics, bivariate and survival analyses were performed.

Results: The study population included 112 individuals. The median age was 55.5 (range 19-94) years. The median delay in diagnosis was 3 (range 0-168) months. When delay was defined as either at least six or twelve months, patients who experienced a delay were significantly more likely to have lower grade tumors ($p<0.001$, $p=0.01$, respectively) and lower stage disease ($p<0.001$, $p=0.02$, respectively) than those who did not experience a delay. Similarly, when stratified by number of months between symptom onset and diagnosis, those who experienced the greatest delay were more likely to have tumors less than 5 cm in size ($p=0.02$), grade 1 tumors ($p<0.01$), and stage I disease ($p<0.01$) than patients who experienced no delay. However, regardless of how delay was defined, survival was no worse for patients who experienced a delay compared to those who did not.

Hazard ratios for risk of death based on various definitions of delay in diagnosis

Definition of Delay	Unadjusted Risk of Death, Unadjusted Hazard Ratio (95% CI)	Adjusted Risk of Death, Adjusted* Hazard Ratio (95% CI)
No Delay	Reference	Reference
≥ 2 months	0.468 (0.180 - 1.215)	0.072 (0.008 - 0.689)
≥ 6 months	0.495 (0.174 - 1.406)	0.452 (0.067 - 3.058)
≥ 12 months	0.720 (0.207 - 2.507)	1.053 (0.113 - 9.785)

*Adjusted for age, sex, race, grade, stage, tumor size, and initial treatment type

Conclusion: Patients who tolerate a delay in diagnosis have less severe disease, which appears to permit equivalent outcomes. Reasons for diagnostic delay should be addressed in an effort to further improve outcomes.

Poster 286 #2790067

RETROSPECTIVE REVIEW OF OLARATUMAB AND DOXORUBICIN (OD) VERSUS DOXORUBICIN, IFOSFAMIDE AND MESNA (AIM) FOR TREATMENT OF SOFT TISSUE SARCOMA (STS)

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Objective: Olaratumab and doxorubicin (OD) has recently been approved for first-line treatment of advanced STS based on reported survival benefit (SB) over doxorubicin monotherapy (DOX; Tap et al., 2016). No improvement in response rate (RR) was reported for OD, although absolute RR was higher. A prior study of Judson et al. (2014) demonstrated increased RR, but no SB for administration of DOX, ifosfamide and mesna (AIM) therapy vs DOX. Here, we seek to compare the outcomes and toxicity of patients with advanced STS when treated with OD vs AIM.

Methods: Retrospective single-center analysis of OD vs AIM for advanced STS during 2012-2017. Criteria for inclusion: age ≥18, unresectable STS treated with palliative intent. Baseline clinico-pathologic, treatment, and outcomes parameters were abstracted. Study endpoints included clinician-reported best tumor RR (based on radiographic imaging or clinical notes at treatment conclusion), progression-free survival (PFS; time to clinician-reported progression, date of last follow-up (FU) or death, whichever first) and overall survival (OS; time from treatment start to death from any cause). Toxicities were assessed by review of clinical observations and laboratory parameters and graded according to CTCAE 4.0. Proportions were compared by Fischer's exact test. Kaplan-Meier and log-rank were used to assess survival outcomes.

Results: We identified 13 patients receiving OD and 17 receiving AIM. Median FU was 4.3 m OD (range 2.8-6.2 m) vs 12.5 m AIM (range 1.9-42.5 m). AIM patients were more likely to receive this therapy first-line (16/17 vs. 6/13; $p<0.02$); otherwise groups were comparable (age, gender, race, ECOG, histologic subtype). RR was similar (41% AIM vs 46% OD). Neither PFS nor OS were statistically different (log-rank $p=0.14$ and $p=0.69$, respectively). Median PFS was 1.7 m (95% CI 1.3-not reached/NR) for OD vs NR (95% CI 1.5-NR) for AIM. Median OS was NR for OD vs 23.1 m (95% CI 13.4-NR) for AIM. More neurotoxicity, renal toxicity, cardiac toxicity, anemia and thrombocytopenia occurred with AIM. Grade 3-4 neutropenia was more frequent for OD, however febrile neutropenia similar.

Conclusion: Treatment with OD in advanced STS demonstrated decreased toxicity vs AIM. We were unable to identify clear differences in efficacy between therapies, based on analyses of RR, PFS and OS. Our relatively small sample size and, for OD patients, short FU duration prevent definitive conclusions from this dataset. Updated results, with extended FU, will be presented.

Poster 287 #2791466

A RETROSPECTIVE STUDY OF PRIMARY CARDIAC SARCOMAS

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Objective: Primary cardiac sarcoma(PCS) is rare and has poor prognosis. There is no established optimal treatment. The objective of this study is to review treatment outcome and to find prognostic factors in patients with PCS.

Methods: We retrospectively reviewed 41 consecutive patients diagnosed with PCS in two tertiary medical centers in Korea,between 1996 and 2013. Survivals were estimated according to Kaplan-Meiere method and were compared using Log-rank test.

Results: Median age was 44 years. Eighteen patients(43.9%) were male. Angiosarcoma was most prevalent (N=20, 48.7%), followed by poorly-differentiated sarcoma (N=7, 17.1%) and others (N=14, 34.1%). Most tumors were located in atriums (N=27, 65.9%). Thirty-one patients (75.6%) had localized disease at diagnosis. Twenty-eight (68.3%) patients received resection of cardial tumor and microscopic complete resection were achieved in 12 localized cases. Median overall survival(OS) of entire cohort was 13.2 months. Median OS of who received complete resection (n=12) was 17.0 months , was 17.9 months after incomplete resection (n=16), and was 5.7 months in patients who did not undergo surgical resection. Among patients who received surgery, adjuvant chemotherapy and/or radiotherapy after surgery was associated with better overall survival (median 21.6 months vs. 11.0 months, p = 0.007).

Conclusion: Primary tumor resection and adjuvant multidisciplinary approach were associated with better survival in patients with cardiac primary sarcoma.

Poster 288 #2791508

ON THE BIOLOGICAL CONSEQUENCE AND PROGNOSTIC RELEVANCE OF PERIPHERAL BLOOD NEUTROPHIL-TO-LYMPHOCYTE RATIO IN METASTATIC SOFT TISSUE SARCOMA

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Objective: Alterations in host inflammatory responses may drive cancer development and metastatic progression. Recently, we have shown that elevated blood neutrophil-to-lymphocyte ratio (NLR) is an independent marker of poor prognosis in localized soft tissue sarcoma (STS). The current study aims to investigate its biological significance and clinical relevance in patients with metastatic STS.

Methods: Seven hundred and twelve patients with STS who had available blood counts at the time of diagnosis and/or metastatic relapse were retrospectively examined. An optimal cutoff for high NLR (> 5.0) in predicting overall survival (OS) in patients with metastatic STS (n=390) was determined using receiver operating curve analyses. Survival analysis was performed using the Kaplan-Meier method and multivariate Cox proportional models.

Results: Median NLR for patients with metastatic STS was significantly higher compared to those without metastasis (3.93 vs 2.84 respectively, Mann-Whitney p<0.0001). This phenomenon was related to concomitant elevation of neutrophils (5.72 vs 4.66 respectively, p<0.0001) and decline in lymphocyte counts (1.48 vs 1.66 respectively, p=0.0007). Amongst metastatic STS, median NLR was significantly higher in de novo (n=183) compared to relapsed (n=207) cases (4.36 vs 3.70 respectively, p=0.0266), as well as in males compared to females (4.40 vs 3.73 respectively, p=0.0243). Correspondingly, 147 patients with metastatic disease (38%) demonstrated high NLR by cutoff >5.0, which was independently associated with male sex (p=0.0024) and de novo metastasis (p=0.0168), but not with age or tumor grade. High NLR was associated with worse OS (HR 2.26; 95% CI 1.75-2.93; logrank p<0.0001), as were advanced age at diagnosis, high tumor grade, male sex and de novo metastasis. In multivariate analysis, only NLR, in addition to age, were independently associated with worse OS (HR 2.44; 95% CI 1.91-3.13; Cox regression p<0.0001).

Conclusion: The NLR is correlated with distinct biological stages of STS. High NLR is an independent marker of poor prognosis among patients with metastatic STS.

Poster 289 #2797425

TREATMENT AND PROGNOSIS OF DESMOID TUMORS: A SINGLE INSTITUTIONAL EXPERIENCE OF 189 PATIENTS

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Objective: Desmoid tumors (DTs) are locally infiltrating soft-tissue neoplasm that grow slowly and arise from musculoaponeurotic stromal elements. DTs usually occurs sporadically but 5~10% of them are associated with familial adenomatous polyposis (FAP). Because of rarity of DTs, there are relatively few data on its epidemiology and long term outcomes.

Methods: We analyzed the data of 189 patients who were diagnosed as DT from October 1992 to August 2015 using Asan Medical Center Sarcoma Registry. Clinicopathologic features and treatment related data were analyzed to identify predictive factor for recurrence.

Results: A total of 189 patients were included for the analysis. The median age of patients was 39 years old (range, 0-96) and 108 patients (57.1%) were female. Familial history of FAP was present in 13 patients (6.8%). The most common primary tumor site was abdominal wall (38.1%), followed by the abdominal cavity (34.9%), retroperitoneum (15.8%) and extremities (5.3%). The median tumor size was 5.0 cm (range, 0.5-25.0 cm). Among 177 patients who underwent treatments, 165 patients (93.2%) received surgery, 11 patients received systemic therapy and one patient underwent radiotherapy for the 1st line treatment. Majority of patients who underwent surgery, had R0, R1 surgical margin (46.1%, 44.8%, respectively). With a median follow-up of 29.7 months, 15 patients (7.9%) showed recurrence after surgery within a median time interval of 15.5 months. In univariate analysis, sex, age, tumor size, tumor location, and surgical margin had no significant impact on recurrence. Out of 15 patients with recurrence, 3 patients had familial history of FAP. When patients were divided into 3 groups according to primary site: abdominal wall, intraabdominal, extraabdominal group, the number of patients with recurrent disease were 5, 4, and 6 (7.0%, 6.0% and 11.8% respectively). Of the 6 recurrent cases in which the primary site was located in the extraabdominal region, 3 patients showed 2nd recurrence, and they underwent resection. Two of 3 patients with 2nd recurrence had 3rd recurrence.

Conclusion: Recurrence remains a problem following surgery of DTs. In the patients with extraabdominal site DTs, the recurrence rate tends to be higher. These patients may recur again even after curative surgical resection, therefore careful follow up is required.

Poster 290 #2798134

USE OF MINIMALLY INVASIVE SURGERY AMONG PATIENTS UNDERGOING PRIMARY RESECTION FOR RETROPERITONEAL SOFT TISSUE SARCOMA

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Objective: The current study sought to describe patterns of minimally invasive surgery (MIS) use and assess the association between MIS and clinical outcomes among patients undergoing surgery for retroperitoneal soft tissue sarcoma (RPS).

Methods: Patients undergoing a primary resection for RPS between 2010 and 2014 were identified using the National Cancer Database. Multivariable logistic and Cox proportional hazards models were used to assess the association between use of MIS and clinical outcomes. Sensitivity analysis was performed using propensity-score matching (PSM) to minimize bias and evaluate the relationship between a MIS approach and clinical outcomes.

Results: A total of 3,185 patients were identified who met inclusion criteria; 89.5% (n=2,850) patients underwent an open surgery, while 10.5% (n=335) underwent MIS. Patients undergoing MIS were more likely to present with smaller tumors (open vs. MIS: median tumor size: 16.8 cm [IQR: 10.0-26.0] vs. 10.0 cm [IQR: 6.1-17.5]), a primary diagnosis of leiomyosarcoma (23.2% vs. 27.2%), and undergo surgery at community hospitals (28.0% vs. 36.4%, all $p<0.05$). Although patients undergoing MIS demonstrated a shorter length-of-stay (LOS: 6 days [IQR: 5-9] vs. 4 days [IQR: 2-7], $p<0.001$), use of MIS was not associated with 30-day readmission, or mortality within 30 or 90 days of surgery (all $p>0.05$). The 1-, 3- and 5-year overall survival (OS) were 87.5% (95%CI: 86.1%-88.7%), 71.5% (95%CI: 69.5%-73.4%), and 57.3% (95%CI: 54.0%-60.4%), respectively; no differences were observed in OS by the operative approach (p=0.102). Rather, patient and tumor-specific characteristics including patient age (hazard ratio [HR]=1.03, 95%CI: 1.02-1.04), Charlson comorbidity score (HR=2.31, 95%CI: 1.58-3.39), tumor size (>20cm vs. ≤10cm: HR=1.58, 95%CI: 1.19-2.11), tumor grade (G3 vs. G1: HR=3.11, 95%CI: 1.99-4.87), tumor stage (stage IV vs. stage I: HR=4.29, 95%CI: 2.57-7.16) and positive surgical margins (HR=1.36, 95%CI: 1.09-1.63) were associated with OS (all $p<0.05$). A similar pattern in clinical outcomes was observed after use of PSM (Figures 1 and 2).

Conclusion: Utilization of MIS for the management of RPS was observed to increase and was not associated with adverse postoperative clinical outcomes. While MIS may be safe among select patients with favorable preoperative disease characteristics, randomized clinical trials are required to assess the efficacy and safety of MIS in the management of RPS.

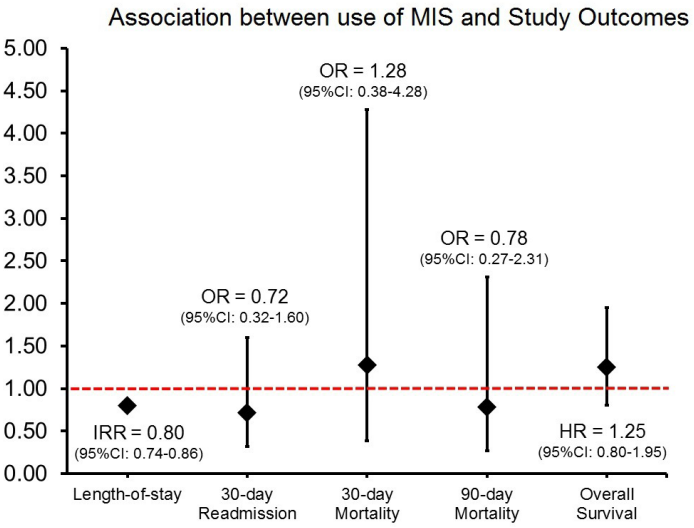

Figure 1: Comparison of postoperative length-of-stay (LOS), 30-day unplanned readmission, 30-day mortality, 90-day mortality and overall survival by operative approach after the use of propensity-score matching. The final matched cohort consisted of 424 patients (212 who underwent an open resection, and 212 patients who underwent MIS). IRR: incidence risk ratio, OR: odds ratio, HR: hazard ratio. Variables used in the propensity score matching algorithm included patient race, patient income quartile, type of hospital where the primary resection was performed, size of the primary tumor, tumor histology, tumor grade and tumor stage at presentation.

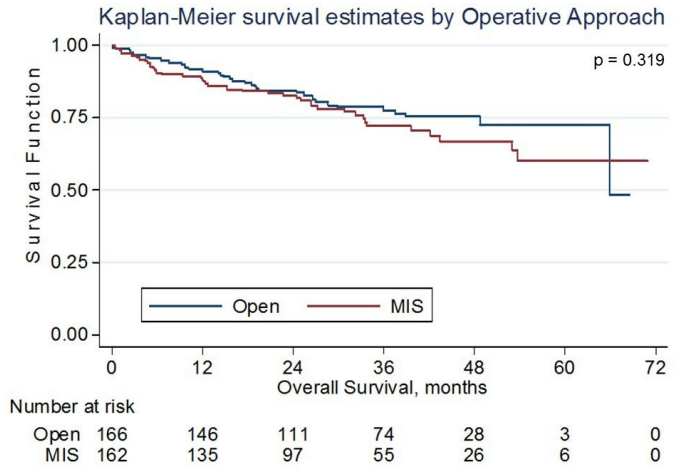

Figure 2: Overall survival by operative approach after the use of propensity-score matching. The final matched cohort consisted of 424 patients (212 who underwent an open resection, and 212 patients who underwent MIS). Variables used in the propensity score matching algorithm included patient race, patient income quartile, type of hospital where the primary resection was performed, size of the primary tumor, tumor histology, tumor grade and tumor stage at presentation.

Poster 291 #2800221

DOES ADJUVANT RADIOTHERAPY MAKE A DIFFERENCE IN EXTRA-UTERINE LEIOMYOSARCOMAS WITH R1 RESECTIONS?

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Objective: Leiomyosarcoma (LMS) are mesenchymal tumours of smooth muscle origin, and make up 25% of soft tissue sarcomas. LMS are generally are divided into uterine or extra-uterine origin, the latter including the retroperitoneum, upper and lower limbs, and gastrointestinal organs. The ideal treatment for localized extra-uterine LMS is complete surgical resection with clear margins. However, surgery is often challenging as the tumour may be densely adherent to major structures such as the inferior vena cava and the abdominal aorta. Adjuvant radiotherapy (RT) would then be given for local control. Here, we review our institutions data on extra-uterine LMS, reviewing the site, treatment, and disease free survival with and without adjuvant RT.

Methods: A retrospective review of prospectively collected data at the National Cancer Centre Singapore (NCCS) between November 1997 and April 2016 was performed. Only patients with non-metastatic extra-uterine LMS who underwent resection at our institution were included. Disease factors and survival data was analysed.

Results: During the study period, 61 patients were treated curatively for non-metastatic, extra-uterine LMS. The mean age of presentation was 55.5 years (15-87 years). 44 patients had optimal debulking surgery with clear margins of at least >1milimetre (R0). Of this group, 31 patients did not receive adjuvant RT. The other 17 patients had microscopically positive margins (R1), of which 11 patients received adjuvant RT. The mean time to recurrence for patients in the R0 group that did not receive RT was 16.8 months, and 15 months for the patients who received RT (p value = 0.874). Conversely, the mean time to recurrence for patients in the R1 group without RT was 10.4 months, but this was increased to 36.7 months with RT (p value 0.174).

Conclusion: In this report, we found that adjuvant RT for extra-uterine LMS may not have an impact if R0 resection was achieved, but may prolong the disease free survival in patients with R1 resection. Values available were not considered to be statistically significant likely due to its small sample size and would need confirmation with a larger study.

Poster 292 #2804321

PROGNOSTIC SIGNIFICANCE OF NEUTROPHIL-LYMPHOCYTE RATIO (NLR) AND PLATELET-LYMPHOCYTE RATIO (PLR) IN SURGICALLY RESECTED RETROPERITONEAL SARCOMAS

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Objective: Accumulating evidence has shown that platelets can support various steps of cancer development and tumor progression by promoting cancer cell proliferation, tumor angiogenesis and metastasis, while lymphocytes are a significant blood parameter related to immune surveillance. Various studies have examined Neutrophil-Lymphocyte Ratio (NLR) and Platelet-Lymphocyte Ratio (PLR) as markers showing the association between the immune system and tumor progression. The aim of this study was to determine whether NLR and PLR before treatment predict overall survival and disease-free survival in patients with retroperitneal sarcomas.

Methods: A retrospective analysis of a prospectively maintained Sarcoma database was performed. All patients with a diagnosis of RPS treated surgically in our institution between January 2000 and May 2014 were included. Basic demographics, clinic-pathological and surgical factors were investigated, and the association with recurrence and survival was performed with univariate and multivariate analyses. All statistical analyses were performed with R 3.3.2.

Results: Eighty five patients underwent 142 sarcoma resections during the study period. The median age for all patients was 56 years (range: 26- 84). 49 were primary tumors while 93 were recurrent tumors. The most common histological subtype was liposarcoma (n=105, 73.9%). The median Disease Free Survival (DFS) was 10 months (range: 1-191), and the median Overall Survival (OS) was 30 months (range: 1-212).
The median NLR was 3.2 and the median PLR was 186.5. On univariate analysis, PLR and NLR were not significant for DFS, but were found to be significant for OS (PLR (P-value <0.01) and NLR (p-value <0.01)). The cut-off for PLR and NLR value for significance was 4 and 100 respectively. Histology and grade of tumor were also significant for OS on univariate analyses (p-value <0.05). On multivariate analyses, PLR and NLR were significant for OS (p-value <0.05).

Conclusion: Our study shows that the PLR and NLR could be used as prognostic variables in terms of OS but not DFS. This suggests that perhaps an immunogenic response is only useful in terms of overall survival but not local failure after treatment of sarcomas.

Poster 293 #2804347

RETROPERITONEAL SARCOMAS: HOW BENEFICIAL IS THE ADYUVANT TREATMENT? EXPERIENCE IN RAMÓN Y CAJAL HOSPITAL OF MADRID

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Objective: Retroperitoneal sarcomas (RPS) are uncommon tumors, generally diagnosed located and their only curative treatment is surgery. Local failure is the most common pattern of recurrence, with a 5-year relapse-free survival (RFS) of 40-50%. Adjuvant radiotherapy (RT) and intraoperative radiotherapy (IORT) have been proposed to improve local RFS and possibly overall survival (OS) rates, based mostly on retrospective dates. Postoperative RT and IORT seem to reduce the risk of local failure and increase the RFS, but without OS benefit. Results with adjuvant chemotherapy (CT) are discordant and it cannot be considered yet a standard approach. Our objective was to analyze the survival benefit obtained with IORT, adyuvant RT and QT in our center.

Methods: We retrospectively included patients with primary localized RPS diagnosed between 1995 and 2016 in Universtary Ramón y Cajal Hospital. Stata 14.1 was used to analyze the data. A multivariable Cox model analyses was carried out. We used de Gronchi's RPS nomogram to classified patients. Gronchi's nomogram establishes a score according to the main prognostic factors known for RTS (age, tumor size, grade, histology, presence of multifocality and extent of resection).

Results: 32 patients were identified. The median follow-up was 30.1 months. The median PFS was 47.67 months and the median OS was 77.18 months.
The effect of the all 3 treatments adjusted by the nomogram seemed to improve OS (HR for RT=0.38, p: 0.23; HR for QT=0.41, p: 0.27; HR for IORT=0.4, p: 0.23). RT showed no effect on RFS (HR for RT=1.03, p: 0.6). QT and IORT showed benefit in OS (HR for QT=0.49, p: 0.24, HR for IORT=0.54, p: 0.62).

Conclusion: QT and IORT seem to improve RFS and the 3 types of adyuvant treatment seem to improve OS in the multivariable analysis adjusted by the Gronchi's nomogram, without, statistically significant differences, that could be influenced by the small size of our sample. Larger randomized trials should be performed to correctly verify the apparently benefit of these therapies in RPS.

Poster 294 #2804523

CLINICAL OUTCOMES OF SURGICAL TREATMENT IN PATIENTS WITH MALIGNANT PERIPHERAL NERVE SHEATH TUMORS

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Objective: Malignant peripheral nerve sheath tumors (MPNST) is a rare soft tissue sarcoma with an aggressive clinical course such as high metastatic and recurrent potential. Approximately half of the patients with MPNST are associated with neurofibromatosis type 1 (NF1), whereas the remainder develop MPNST sporadically. We have treated localized MPNST by means of surgical resection with adequate margins when tumor resection is considered to be feasible. The aim of this study is to evaluate clinical outcomes of surgical treatment in patients with MPNST at our institution.

Methods: We reviewed 43 patients with MPNST, who treated with surgical resection at our institution between 1987 and 2015. One patient with lung metastasis at the diagnosis was included in this study. The resection of metastatic MPNST was excluded from this study. There were 19 male and 24 female with a mean age was 45 years at the diagnosis. The mean duration of follow-up was 62 months. Twenty-three patients were associated with NF1. Nineteen tumors were located in the trunk, and 24 were in the extremity. Thirteen tumors were located in the subcutaneous tissues, and 30 were in deeper tissues. Thirty-two tumors were classified as high grade and the remaining 11 as low grade. The average tumor size was 8.2 cm.

Results: At the final follow-up, 26 patients were free from disease, 13 had died of the disease, and four was alive with disease. The R0 resection was achieved in 33 patients. The overall survival and local recurrence-free survival rates at 5 years were 74.9 % and 85.7 %, respectively. Univariate analysis revealed large-sized tumors, histologically high grade, and the presence of NF1 were significantly associated with decreased overall survival. In multivariate analysis, there was no independent prognostic factor for overall survival. Five patients (13%) developed recurrent disease with a mean duration to local recurrence of 16.0 months, and an average size of their tumors was 8.2 cm. All five recurrent tumors were high graded, four were deep-seated, and three were located in the trunk. Three patients were associated with NF1. Two patients were treated with re-resection after local recurrence, whereas a patient who developed recurrence in the retroperitoneum and two with distant metastasis did not undergo surgical treatment. No significant factor associated with local recurrence was detected in univariate analysis.

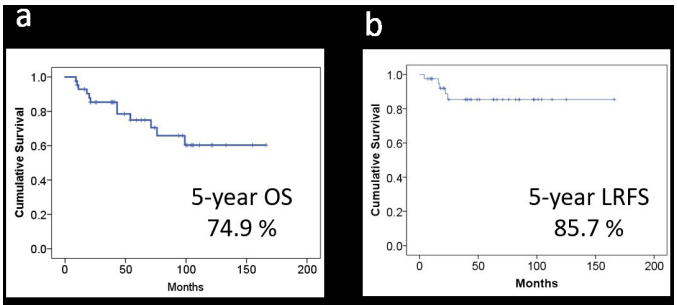

Fig. 1 Graphs show Kaplan-Meier curve for (a) overall survival and (b) local recurrence-free survival.

Conclusion: Previous studies reported that local recurrence rate after surgical resection of MPNST was relatively high, ranging 27% to 49% because they included many cases with histologically positive margin. This study suggested that surgical resection with adequate margin provided a benefit to control local recurrence in patients with MPNST. Alternative or adjuvant therapies should be required for local control of MPNST in cases that a safe surgical margin may not be obtained due to tumor size or location.

Poster 295 #2804827

RETROPERITONEAL SARCOMAS: DOES LATERALITY MATTER?

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Objective: Retroperitoneal Sarcomas (RS) are malignant tumors of connective tissue that can vary widely in their etiology, with liposarcoma and leimyosarcoma being two of the most common subtypes. Parameters such as grade, extent of resection, and tumor integrity have been shown to affect prognosis. The principle aim of this investigation was to examine the relationships between the laterality of RS and tumor characteristics, treatment and outcomes.

Methods: Patients with a diagnosis of primary RS were identified using the tumor registry at our institution. Those who underwent surgical resection were included in the study. Clinical and pathologic data were collected retrospectively from patient medical records. Categorical variables were compared using the Chi-square test while continuous variables were compared using one-way ANOVA. Cox regression was used to estimate the risk of death.

Results: Data from 106 patients were analyzed. Mean age at diagnosis was 58.7 years and 41.6% were male (n=44). Caucasians made up 91.5% (n=97) of patients

and 81.9% had no history of previous cancer (n=86). There were 52 right-sided (49.1%), 47 left-sided (44.3%), and 7 bilateral or mid-line sarcomas (6.6%). No statistically significant relationship was found between tumor laterality and patient age, gender, race, or cancer history. A greater proportion of bilateral or midline tumors were leiomyosarcomas (midline 42.9% vs left 26.1% vs right 25.5%, p=0.02), while right-sided tumors were more likely to be liposarcoma (right 68.6% vs left 63.0% vs midline 14.3%, p=0.02). While there was no statistically significant relationship between laterality and tumor grade, stage, T stage, or N stage, there was a trend towards more patients with metastatic disease having left-sided tumors (left 14.9% vs right 9.6% vs mid-line 0%, p=0.07). Additionally, there was no significant relationship between laterality and mean time to surgery, margin status, local recurrence, post-operative complications, radiation, or chemotherapy. There was no significant relationship between neoadjuvant radiation and laterality, but patients with midline tumors were more likely to receive neoadjuvant chemotherapy (midline 42.9% vs left 19.2% vs right 0.6%, p=0.06) although not statistically significant. When adjusted for age, sex, race, grade, stage, histology and treatment, there was no increased risk of death or tumor recurrence based on laterality.

Conclusion: While laterality does not seem to have a measurable relationship with patient outcomes or survival, there is an association between laterality and certain tumor characteristics. Patients with midline tumors were more likely to have leiomyosarcomas. A greater proportion of right-sided tumors were liposarcomas. Patients with left-sided tumors trend towards having a higher chance of metastatic disease. These preliminary findings warrant further investigation with a larger sample size across different institutions.

Poster 296 #2758532

PHASE 1A/1B STUDY OF OLARATUMAB PLUS PEMBROLIZUMAB IN PATIENTS WITH SOFT TISSUE SARCOMA

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Objective: Background: Olaratumab is a human IgG1-type monoclonal antibody (mAb) that binds to PDGFRα with high affinity and blocks its ligand-dependent activation by PDGF-AA, -BB, and -CC. Pembrolizumab is a mAb targeting the programmed cell death 1 (PD-1) receptor. Recent studies of PD-1-directed agents in soft tissue sarcoma have shown promising single-agent activity in certain subtypes. Targeting PDGFRα by olaratumab is hypothesized to alter the tumor microenvironment and may lead to a more pronounced activity of PD-1 targeting agents in soft tissue sarcoma. This study will explore safety and preliminary activity of combination treatment with olaratumab and pembrolizumab in patients with advanced soft tissue sarcoma.

Methods: This is an open-label, multicenter, nonrandomized, Phase 1a/1b dose-escalation study (NCT03126591). This study will evaluate patients ≥18 years of age with locally advanced or metastatic soft tissue sarcoma, not amenable to curative treatment and after available standard therapies fail to provide clinical benefit or are deemed inappropriate by the investigator. Patients with Kaposi's sarcoma or gastrointestinal stromal tumors are excluded from the study.

The primary objectives of the study are to assess safety and tolerability of olaratumab plus pembrolizumab and to determine a recommended Phase 2 dose. Secondary objectives include pharmacokinetics, pharmacodynamics, immunogenicity, and antitumor activity (using RECIST v1.1 and irRECIST) as assessed by overall response rate, disease control rate, progression-free survival, and overall survival.

In the phase 1a dose-escalation portion of the study, approximately 12 eligible patients will receive increasing dose levels of olaratumab on Day 1 and 8 plus pembrolizumab administered at a fixed dose on Day 1 of a 21-day cycle. Dose escalation of olaratumab will follow a 3+3 design; intrapatient dose escalation is not permitted. A minimum of 6 patients will be enrolled at the highest dose level tolerated.

Upon completion of the dose escalation portion, the Phase 1b expansion cohort will open. Eligible patients will receive the recommended dose of olaratumab plus pembrolizumab to confirm safety and tolerability and assess preliminary anti-tumor activity. Approximately 25 patients will be enrolled in the in Phase 1b portion.

Results: NA (TIP)

Conclusion: NA (TIP)

Poster 297 #2759922

TRABECTEDIN FOR ADVANCED SOFT TISSUE SARCOMA: TEN-YEAR PERSPECTIVE

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Objective: Trabectedin lately received FDA approval for use in anthracycline resistant advanced soft tissue sarcoma (STS), especially liposarcoma and leiomyosarcoma. We report our ten-year real-life experience with the drug, regarding safety and efficacy in a cohort of 86 patients.

Methods: The medical records of patients with advanced STS, treated as in-patients at the oncology ward at Tel-Aviv Sourasky medical center, in the years 2007-2015 were retrospectively evaluated.
Trabectedin was given through a central venous catheter, at a dose of 1.5 mg/m2 for 24 hours, on day 1 of each 21-days cycle.

Results: Trabectedin was most commonly given as a second (46 patients (53.48%)) or third (22 patients (25.58%)) line therapy. Ten patients (11.62%) received it as a first line treatment for metastatic disease, either due to a short disease-free-interval from adjuvant doxorubicin-based chemotherapy (six patients) or due to medical conditions prohibiting Doxorubicin and Ifosfamide administration (four patients). Eight patients were treated after being exposed to more than three prior lines of treatment.
Forty liposarcoma patients received a total of 381 courses, with a median of 5 courses per patient (range 1-59). Median time on treatment was 4 months (range 1-58). Median overall survival from the first day of Trabectedin and until death or last follow up was 11 months. There was no statistically significant difference in OS whether the drug was given as a first, second or third treatment line.
Overall response rates (ORR) to Trabectedin were 15%, with fourteen patients (35%) achieving disease stabilization, for a clinical benefit rate (CBR) of 50%.
Thirty seven leiomyosarcoma patients received a total of 266 courses, with a median of 6 courses per patient (range 1-25). Median time on treatment was 5 months.
Trabectedin was given as first line in 3 patients (8%), second line in 17 patients (46%) and third line in 11 patients (30%). Six patients (16%) were heavily pretreated before receiving the drug.
Median overall survival from the first day of Trabectedin and until death or last follow up was 15 months (range 1-35). There was no statistically significant difference in OS whether the drug was given as a first, second or third treatment line.
Overall response rates (ORR) to Trabectedin were 32%, with thirteen patients (35%) achieving disease stabilization, for a clinical benefit rate (CBR) of 67%.

Conclusion: Trabectedin is an effective and highly tolerated treatment modality in Anthracyclin-refractory STS

Poster 298 #2761113

THE ROUTINE REAL-LIFE USE OF TRABECTEDIN IN PATIENTS WITH ADVANCED SOFT TISSUE SARCOMA (STS) ACROSS EUROPE: AN ANALYSIS OF OVERALL VS. PER COUNTRY RESULTS FROM Y-IMAGE STUDY

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Objective: The prospective, non-interventional, phase IV Y-IMAGE study evaluated the use of trabectedin in real-life clinical practice across Europe in patients with advanced STS.

Methods: Data from adult STS patients treated with trabectedin 1.5 mg/m2 given as 24-h i.v. infusion every three weeks were collected. Patients must have received at least 1 cycle of trabectedin and currently be on trabectedin treatment. The primary endpoint was progression-free survival (PFS) as defined by investigators. The analyses were conducted in the overall population (OP) and separately in countries with the highest recruiting rate to cover inter-country variations: France (F), Germany (G), Italy (I) and the UK.

Results: A total of 218 patients from 41 centers and 9 European countries were evaluated. Demographics and baseline characteristics of patients recruited in the 4 countries of interest were well-balanced and comparable to those observed in OP. Patients received a median of 6 cycles of trabectedin (range: 1-44), mostly on an outpatient basis (n=132; 60.6%). Across all centers the median cycle duration, and median dose and dose intensity were similar to those observed in OP. Analysis of PFS data showed a similar outcomes in G (median PFS: 5.9 months) to that observed in OP (5.9 months), and a rather higher PFS in the UK (8.3 months), F (7.6 months) and I (6.8 months). The patients from the UK received the highest median number of cycles (10.5) and cumulative dose of trabectedin (26.2 mg) as compared to F, G and I. This was associated with favorable efficacy outcomes in those patients, particularly in terms of improved PFS (8.3 months), responses (overall response rate [ORR]: 38.5%; disease control rate [ORR + stable disease]: 84.6%) and a high growth modulation index of 2.3. Trabectedin treatment resulted in a comparable median overall survival in all patients (21.3 months), being somewhat larger among patients treated in sites across G (27.3 months). Febrile neutropenia (2.3% of patients), neutropenia, nausea, and pneumonia (1.4% each) were the most common trabectedin-related grade 3/4 adverse drug reactions.

Conclusion: In real-life setting trabectedin confers meaningful benefits to patients with multiple STS histotypes

with a manageable safety profile regardless of small country variations.

OVERALL VS. PER COUNTRY RESULTS (Y-IMAGE STUDY)

	Full analysis set, n (%)				
	France (n=26)	Germany (n=29)	Italy (n=69)	UK (n=26)	Overall population (n=218)
Age at study entry (years); Median (range)	58.5 (22-77)	58 (23-79)	59 (26-79)	56.6 (25-73)	58.0 (21.0-79.0)
Female	15 (57.7)	15 (51.7)	44 (63.8)	13 (50.0)	123 (56.4)
Histology	≥10% of patients				
Leiomyosarcoma	11 (42.3)	11 (37.9)	29 (42.0)	16 (61.5)	92 (42.2%)
Liposarcoma	5 (19.2)	-	23 (33.3)	7 (26.9)	51 (23.4)
Synovial sarcoma	4 (15.4)	5 (17.2)	-	-	23 (10.6%)
Cycles per patient Median (range)	5.5 (2-29)	6.0 (2-18)	6.0 (1-30)	10.5 (1-44)	6.0 (1-44)
Cumulative dose received mg/patient	12.1 (3.7-48.2)	20.8 (5.6-51.0)	14.3 (1.9-60)	26.2 (3-116.4)	14.7 (1.8-116.4)
Cycle duration (days)	24.9 (21-41)	26.8 (21-44.4)	23.7 (20.5-32.5)	24.2 (21-30.6)	24.1 (20-47.5)
Dose intensity (mg/m2/week)	0.7 (0.2-1.0)	0.6 (0.4-1.1)	0.6 (0.3-1.0)	0.7 (0.5-1.0)	0.7 (0.2-1.1)
Median PFS (months) [95% Confidence interval]	7.6 [3.3-NR]	5.9 [3.4-11.2]	6.8 [3.4-10.2]	8.3 [5.5-11.4]	5.9 [4.9-7.8]
Objective response rate (ORR) (Complete + partial response) [95% Confidence interval]	6 (23.1) [9.0-43.6]	9 (31.0) [15.3-50.8]	15 (21.7) [12.7-33.3]	10 (38.5) [20.2-59.4]	58 (26.6) [20.9-33.0]
Disease control rate (DCR) (ORR + stable disease) [95% Confidence interval]	17 (65.4) [44.3-82.8]	20 (69.0) [49.2-84.7]	48 (69.6) [57.3-80.1]	22 (84.6) [65.1-95.6]	143 (65.6) [58.9-71.9]
Time to progression (TTP), median (months) [95% Confidence interval]	7.8 [4.9-NR]	6.9 [4.2-11.2]	6.8 [3.4-10.2]	8.3 [5.5-11.4]	5.9 [4.9-8.1]
Overall survival (OS), median (months) [95% Confidence interval]	20.3 [9.6-NR]	27.3 [9.2-NR]	22.5 [19.0-NR]	20.0 [18.2-23.6]	21.3 [18.8-24.3]
Growth modulation index (GMI), median (a) Range (min-max) ≤1.1, n (%) >1.1 - <1.33, n (%) ≥1.33, n (%)	0.7 (0.1-16.3) 15 (65.2) 1 (4.3) 7 (30.4)	0.9 (0.0-15.0) 12 (50.0) 2 (8.3) 10 (41.7)	0.7 (0.0-16.7) 35 (62.5) - 21 (37.5)	2.3 (0.1-15.4) 11 (42.3) - 15 (57.7)	0.8 (0.0-42.5) 110 (56.1) 10 (5.1) 76 (38.8)

(a) The GMI (TTP trabectedin/TTP prior chemo) was assessed on 196 patient : France, n=23; Germany, n=24; Italy, n=56; UK, n=26. NR, not reached.

Poster 299 #2762888

ANALYSIS OF OUTCOME AND PROGNOSTIC FACTORS IN THE WORLD CASE SERIES OF 67 RENAL VEIN LEIOMYOSARCOMA PATIENTS

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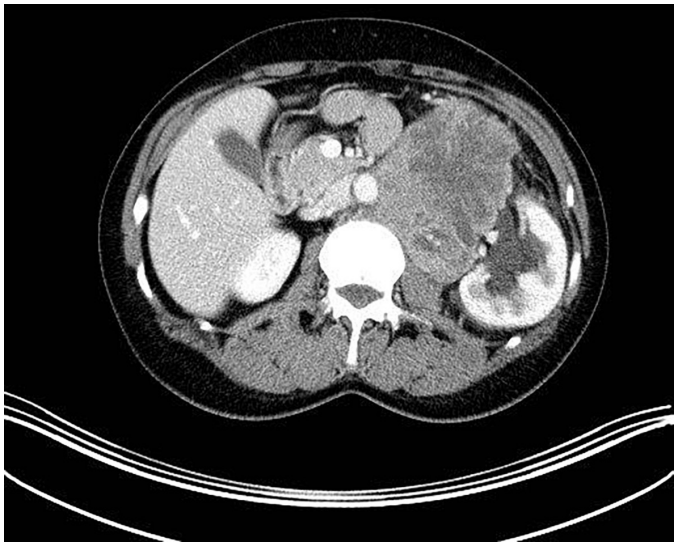
Objective: Leiomyosarcoma is a rare malignant mesenchymal tumour. Some cases of the leiomyosarcoma of the renal vein (LRV) have been reported in the literature, but analysis of data and search for prognostic factors have not been done so far. The aim of our review was to describe the LRV, to analyse overall survival (OS), local recurrence free survival (LRFS) and distant metastases free survival (DMFS) in LRV world case series and to identify significant predictors of OS, LRFS and DMFS.

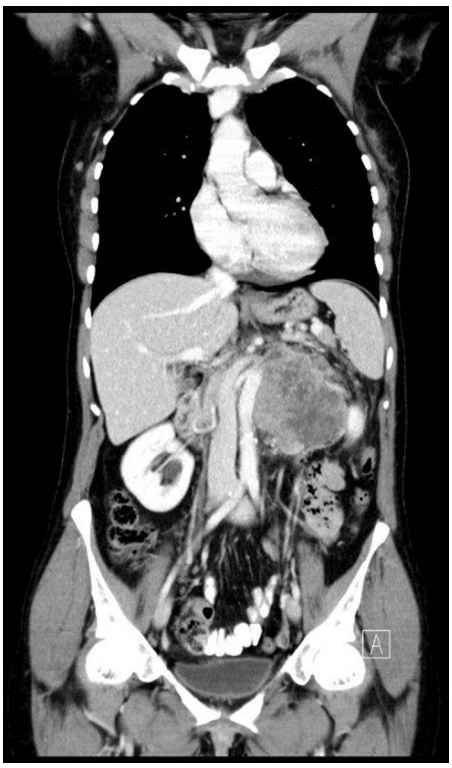
Methods: LRV is extremely rare. The first case was reported by Lopez Varela and Pereira Garro in 1967. Cases from the literature based on PubMed search and a case from our institution were included.

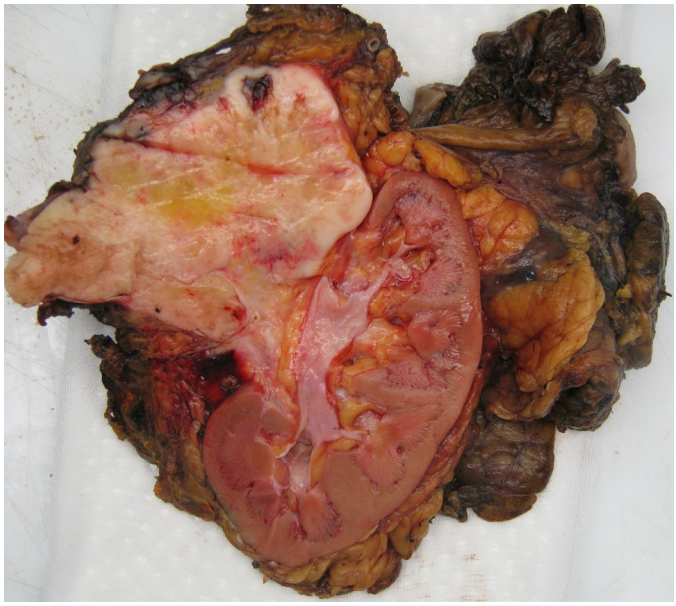
Results: Sixty-seven patients with a mean age of 56.6 years were identified; 76.1% were women. Mean tumour size was 8.9 cm; in 68.7% located on the left side. Tumour thrombus extended into the inferior vena cava lumen in 13.4%. All patients but one underwent surgery (98.5%). After a median follow up of 24 months, the OS was 79.5%. LRFS was 83.5% after a median follow up of 21.5 months and DMFS was 76.1% after a median follow up of 22 months. Factors predictive of OS in univariate analysis were surgical margins, while factors predictive of LRFS were inferior vena cava luminal extension and grade. No factors predictive of DMFS were identified. Because of in-

sufficient histologic data and follow up, we were not able to identify prognostic factors in multivariate analysis.

Cases from this review are dispersed world wide and through half of the century, lacking data for tumour grade (58.2%; 39/67), surgical margin status (73.1%; 49/67) and follow up (16.4%; 11/67). As a consequence, there was a limitation in the statistical analysis and the conclusions that could be drawn from it, particularly in patients' outcome.







Conclusion: LRV is usually located in the hilum of the kidney. It should be considered in differential diagnosis of renal and retroperitoneal masses, particularly in women over the age 40, on the left side and in the absence of haematuria. Core needle biopsy should be performed. Patients should be managed by sarcoma multidisciplinary team. LRV should be surgically removed, with negative margins.

Poster 300 #2767204

SINGLE-CENTER EXPERIENCE WITH INTRAABDOMINAL LIPOSARCOMA: OPTIMAL MINIMUM DURATION FOR POSTOPERATIVE REMNANT TUMOR SCREENING

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Objective: This study sought to identify factors related to the prognosis of intraabdominal liposarcoma and to determine the optimal minimum duration for remnant tumor screening. Intraabdominal liposarcoma is associated with high rates of incomplete resection and recurrence requiring a sophisticated follow-up strategy.

Methods: Patients who underwent surgery for intraabdominal liposarcoma were included. Cox analyses were used to analyze factors related to recurrence and survival. To determine the optimal minimum duration for remnant tumor screening, patients with recurrence after surgery despite gross complete resection were grouped by a postoperative detection time of 1, 3 or 6 months. Their survivals were compared to the gross incomplete resection group.

Results: A total of 168 patients were included. Kaplan-Meier 5-year disease-free survival was 35.9% and overall survival was 66.5%. Multiplicity (HR=2.528, CI=1.585–4.033, p<0.001), organ invasion (HR=1.628, CI=1.020–2.598, p=0.041) and FNCLCC grades (G2, HR=1.730, CI=1.000–2.994; G3, HR=3.812, CI=2.112–6.880; p<0.001) were related to recurrence. Multiplicity (HR=2.131, CI=1.050–4.329, p=0.036), organ resection ≥3 (HR=2.857, CI=1.322–6.174, p=0.008), gross incomplete resection (HR=4.368, CI=1.890–10.097, p=0.001), positive margin (HR=2.766, CI=1.367–5.600, p=0.005), FNCLCC grade (G2,HR=2.044, CI=0.937–4.459; G3, HR=4.470, CI=1.893–10.557; p=0.003) and RT (HR=0.322, CI=0.160–0.648, p=0.001) were related to overall survival. Dividing patients into 1 month (p = 0.097) and 3 months (p=0.063) did not yield significant differences in univariate analyses while 6 months showed significant difference (p=0.015) compared to gross incomplete resection group. Patients with tumors detected within 6 months showed similar survival to the gross incomplete resection group (HR=0.552,CI=0.241–1.260,p=0.158) while patients with tumor detection after 6 months showed better survival (HR=0.325,CI=0.149–0.708,p=0.005).

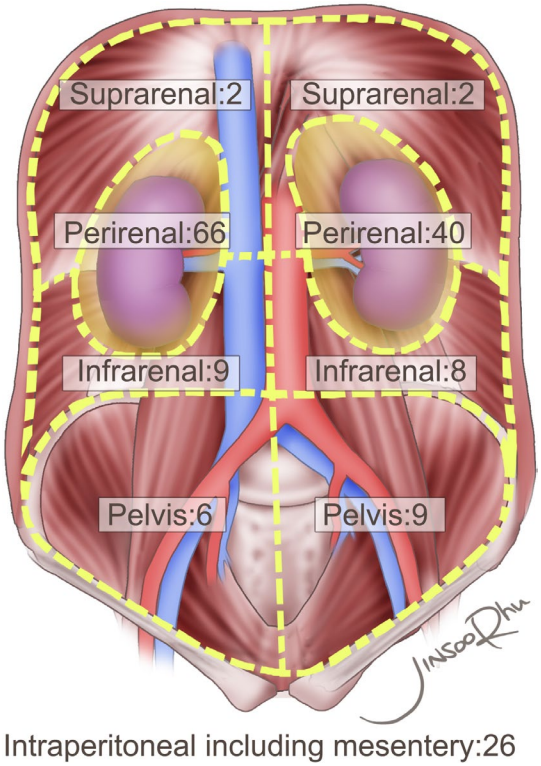

Figure 1. Anatomical location of intraabdominal liposarcomas in patients who underwent surgery.

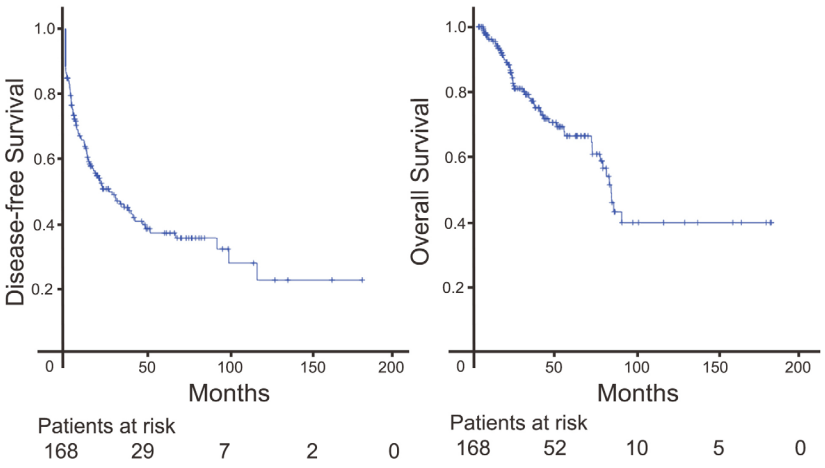

Figure 2. Kaplan-Meier survival curve and disease-free survival curves.

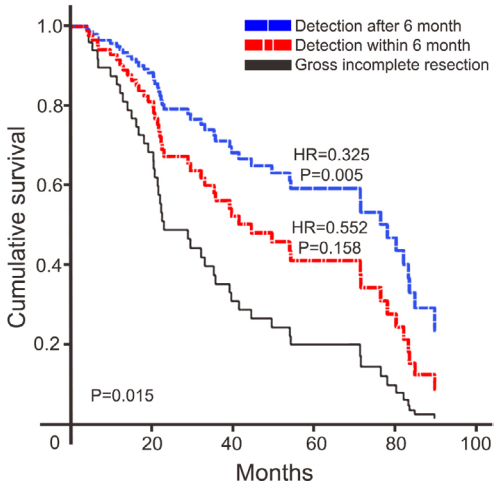

Figure 3. Overall survival of patients with recurrence after surgery for intraabdominal liposarcoma, by time of tumor detection during follow-up.

Conclusion: In conclusion, minimum duration of 6 months for remnant tumor screening using CT seems optimal.

Table 4.
Multivariable Cox proportional hazard model of prognostic factors for overall survival in patients with recurrence after operation.

Factors		Univariable			Multivariable		
	No	HR	95% CI	P	HR	95%CI	P
Sex	.	.	.				
Male	54	.	.	0.544			
Female	41	0.829	0.453–1.518				
Age (years)	.	.	.				
≤60	56	.	.	0.111			
>60	39	1.594	0.898–2.828				
Status	.	.	.				
Primary	55	.	.	0.895			
Recur	40	0.961	0.531–1.738				
Multiplicity	32	1.115	0.603–2.063	0.728			
Organ invasion	53	1.657	0.922–2.979	0.091			
3 or more resected organs	20	1.856	0.921–3.742	0.084			
Histological margin	.	.	.				
Unknown	62	.	.	0.077			
Positive	33	1.693	0.944–3.036				
Differentiation	.	.	.		.	.	
WDPLS	26	.	.	0.037	.	.	0.029
others	69	1.986	1.041–3.790		2.114	1.078–4.146	
FNCLCC Grade	.	.	.	0.088			
1	25	.	.	.			
2	34	2.327	1.027–5.274	0.043			
3	27	2.222	0.954–5.174	0.064			
Radiotherapy	40	0.454	0.239–0.863	0.016	0.438	0.229–0.840	0.013
Time of tumor detection	.	.	.	0.097			
Gross incomplete resection	18	.	.	.			
Within 1 month	9	0.371	0.080–1.709	0.203			
After 1 month	68	0.472	0.233–0.955	0.037			
Time of tumor detection	.	.	.	0.063			
Gross incomplete resection	18	.	.	.			
Within 3 months	16	0.679	0.256–1.800	0.436			
After 3 months	61	0.433	0.211–0.889	0.022			
Time of tumor detection	.	.	.	0.043	.	.	0.015
Gross incomplete resection	18	.	.	.	.	.	.
Within 6 months	30	0.659	0.294–1.473	0.309	0.552	0.241–1.260	0.158
After 6 months	47	0.388	0.183–0.821	0.013	0.325	0.149–0.708	0.005

Poster 301 #2767581

BIZARRE MULTINUCLEATED GIANT CELLS IN HUMAN ANGIOSARCOMA: INITIAL ANATOMICAL AND CLINICAL CHARACTERIZATION

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Objective: Preclinical studies suggest multinucleated giant cells (MGCs) contribute to tumor heterogeneity and promote chemoresistance in various cancer types. In this study, we aim to provide an initial anatomical and clinical characterization of MGCs in human angiosarcoma and to explore their potential contribution to chemoresistance.

Methods: Angiosarcoma cell lines (MO-LAS-B and ISO-HAS-B) and archival H&E-stained slides from primary angiosarcoma tissue (n = 29) were examined under light microscopy for the presence of MGCs, defined as atypical large cells harboring bizarre hyperchromatic nuclei. Additional characterization of the cell lines were conducted via CD31 immunohistochemistry and transmission electron microscopy (TEM). Both cell lines were treated with paclitaxel or doxorubicin at varying concentrations (5 to 50 ng/ml) for 120h. Trypan blue exclusion test was used to assess cell viability.

Results: MO-LAS-B and ISO-HAS-B cell lines contained a rare subpopulation of large, flattened cells with multiple

irregular hyperchromatic nuclei. These cells were morphologically distinct and were between 3 to 10-fold larger than surrounding cells. TEM of 100 MGCs in both cell lines revealed significant cellular and nuclear pleomorphism. These MGCs contained numerous mitochondria (sometimes swollen) and included cells in mitosis. Like their surrounding cells, MGCs stained positive for CD31 via immunohistochemistry, confirming their endothelial phenotype. Exposure of both cell lines to either paclitaxel or doxorubicin at increasing concentrations demonstrated a relative chemoresistance of MGCs. In contrast to non-MGCs, MGCs remained viable even at high drug concentrations at 50ng/ml in both cell lines. In primary tumor samples, 14 of 29 (48.3%) were found to contain MGCs. In an exploratory analysis, the presence of MGCs may be correlated with poorer overall survival (HR 2.29; 95% CI 0.64-8.11, p=0.202; Cox regression model including age, sex, grade, tumor depth, metastasis at diagnosis).

Conclusion: MGCs are frequently observed in human angiosarcomas. Our preliminary results suggest that these bizarre cells are mitotically active and may represent a chemoresistant subpopulation of angiosarcoma cells.

Poster 302 #2769727

PHASE II STUDY OF NEOADJUVANT CHECKPOINT BLOCKADE IN PATIENTS WITH SURGICALLY RESECTABLE UNDIFFERENTIATED PLEOMORPHIC SARCOMA AND DEDIFFERENTIATED LIPOSARCOMA

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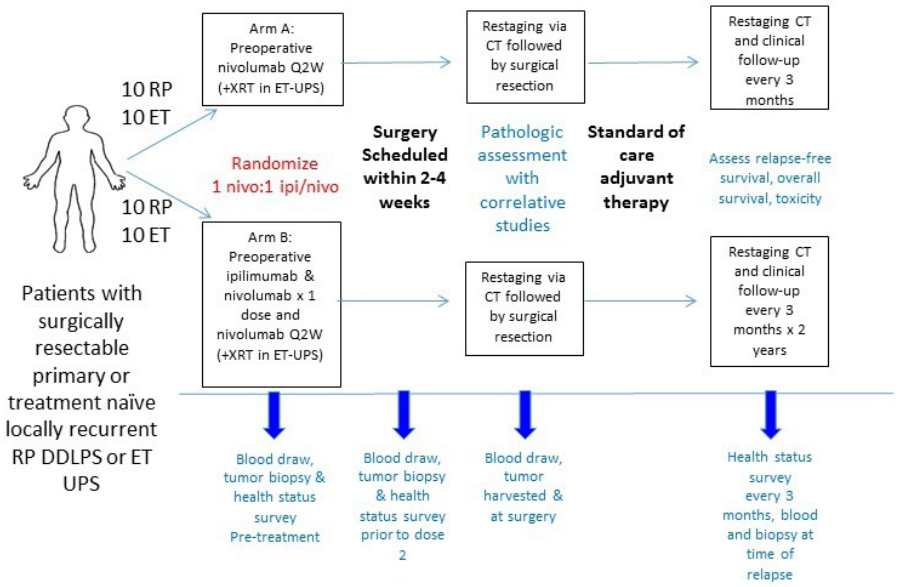
Objective: Preliminary data from SARC-028 demonstrate favorable responses to PD-1 blockade in patients with undifferentiated pleomorphic sarcoma (UPS) and dedifferentiated liposarcoma (DDLPS). However, a significant subpopulation of patients treated with immunotherapy will not respond. Used together, RT and immunotherapy may have synergistic effects, which are being explored in other cancers. Recent data suggest that combination anti-CTLA-4 therapy can enhance immune cell infiltration into tumors that are otherwise considered immunologically "cold." Neoadjuvant studies are critical to provide mechanistic insight of the impact of checkpoint blockade on the tumor microenvironment. We hypothesize that checkpoint blockade will be associated with a pathologic response when administered in a neoadjuvant setting.

Methods: This is a randomized, non-comparative Phase II study designed to detect pathologic and immunologic biomarkers of response to checkpoint blockade in resectable, treatment naive primary or locally recurrent DDLPS of the retroperitoneum (RP) and UPS of the extremity or trunk (ET). Patients with surgically resectable primary or recurrent disease, with at least one tumor amenable to serial biopsy who are determined to be candidates for upfront surgery by a multidisciplinary consensus will be randomized to preoperative nivolumab (Figure, Arm A) or combination nivolumab & ipilumumab, followed by nivolumab (Figure, Arm B). Exclusion criteria will be prior systemic or radiation therapy for the current sarcoma. In arm A, 10 patients with RP DDLPS will receive 3 upfront doses of nivolumab and 10 ET UPS patients will receive 1 dose of nivolumub followed by combination nivolumab + XRT. In arm B, 10 patients with RP DDLPS will receive 1 dose of ipilimumab combined with nivolumab followed by 2 doses of nivolumab and 10 ET UPS patients will receive 1 dose of combination nivolumab & ipilumumab, followed by combination nivolumab + XRT. After restaging, all patients will undergo surgical resection. Baseline and on treatment biopsies and blood for genomic and immunologic analyses will be obtained. An optional health status survey will also be administered. The primary endpoint is pathologic response as assessed at time of surgical resection by percentage (%) of viable tumor cells, % tumor necrosis, amount of fibrosis and proliferation by phosphohistone H3 from baseline to surgical specimen.

Results: Opening for enrollment: Fall 2017

Conclusion: Support: Bristol Meyers Squibb



Patients with resectable primary or treatment naïve locally recurrent retroperitoneal DDLPS or extremity/trunk UPS will be randomized 1:1 to A: 3 doses of upfront nivolumab (RP DDPLS) or combination nivolumab + XRT (ET UPS) or B: combination ipilumumab & nivolumab x 1 dose followed by 2 doses of nivolomab (RP DDLPS) or 1 dose of combination nivolumab & ipilumumab, followed by combination nivolumab + XRT (ET UPS). After restaging, all patients will undergo surgical resection. Longitudinal biopsies, blood and health status assessment will be obtained. Tumors will be assessed for pathologic response and changes in immune cell infiltration throughout treatment.

Poster 303 #2781855

PRELIMINARY REPORT ON CLINICAL USE OF 5-AMINOLEVULINIC ACID (5-ALA) AS A PHOTOCENSITIZER PRECURSOR FOR SOFT TISSUE SARCOMAS

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Objective: Surgery remains a mainstay of treatment for the majority of soft tissue sarcomas, but adjuvant therapy is desirable when surgeons are obliged to perform marginal or intralesional resection, such as in retroperitoneal sarcomas. 5-aminolevulinic acid (5-ALA) is a natural amino acid that is metabolized in the heme biosynthesis pathway to the protoporphyrinogen IX in mitochondria and then converted to protoporphyrin IX (PpIX). Because PpIX tends to densely accumulate in tumor cells and thus show bright fluorescence on excitation with blue light, 5-ALA is currently applied as a photosensitizer precursor for photodynamic diagnosis and photodynamic therapy among various other cancers in several countries including Japan. This study is a preliminary report of our experience regarding the clinical potential of 5-ALA application in soft tissue tumor surgery.

Methods: This is a clinical study to examine the effectiveness of 5-ALA as a photosensitizer for soft tissue sarcomas. The institutional board approval was obtained prior to this study. After informed consent, five patients with recurrent or metastatic soft tissue tumors underwent surgeries 3–4 hours after oral administration of 20 mg/kg of 5-ALA, from August 2015 to July 2016. There were four males and one female, aging 67–79 (mean, 71) years. Histological types were de-differentiated liposarcoma (DDLS), high-grade malignant peripheral nerve sheath tumor (MPNST), desmoid-type fibromatosis, high-grade myxofibrosarcoma (MFS), and undifferentiated pleomorphic sarcoma (UPS). Evaluated surgical margins were wide (MPNST), marginal (UPS), and intra-lesional (the others). All the intra-lesional surgeries were peformed with palliative intent because of patient refusal of amputation. Intra-operatively and after tumor removal, bright fluorescence (at wave length of approximately 600 nm) on excitation with blue light (at length of 400–410 nm) was detected through an analytical probe. After the evaluation of fluorescence positivity, the operative field was irradiated using the blue light for a few minutes. The results of fluorescence positivity and oncological outcomes were reported in a descriptive manner.

Results: Intraoperatively, none of the cases showed 5-ALA-induced positive fluorescence signal on excitation with blue light. In contrast, after tumor removal and immediate examination through the specimen dissection, the fluorescence signal was heterogeneously positive in two (MPNST and UPS, Fig.1), moderately positive in one (desmoid-type fibromatosis), but negative in two (DDLS and MFS). One patient with recurrent DDLS in the upper arm received three surgeries after 5-ALA administration, but all the three surgeries resulted in the negative fluorescence signal even on dissected surface. Oncologically, all the intra-lesional three surgeries resulted in another local recurrence, one of which eventually underwent forequarter amputation two months later, whereas the other two surgeries had no local recurrence (Table 1). Of note, the UPS case with marginal margin continued free of local recurrence at 1 year follow-up in spite of microscopically positive surgical margin observed widely.

Conclusion: Our results suggested that 5-ALA can be a photosensitizer precursor even for soft tissue sarcomas.

Considering no visible emission during surgery in this case series, the clinical benefit of using this agent may be limited to photodynamic therapy, but 5-ALA still has the potential of improving local control acting as photosensitizer or even as radiosensitizer.

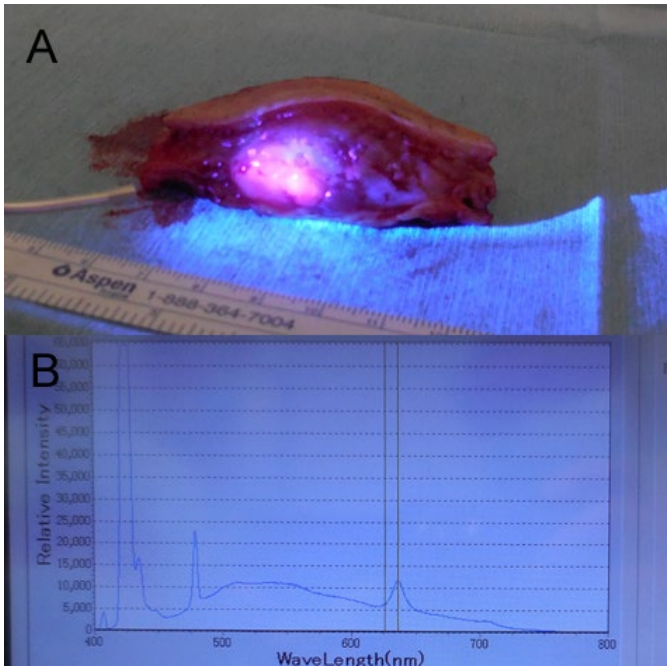

Fig1. Positive fluorescence signal observed after tumor removal and immediate examination through the specimen dissection (MPNST). (A) Bright fluorescence signal was visible. (B) A peak was detected at wave length of 630 nm through the analytical probe.

Summary of five cases

Case	Age, Sex	Surgical margin	LR	Oncological Status
1. Recurrent DDLS (upper arm)	78, M	intralesional (R2)	+ (2m, amputation)	NED
2. Recurrent MPNST (knee)	69, M	wide (R0)	- (18m)	NED
3. Recurrent demoid-type fibromatosis (back)	71, M	intralesional (R1)	+(14m, no surgery)	N/A
4. Recurrent MFS (forearm)	67, M	intralesional (R1)	+(10m, re-surgery)	AWD
5. Soft tissue metastasis of UPS (upper arm)	79, F	marginal (R1)	- (11m)	NED

DDLS=dedifferentiated liposarcoma; MPNST=malignant peripheral nerve sheath tumor; MFS=myxofibrosarcoma; UPS=undifferentiated pleomorphic sarcoma; LR=local recurrence; NED=no evidence of disease; AWD=alive with disease

Poster 304 #2790249

RESECTION OF SOFT TISSUE SARCOMA WITH ADEQUATE WIDE MARGIN CAN LEAD TO GOOD LOCAL CONTROL WITHOUT ADJUVANT RADIATION THERAPY

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Objective: The concept of surgical margin in Japan was published in 1989 by Japanese Orthopaedic Association (JOA). Initially, at least 5cm-wide surgical margin was necessary to treat soft tissue sarcoma (STS) and the barrier concept was distinctive. Lately, high-resolution MRI is available and provides good anatomical location, and 2-cm wide margin can be considered as adequate margin. We evaluated local control and prognosis following resection of STS using JOA surgical margin concept.

Methods: Surgical resection with at least 2cm-wide margin was attempted whenever possible. Marginal or 1cm-wide margin are acceptable when preserving critical organs. Radiotherapy (RT) is conducted postoperatively only for marginal margin or R1 assessed in resected specimen.

Inclusion criteria are localized STS in the extremities or trunk, larger than 5cm, intermediate to high grade, limb sparing surgery, primary complete resection at our institution, and minimum 4 years of follow-up. We excluded tumors arising from genetic disease such as NF1. We retrospectively analyzed 63 patients treated between 2007 and 2012 (11 UPS, 9 MFS, 9 myxoid liposa, 6 synovial sa, 6 MPNST and 22 others).

Results: Median follow-up was 70 (8-118) months. 11 patients received unplanned (whoops) resection before referring to our hospital. 9 patients underwent postoperative RT according to our treatment strategy. 18 patients received chemotherapy. There were 6 (9.5%) local recurrences with average 13 (5-44) months after surgery. Only 1 of 9 patients treated with postoperative RT developed local recurrence. There was no statistical difference of local recurrence-free survival between wide resection alone and inadequate resection plus postoperative RT. Distant metastasis was shown in 20 patients with average 20 months after surgery. 5 year overall survival was 82% for wide resection alone and 89% for inadequate resection plus postoperative RT, which showed no statistical difference.

Conclusion: Many papers demonstrated that resection in combination with RT improved local control rates. Historically in Japan, surgeons have treated STS by achieving safe surgical margin rather than by using adjuvant RT. In this series, resection alone with 2cm-wide margin led to good local control with limb sparing, which is identical to previous reports with surgery plus RT. Adjuvant RT should be given for resection with marginal margin or R1 margin of the resected specimen.

Poster 305 #2790288

A REAL-WORLD OBSERVATIONAL STUDY OF ERIBULIN IN PATIENTS WITH SOFT-TISSUE SARCOMA IN JAPAN

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Objective: Eribulin mesylate (ERI), a non-taxane microtubule dynamics inhibitor, shows antitumor activity. Based on results from a phase II trial in Japan and phase III trial overseas, ERI was approved for use in Japan in the treatment of soft-tissue sarcomas (STSs). However, efficacy and safety information about ERI for STSs other than liposarcoma and leiomyosarcoma remains insufficient. The objective of this study is to gather additional information through a post-marketing study.

Methods: A nationwide, multicenter, observational study is being conducted among STS patients who spent up to 2 years receiving ERI in clinical settings. ERI was infused intravenously at 1.4 mg/m2 on days 1 and 8 of each 3-week cycle. This interim analysis investigates efficacy and safety of ERI based on imaging studies in 171 patients within 3 months after starting ERI.

Results: Patients comprised 82 males and 89 females with a mean (±standard deviation) age of 59.5 ± 13.7 years. The median number of ERI cycles was 3.1 and 104 patients (60.8%) completed ERI treatment within 3 months. ERI was first-line treatment in 15 patients (8.8%) and second-line treatment in 53 patients (31.0%). The major tissue types were: liposarcoma in 53 patients (well-differentiated, n=4; myxoid, n=9; pleomorphic, n=2; dedifferentiated, n=33; unknown, n=5), leiomyosarcoma in 45 patients, undifferentiated pleomorphic sarcoma in 13 patients, angiosarcoma in 11 patients, and rhabdomyosarcoma in 10 patients. Overall response rate (Complete response + Partial response) was 9.4%. Overall response rates for the five tissue types were 3.8% (myxoid, n=2), 11.1%, 15.4%, 9.1%, and 10.0%, respectively, and disease control rates (CR+PR+ stable disease) were 43.4%, 57.8%, 30.8%, 36.4%, and 10.0%, respectively. Adverse events occurred in 134 patients (78.5%). Grade 3 or 4 adverse drug reactions included neutropenia in 78 patients (45.6%) and leukopenia in 61 patients (35.7%).

Conclusion: These results suggest that ERI is tolerable and may be a potential treatment option not only in patients with liposarcoma or leiomyosarcoma, but also in patients with other types of STS.

Poster 306 #2791276

SEQUENCE-SPECIFIC ANTIBODIES FOR IDENTIFICATION, CAPTURE AND CHARACTERIZATION OF CIRCULATING SARCOMA CELLS AND CELLS UNDERGOING EPITHELIAL TO MESENCHYMAL TRANSITION

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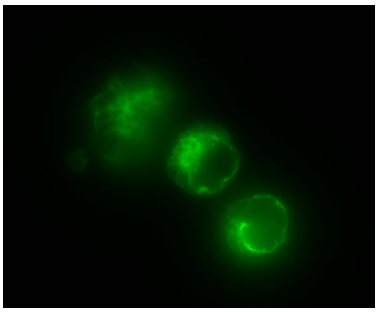
Objective: Molecular profiling of sarcomas has revealed certain chromosomal translocations resulting in fusion gene rearrangements and dysregulation of cooperating oncogenic drivers. These genetic alterations can serve as molecular targets for biologic and immunologic therapies in development. Objective: To develop sequence-specific antibodies for identification, capture and characterization of circulating sarcoma cells and cells undergoing epithelial to mesenchymal transition (EMT).

Methods: Collagen and vimentin are expressed in normal mesenchymal cells, in sarcoma circulating tumor cells (CTCs), and in epithelioid CTCs that have undergone EMT in the course of metastatic progression. To map the vimentin protein, sequence-specific anti-vimentin antibodies were produced in rabbits and used as experimental probes for the purpose of defining useful unstructured (linear) epitopes for CTC-binding, capture, and characterization.

Results: Four high titer (1:64,000) sequence specific polyclonal antibodies were generated and tested in an in vitro cell culture system. Adherent A549 cells were fixed, permeabilized, and stained using known antibodies against vimentin (V9 and 84-1) and four affinity-purified rabbit polyclonal antibodies. Positive control (V9 and 84-1) and pAb CB3 showed canonical intracellular filamentous vimentin staining pattern in A549 cells (See Image). In contrast, 84-1 and pAb CB3 but not V9 showed the intracellular canonical staining in HT29 cells.



A549 cells showing canonical intercellular vimentin staining with pAb CB3

Conclusion: Polyclonal antibody CB3 is a useful biomarker for identification of sarcoma CTCs and cells undergoing EMT. Studies are in progress to evaluate cell surface binding of pAb CB3 and other CTC-targeted reagents in live sarcoma cells.

Poster 307 #2791758

A RARE CARE OF INTRACARDIAC MYOEPITHELIAL CARCINOMA AND LITERATURE REVIEW

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Objective: Myoepithelial Carcinomas (MC) represent extremely rare and aggressive tumors that occur in a wide array of ages and anatomic locations. Soft tissue MC have essentially identical histology, though may be an entirely different pathobiologic entity. These tumors are more prevalent in patients less than 50 years of age, with about 10-20% of the reported cases occurring in children. The rarity of the tumor and histological similarity with other tumor types makes it difficult to diagnose. Data suggests that children experience an overall worse prognosis. Here, we report an extremely rare case of an intracardiac MC occurring in an infant.

Methods: A previously healthy 4 month old male developed a systolic murmur, which was identified at a well child visit. An echocardiogram revealed a mass cauing obstruction of the right ventricular outflow tract (RVOT). A subsequent cardiac MRI confirmed a free wall mass in the RVOT with secondary pulmonary stenosis. The MRI characteristics were most suggestive of a rhabdomyoma, a benign tumor seen in infants, so the decision was made to follow conservatively. Over the next 2 months, the mass increased in size, causing an increase in RVOT obstruction, and he devloped a pericardial effusion. He underwent a maximal resection; however, there was involvement of tumor with the left anterior descending coronary artery, which could not be safely explanted. Pathologic review proved diagnosis of MC, with an intriguing finding of EWSR1-KLF15 translocation. He underwent treatment using a protocol adapted from that reported by the TREP (Tumori Rari in Eta Pediatrica) consortium. He recevied 8 cycles of chemotherpay (5 cycles of ifosfamide, cisplatin, etoposide; 3 cycles of ifosfamide, vincristine, etoposide). Radiation was not done given the location of the tumor and age at diagnosis.

Results: Sixteen months from initial diangosis, he was found to have a recurrent cardiac mass with metastasis. He died 22 months after initial diagnosis. He had an excellent quality of life for the duration of his course.

Conclusion: MC is uncommon and aggressive in children. Intracardiac manifestation of MC is even more infrequent. The rarity, location, and difficulty of diangosis resulted in a complicated treatment course for our patient. However, despite these difficulties, he completed treatment using a modified version of the protocol reported by the TREP consortium. Local control was complicated by tumor location. Overall, he had an impressive length of survival of 22 months, during which he sustained a good quality of life. His pathology revealed an EWSR-KLF15 translocation, which has only been reported in 2 cases of renal MC in children. Interestingly, KLF15 has also been noted to play an important role in cardiovasular remodeling and hypertrophy.

Poster 308 #2804164

NEW PROGNOSTIC SCORE BASED ON GROWTH MODULATION INDEX (GMI) IN ADVANCED SOFT TISSUE SARCOMAS (ASTS) TREATED WITH TRABECTEDIN (T): A SPANISH GROUP FOR RESEARCH ON SARCOMAS (GEIS-38 STUDY)

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Objective: The GMI is a marker of drug activity and represents an intra-patient comparison of successive time to progression (TTP), defined as the TTP ratio between the second (or later) line (TTPn) of therapy divided by the prior line (TTPn−1). Defining a clinical profile of pts with GMI ≥ 1.33 could help to identify pts who can gain greater benefit from T

Methods: We retrospectively evaluated the concordance between the GMI and the efficacy outcomes and clinical profiles of 198 pts with A STS treated with trabectedin 1.5 mg/m2 (24-h infusion q3w) as a 2nd or further-line treatment from Jan 2007 to Jun 2016

Results: After a median follow-up of 58 months (m) range:18-172) median overall survival from AS TS diagnosis (MOS) and from T (MT-OS) were 38 m (8-106) and 10.8 m (8.9-12.7), respectively, while median TTP from T (MT-TTP) and T-1 were 3.4 m(2.8-4) and 3.5 m (2.8-4.2). Overall, 106 p ts (53%) had a GMI <1; 22 (11%)

a GMI=1- 1.33 and 70 pts (35%) a GMI >1.33. A high GMI (<1.33 vs1.33) correlated with favorable efficacy outcomes: MT-OS: 23 vs 36 m (p<0.001), MT-TTP 2.3 vs 8.2 m (p<0.001) and clinical benefit (objective response + stable disease) 23% vs 68% (p=0.001). The multivariate analysis identified L-type sarcoma (Odds ratio:1.99, 95%CI 1.06-3.71), metastatic free interval (MFI) from ini tial diagnosis ≥ 8.1 m (2.24,95%CI 1.19-4.18) and Karnofsky >80 (2.3,95%CI 1.00-5.28) as factors independently associated to GMI ≥1.33. Based on these 3 variables we defined a new GEISTRA score assigning 1 point for each adversely affected variable: non L-Sarcoma,MFI<8.1m or Karnofsky <80. This score showed a strong correlation with MT-TTP (p<0.001) and MT-OS (p<0.001).

Conclusion: Based on the high GMI we defined a new GEISTRA score, which is strongly associated with favorable efficacy outcomes in pts with ASTS treated with T. GEISTRA score could be a potentially useful predictable clinical tool for T benefit.

Multivariate analysis. GEISTRA Score

GEISTRA Score	MT-TTP m (range)	p	MT-OS m (range)	p
0	7.4 (5.8-9)	<0.001	25.7 (11.4-40)	<0.001
1	4.2 (2.7-5.8)		11.3 (8.6-14)	
2	2.5 (1.9-3.1)		6.4 (4.3-8.6)	
3	1.9 (0.7-3.2)		2.5 (0.2-4.8)	

Poster 309 #2804314

ADJUVANT RADIATION THERAPY PROLONGED PROGRESSION-FREE SURVIVALS IN MODERALTELY CHEMOSENSITIVE AND RELATIVELY CHEMO-INSENSITIVE SOFT TISSUE SARCOMA

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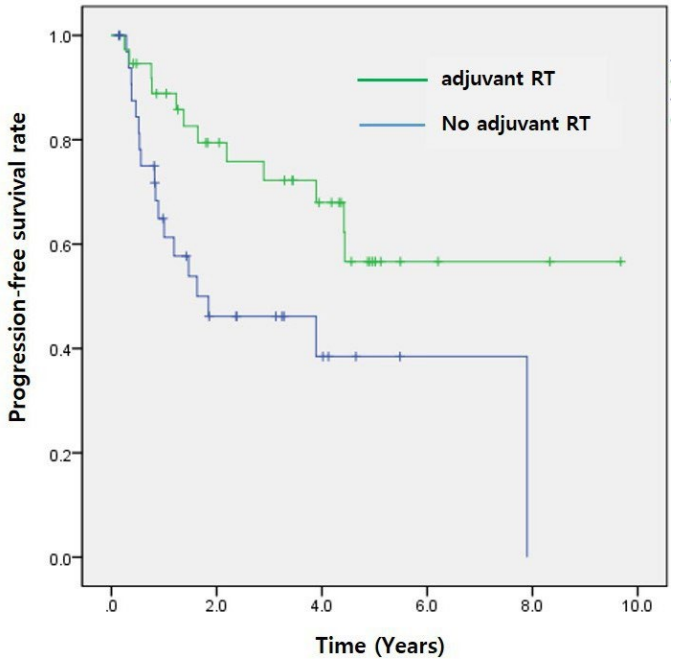
Objective: Soft tissue sarcoma (STS) is a rare and heterogenous disease entity. The heterogeneity includes pathologic subtypes which are more than 50 and anatomical locations. The rareness and heterogeneity of STS hinder revealing clear data on beneficial adjuvant treatment. We tried to reduce the heterogeneity and reveal the benefit of adjuvant treatments.

Methods: We reviewed medical records of Pusan national university hospital and Kosin university gaspel hospital which have details of initial pathological report between 2006 and 2016. The inclusion criterion was resection with curative intent. We selected subtypes which have been known to be moderately chemosensitive or relatively chemo-insensitive for less heterogeneity.

Results: We investigated subtypes of STS which have been known to have similar chemosensitivity : angiosarcoma(n=4), dedifferentiated liposarcoma(n=7), epithelioid sarcoma(n=4), leiomyosarcoma(n=15), malignant peripheral nerve sheath tumor(n=5), myxofibrosarcoma(n=14), pleomorphic liposarcoma(n=4), pleomorphic rhabdomyosarcoma(n=1) and pleomorphic undifferentiated sarcoma(n=18).

The Log Rank test showed that adjuvant radiation therapy (RT) prolonged progression-free survival (PFS). Clear resection margin and adjuvant chemotherapy did not show significant effect on PFS or overall survival. The multivariate analysis by Cox proportional model which had included pathological subtypes, anatomical locations, stage at the diagnosis, resection with clear margin, adjuvant chemotherapies and adjuvant RT revealed that adjuvant RT significantly prolonged PFS (odds ratio=2.522, P=0.014). The multivariate analysis for overall survivals did not show any significance with any variables including adjuvant RT.



Conclusion: Adjuvant RT prolonged PFS in moderately chemosensitive or relatively chemo-insensitive STS regardless of complete resection with clear margin or adjuvant chemotherapy. Adjuvant chemotherapy did not prolonged PFS and overall survival in this group of STS.

Poster 310 #2804751

WHOLE EXOME SEQUNECING REVEALS THE ORDER OF GENETIC CHANGES DURING METASTASIS IN TWO INDIVIDUALS WITH NF1-MPNST

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Objective: Malignant peripheral nerve sheath tumors (MPNSTs) are aggressive sarcomas that occur at increased frequency in individuals with neurofibromatosis type 1 (NF1). These tumors have limited treatment options and a high propensity to metastasize leading to a dismal overall survival. While previous studies have employed a variety of discovery approaches to identify genes associated with MPNST pathogenesis, little is known about the genetic events leading to metastasis of these tumors.

Methods: Whole exome sequencing was performed on biopsy materials from two patients with NF1-MPNST. Samples from patient one included primary tumor, a lung metastasis, and a bone metastasis. Samples from patient two included primary tumor, and two different lung metastases.

Results: We demonstrate several interesting points. First, we identified the NF1 mutations in each patient as well as copy number loss of CDKN2A across all primary and metastatic samples consistent with these genes serving as drivers of progression. Second, we have identified a limited number of exonic mutations in both primary tumors which include mutations in PLEC, DDX11, TAF5, and OR2L3. Finally, mutations in TRIM family members were identified in all metastatic lesions: TRIM7 and TRIM23 in lung metastases and TRIM49 was found to be mutated in the bone metastasis suggesting that the TRIM family of genes may be important for metastasis of MPNSTs.

Conclusion: Collectively, the ability to track the molecular evolution of MPNST in two individuals with metastatic disease offers new insights into genetic events important for metastatic progression for future mechanistic studies which are underway currently and will be presented this fall.

Poster 311 #2804862

EVIDENCE MAPPING BASED ON SYSTEMATIC REVIEWS OF THERAPEUTIC INTERVENTIONS FOR SOFT TISSUE SARCOMAS

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Objective: The purpose of this evidence mapping is to identify, describe and organise the current available evidence about therapeutic interventions on sarcomas.

Methods: We followed the methodology of Global Evidence Mapping (GEM). We searched Pubmed, EMBASE, The Cochrane Library and Epistemonikos in order to identify systematic reviews (SRs) with or without meta-analyses published between 1990 and March 2016. Two authors assessed eligibility and extracted data. Methodological quality of the included systematic reviews was assessed using AMSTAR. We organised the results according to identified PICO questions and presented the evidence map in tables and a bubble plot.

Results: A total of 24 SRs met eligibility criteria. These reviews included 66 individual studies, of which three quarters were either observational or uncontrolled clinical trials. Overall, the quality of the included SRs was moderate or high. In total, we extracted 64 PICO questions from them and the corresponding results mostly favoured the intervention arm.

Conclusion: This evidence mapping was built on the basis of SRs, which mostly included non-experimental studies and were qualified by the AMSTAR tool as of moderate quality.The evidence mapping created from PICO questions is a useful approach to describe complex and huge clinical topics through graphical media and orientate further research to fulfil the existing gaps. However, is important to delimitate the steps of the evidence mapping in a pre-established protocol.

Poster 312 #2796188

CLONAL DYNAMICS IN LIPOSARCOMAS FOLLOWED FOR UP TO 25 YEARS

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Objective: While intercellular genetic heterogeneity among cancer cells has been amply demonstrated, less is known about how evolution acts on such variation. We evaluated the waxing and waning of mutations in two pathogenetically distinct types of liposarcoma: gene fusion-driven myxoid liposarcoma (MLS) and amplicon-driven well-differentiated liposarcoma (WDLS).

Methods: Whole Exome Sequencing
TSCA-Sequencing
SNP-Array
Cytogenetic analysis

Results: Some surprising observations were made when the chromosome and nucleotide level mutations in primary tumors (PT) were compared with those in local recurrences (LR) and/or metastases (Met) occurring 1-25 years later. First, MLS displays few mutations other than the FUS-DDIT3 fusion, and the PT is genetically sometimes much more complex than its LR or Met. Second, although WDLS displays extreme intercellular variation at the cytogenetic level, this has only minor impact on the structure of core amplicons in chromosome arm 12q.

Conclusion: Thus, some sarcomas seem to obtain a genetic fitness maximum early in tumor development.

– SURGICAL ONCOLOGY –

Poster 313 #2760245

THE PROPHYLACTIC ANTIBIOTIC REGIMENS IN TUMOR SURGERY (PARITY) INTERNATIONAL RANDOMIZED CONTROLLED TRIAL

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Objective: PARITY is an international multi-center randomized controlled trial (RCT) in which patients with a primary bone tumor or oligometastatic bone disease of the lower extremity undergoing endoprosthetic reconstruction are randomized to one of two study arms: 1 day of post-operative antibiotics (cefazolin), or 5 days of post-operative antibiotics (cefazolin). PARITY is the first ever multi-center international RCT in orthopaedic oncology. Over the last year, the trial has experienced a major breakthrough with global participation.

Methods: PARITY patients are randomized by the pharmacy team at each site through an online randomization program (www.randomize.net). The remaining study participants (patients, surgeons, nurses, study personnel) are blinded to treatment allocation. The primary outcome is surgical site infection and outcomes are adjudicated by the PARITY Adjudication Committee through an online secure platform (Global Adjudicator™). Data is monitored for patient safety by an independent Data Safety and Monitoring Committee. Data quality is screened at regular intervals to maintain high standards of data quality.

Results: A total of 45 clinical sites across 9 countries and 5 continents have opened for enrolment in the PARITY trial. At the time of abstract submission, 254 patients have been randomized across sites in the United States, Canada, Argentina, Brazil, South Africa, Spain, the Netherlands, Australia and India. Sites recently open to enrolment or currently in the active start-up phase represent the United States, the Netherlands, Spain, India, Austria, Israel, Egypt, Singapore, Latvia, Slovenia and Italy. The baseline infection rate for these reconstructive surgeries based on the PARITY pilot data is 15%. The enrolment target is 600 patients, and the study is on pace to reach 50% of this target number by the end of 2017. Funding is available until 2021.

Conclusion: Infection rates are high in lower extremity bone cancer surgery. Peri-operative antibiotics can be extended past the date of surgery, but this intervention may not improve outcomes. PARITY has proven the feasibility of prospective international collaborative RCTs in orthopaedic oncology. Due to widespread international participation, the PARITY investigators have achieved sufficient momentum to reach the mid-point of enrolment by the end of this year, thus instilling confidence in study completion in the expected timeframe.

Poster 314 #2804796

SURGICAL OUTCOMES AND RECURRENCE FOLLOWING NEOADJUVANT DENOSUMAB TREATMENT IN PATIENTS WITH RESECTABLE GIANT CELL TUMOR OF BONE (GCTB): RESULTS OF A PHASE 2, OPEN-LABEL TRIAL

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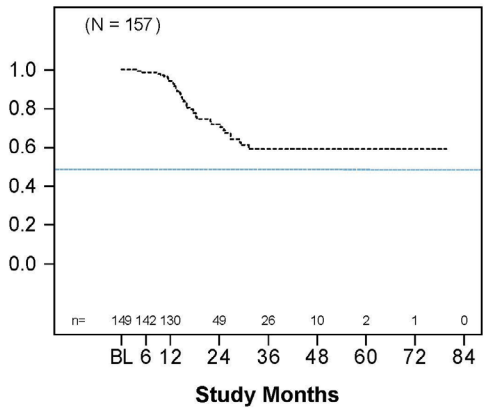
Objective: Surgical resection is standard treatment for many GCTB patients but may be associated with severe morbidity. Interim results from an open-label phase 2 study showed that denosumab was associated with a less morbid procedure in most patients with resectable GCTB. This updated analysis evaluates surgical invasiveness and recurrence after denosumab treatment in patients with resectable GCTB where planned surgery carried high morbidity.

Methods: Adults or skeletally mature adolescents with resectable GCTB whose planned surgery was associated with high morbidity (eg, joint resection, amputation) received neoadjuvant denosumab 120 mg SC every 4 weeks (loading doses on days 8 and 15) and 6 doses postoperatively. Planned and actual GCTB-related surgical procedures before and after denosumab treatment were reported.

Results: 248 patients, including 14 adolescents, enrolled in the planned surgical cohort and were evaluable for ef-

ficacy. Median (range) age was 34 (13–82) years. 168 (66%) patients had primary disease and 85 (34%) had recurrent disease at enrollment. Median (IQR) follow-up was 44 (26–59) months and median (IQR) denosumab administered was 20 (15–43) doses. 157 (63%) underwent surgery on-study. Kaplan-Meier (KM) estimate of time to surgery was 9.2 (95% CI, 8.5–10.5) months. The majority of patients who underwent surgery achieved complete resection (151; 96%), with 106 (68%) undergoing a less morbid procedure than planned at enrollment. The most common GCTB surgeries performed were intralesional curettage (90, 57%), en bloc resection (30, 19%) and joint replacement/prosthesis (10, 6%). GCTB recurrence following any surgery was observed in 42 (27%) patients; median time to recurrence was not estimable (Figure; 25th percentile KM estimate for time to recurrence was 18.5 [95% CI, 15.9–24.3] months). Compared to en bloc resections, recurrence after curettage was more frequent (34% vs 12%). Clinical benefit (pain reduction, improved mobility/function) was reported in 79% (197/248) of patients.

Figure. Kaplan-Meier Curve for Time to Disease Progression or Recurrence After First On-Study GCTB Surgery



BL=baseline; N=number of enrolled patients who received at least one dose of denosumab and who had on-study GCTB surgery.

Conclusion: In patients with resectable GCTB where surgery carries high morbidity, denosumab treatment decreased the invasiveness of surgical interventions without a compromise in complete resection rates. A 27% recurrence rate following surgery was seen in this high-risk population (34% had recurrent disease at enrollment). Recurrence following curettage was higher than after resection, indicating careful selection of surgical procedure is warranted.

Poster 315 #2804199

LONG-TERM, PATIENT-REPORTED OUTCOMES AFTER TUMOR RESECTION AND OSTEOARTICULAR ALLOGRAFT RECONSTRUCTION OF THE DISTAL RADIUS

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Objective: What are the long-term, patient-reported outcomes associated with distal radius osteoarticular allograft reconstruction?

Methods: We retrospectively identified patients treated with an osteoarticular allograft reconstruction after oncologic distal radius resection between 1976 and 2015. Only patients aged 18 years or older were included. We identified 21 patients for which we collected patient-, tumor- and treatment characteristics through a chart review. The median age at osteoarticular allograft reconstruction was 40.1 years (IQR 27.5 – 46.6). All tumors were primary sites (no metastases). To evaluate the long-term patient reported outcomes we used the PROMIS Physical Function, Toronto Extremity Salvage Score (TESS) for the Upper Extremity, and the QuickDASH. We approached 17 patients, as 4 had passed away, and received responses from 8 patients that had a median follow up of 13 years (IQR 10.1 - 28.8). The histopathological diagnoses were giant cell tumor (7) and leiomyosarcoma (1).

Results: No patients required amputations for definitive treatment, and no patients developed local recurrence. The most common complication was joint degeneration (75%), followed by proximal migration (62.5%), ulno-carpal impaction (62.5%), radiocarpal subluxation (37.5%), and allograft fracture (25%). Only 1 out of 8 (12.5%) patients required revision surgery during this follow up period. The median PROMIS score was 56.9 (IQR 44.7-60), median QuickDASH score was 11.4 (IQR 4.6-21.6), and the median TESS score was 95.5 (IQR 83.5-97.7), see Table 1.

Table 1: Patient-reported outcomes

Patient-Reported Outcome Measure	Overall Results [median, (IQR)]
PROMIS Physical function	56.9, (44.7 - 60)
QuickDASH	11.4, (4.6 - 21.6)
TESS Upper Extremity	95.5, (83.5 - 97.7)

Conclusion: Functional limitations are commonly reported consequences of osteoarticular allograft reconstruction, and this concept was further investigated in this study. In this cohort, nearly all patients reported intact sensation, good strength, and moderate range of motion. This is supported by good long-term patient reported outcomes. Complications such as articular degeneration, proximal carpal migration and ulno-carpal impaction

seem to not significantly impact the functional outcomes. The limitations of this study include its retrospective design, small sample size, and potential for recall bias. Despite these limitations, helpful data was gathered to better understand the efficacy of osteoarticular allograft reconstruction. We highlight the good surgical and functional results of osteoarticular allograft reconstruction as the treatment for tumors of the distal radius.

Poster 316 #2782209

MOVING FORWARD THROUGH CONSENSUS-USING A MODIFIED DELPHI APPROACH TO DETERMINE TOP RESEARCH PRIORITIES IN THE FIELD OF ORTHOPAEDIC ONCOLOGY

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Objective: Orthopaedic oncology has lagged behind other surgical specialties in the development of high level evidence through the execution of randomized controlled trials (RCTs) and collaborative prospective studies. In order to move forward as a specialty, it would be beneficial to the orthopaedic oncology community to identify research priorities through a consensus-based approach.

Methods: A *modified* Delphi process was employed to identify priority research questions relevant to musculoskeletal oncology. This process included:

Phase I – Identification of Research Questions
Potential research questions were identified through an open-ended questionnaire asking participants to identify up to three research questions that they believed were of importance to the field.

Phase II – Assessment of Research Questions
A second questionnaire was administered asking participants to rate the proposed research questions individually on a five-point Likert scale on five criteria: scientific merit, significance, innovation, relevance and feasibility.

Phase III – Deliberation and Prioritization
An Expert Panel consensus meeting (Table 1) was held to deliberate the results from the previous phase, and prioritize the research questions based on criticality and feasibility. Following these discussions, the Expert Panel was asked to assign scores for each research question, and those that met predetermined criteria were brought forward for final ranking.

Results: The research questions with the four highest scores in the final ranking stage were:
First: Does less intensive surveillance of sarcoma patients affect survival?
Second: What are the outcomes over time of orthopaedic oncology implants?
Third: Does resection vs. stabilization improve oncologic outcomes in oligometastatic bone disease without compromising functional and surgical outcomes?
Fourth: What is the natural history of untreated fibromatosis?

Demographic characterisitcs of the Consensus Expert Panel

Total No. of Participants	44
Gender	
Male	36
Female	8
Age	
Less Than 30	0
30 – 40	21
41 – 50	13
51 – 60	9
Over 60	1
Country	
Africa	***1***
South Africa	1
Asia	***3***
India	1
Israel	1
Japan	1
Europe	***4***
Austria	1
Denmark	1
Netherlands	1
Spain	1
North America	***32***
Canada	3
United States of America	29
South America	***4***
Argentina	1
Brazil	3
Occupation	
Orthopaedic Surgeon	42
Clinical Research Manager	1
Patient Representative	1
Completion of Orthopaedic Oncology Fellowship	
Yes	37
No	3
Not Applicable	4
Years in Practice	
Less Than 5	12
5 – 10	13
11 – 15	5
16 – 20	5
Over 20	7
Not Applicable	2
Type of Institution	
Academic	42
Non-Academic	1
Not Applicable	1
Proportion of Practice Constitutes Management of Orthopaedic Oncology Patients	
0 – 25%	1
26 – 50%	4
51 – 75%	9
76 – 100%	26
Not Applicable	3

Conclusion: A systematic, consensus-based approach was used to determine the top research priorities in the field of orthopaedic oncology. It is anticipated that the results of this initiative will support the development of international prospective studies in the field, which will ultimately generate research findings that will enhance orthopaedic oncology clinical practice. Working groups will be established to advance progress on these key research priorities.

Poster 317 #2803377

3D PRINTED PATIENT SPECIFIC MODELS AND SURGICAL CUTTING TOOL GUIDES IN BONE SARCOMAS HELP ACHIEVE ACCURATE RESECTION AND RECONSTRUCTION

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Objective: The purpose of this study was to assess the accuracy of 3D printed cutting guides in complex resections of bone sarcomas and the short term follow-up.

Methods: Fifteen patients with bone sarcomas underwent surgery from January 2016 to June 2017 at a tertiary sarcoma center and are included in this study. All patients had a surgical plan based on a CT and MRI scan.The tumor and resection margins were first segmented on the imaging and resection plains were then placed just outside the margins. A model was printed for improved preparation and planning. Based on the surgical approach, planned neurovascular dissection and bone surface exposure; resection guides were planned and printed. These tools enable accurate execution of the planned cutting plains by including a slit through which cutting tools are guided; such as an oscillating saw, osteotome and a Gigli saw. The printed guide conforms to the bone surface and the cutting slit aligns the cutting tool to the planned resection plain.
Tumor subtypes included Ewing sarcoma 6, high grade Osteosarcoma 6, bone MFH 1, Parosteal osteosarcoma 1, Chondrosarcoma 1. Anatomic locations included pelvis 5, distal femur 4, tibia 5, fibula 1. Surgical resection types included partial pelvic resection type I - 2, type II+III - 3, joint sparing intercalary resection - 8, geometric resection - 2. Resections were reconstructed with implants - 4, allograft - 4, vascularized fibula and allograft - 2, nonvascularized fibula - 1, reimplanted autograft - 1 cement 1 and no reconstruction - 2. Models and cutting guides were printed for all 15 cases, custom printed tools were used to guide reconstruction in 7 cases. Patients aged from 6 to 46 years, gender (females 4, males 1) and follow-up ranged up to 18 months.

Results: All fifteen patients had negative resection margins on pathology analysis. None of the 3D resections were aborted during surgery because of inability to correctly locate the cutting guide. Complications included one vascular surgical complication while no infections or wound complications were noted. There have been no local recurrences and all patients ambulate. Given the short follow-up and variation in anatomic locations distant metastases and functional scores are not reported.

Conclusion: Precision in surgery as measured by negative margin resections on pathology analysis was achieved using patient specific 3D planning, models and custom cutting guides.

Poster 318 #2777828

TRABECULAR METAL COLLARS IN ENDOPROSTHETIC REPLACEMENTS: DO THEY OSTEOINTEGRATE?

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Objective: Trabecular metal (TM) is a biomaterial that is inert, strong and elastic making it ideal for osteointegration. It has been used successfully in orthopaedics for >15 years. To our knowledge no previous study has investigated bone ingrowth with TM collars in endoprosthetic replacements (EPR) for tumour. We have used the Zimmer system with TM collar since 2010.
We aimed to assess radiological ingrowth into TM collars in tumour EPRs. We wished to identify if osteointegration was achieved and the time period for this.

Methods: All patients undergoing an EPR for tumour were identified using our prospectively collected database. We performed a retrospective casenote review assessing oncological and functional outcomes.
Osteointegration was analysed on AP and lateral radiographs. Each collar region was divided into four. If radiolucent lines were present, no osteointegration occurred. This was then scored 0 to 4 based on numbers of integrated interfaces observed. Two orthopaedic consultants independently graded ingrowth at three months, one year and last appointment.

Results: 49 patients were included. The BMI ranged from 19 to 47 (mean 26). The modified Glasgow Prognostic Score was 0 in 22, 1 in 13 and 2 in 14 patients. 82 percent had tumours in their femora, 6 percent in their tibia and less than 1 percent involving their pelvis. 11 percent had tumours in another location. 49 percent had a primary bone tumour, 8 percent had a soft tissue sarcoma, 31percent had metastatic disease and 12 percent had a haematological malignancy. Post operatively 76 percent were allowed to partially weight bear, 16 percent fully weight beared and 4 percent were kept non weight bearing. 2 patients underwent revision surgery for infection, none for aseptic loosening. Follow up ranged from 3 to 60 months, with a mean of 25.
Osteointegration as noted radiographically is summarised in table 1.
The radiographic analysis results of both orthopaedic oncology consultants correlated strongly, Spearman's coefficient equaled 0.92.

Bone ingrowth score	3 months (no. of patients n=49)	12 months (no. of patients n=38)	Last appt (no. of patients n=49)
4	9	11	14
3	2	0	1
2	14	11	18
1	0	0	0
0	24	16	16

Table 1, Number of patients with radiographic osteointegration at 3 months, 12 months and at last appointment post operatively.

Conclusion: TM collar osteointegration improves with time often taking over 12 months. Those with no evidence of integration at 3 months are at high risk of never osteointegrating. This does not necessarily adversely affect the outcome. A larger series, with longer follow up, will aid our understanding of the TM collar role in improving implant longevity and potential effect on the need for revision surgery. Early results are encouraging, with low implant failure and revision rates in the short term.

Poster 319 #2786151

DUODENAL RESECTION FOR RETROPERITONEAL SARCOMA AND GIST: SHORT-TERM OUTCOMES

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Objective: Surgery is the mainstay of retroperitoneal sarcomas (RPS) and gastrointestinal stromal tumours (GISTs) treatment. Duodenal resections are sometimes necessary to achieve radicality, but surgical short-term outcomes are unclear due to lack of data and rarity of disease. The aim of this study was to review our experience in patients with RPS and GISTs involving the duodenum, and to analyse the surgical approach and outcome.

Methods: We identified all patients who underwent surgery with duodenal resection for RPS and GISTs, at our Institute between 2000 and 2016. Medical records, operative reports, radiological charts and pathology were reviewed. Demographics, clinical, pathologic and treatment variables were analysed.

Results: Thirty-one patients (19 males, 13 females) were treated: 16 for GISTs and 15 for RPS. The median age was 58 years. Preoperative treatment was given to 10 patients: chemotherapy (6) or combined chemo-radiotherapy (4). Sixteen duodenal wedge resections (WR) and 15 segmental resections (13 of which included Treitz's loop resection) were performed. Multi-organ resection was performed in 71% of cases. The median time to flatus and bowel movement was 3 and 5 days. Oral refeeding started after a median of 5 days. Median post-operative hospital stay was 11 days. The overall 30-day postoperative morbidity rate was 65%, while the duodenal-related complication rate was 28%. Morbidity rates were higher in segmental resections compared to WRs: delayed gastric emptying/paralytic ileus 4/15 vs 1/16; duodenal leak 3/15 vs 0/16; volvulus 1/15 vs 0/16. All 3 patients with duodenal leak had previous abdominal surgery and 2 also chemotherapy. No correlations were found between complications and type of anastomosis or duodenal portion resected.

Conclusion: Duodenal resections for RPS and GISTs have significant rates of morbidity and should be performed in specialized centers. When possible, WR is preferred to segmental resection as it is associated with a lower morbidity rate.

Poster 320 #2791684

AUGMENTED-REALITY NAVIGATION ASSISTANCE IN PELVIC BONE CANCER SURGERY: AN EXPERIMENTAL STUDY

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Objective: Even with improvement in treatment modalities, patients with malignant neoplasm of the pelvic girdle are still at a high risk of having treatment failure because of inadequate surgical margin obtained. Introduction of navigation-assistance may improve oncological and functional outcomes in pelvic bone cancer treatment. However, somewhat cumbersome process and high cost may hinder the use of navigation. To address this issue, we developed an Augmented-Reality (AR) based navigation system which simply requires tablet PC instead of complex navigation system. In this study, we evaluated the accuracy of AR-based navigation assistance in resection of the bone tumor model of pig pelves.

Methods: We developed an AR program for pelvic cancer resection, which can display resection margin from all directions and run on a tablet PC. We designed an experimental bone tumor model in pig pelves for the simulation of tumor resection. A cortical window was made on the acetabulum and bone cement was inserted. Thirty six bone tumor models were created around the acetabulum and assigned through 1:1 allocation to the AR-assisted resection group and conventional resection group. The tumor resection was simulated in two manners. One was AR assisted resection performed by an orthopedic resident and the other was conventional resection by an expert orthopedic oncologist. For both groups, the bone tumor resection was planned with 10-millimeter safety margin from the edge of bone cement. In the conventional group, the resection was performed based on CT images. In AR group, the resection was performed under AR-guidance. The distance from the edge of cement to the resection margin was evaluated by an independent orthopedic surgeon. Seventy-two surgical margins of 36 pelves were evaluated.

Results: The mean resection error of 36 resections in 18 pelves in the AR group was 1.59 ± 1.35mm (range, 0-6 mm). The mean error of 36 resections in 18 pelves in the conventional group was 4.55 ± 3.17 mm (range, 0-11 mm). A statistically significant difference was observed between AR-assisted and conventional resections ($p <$

0.00) (figure 2). The probabilities of a surgeon obtaining a 10-millimeter safety margin with a 5-mm tolerance were 100% in AR group, 73.7% in conventional group.

Conclusion: We demonstrated that accuracy of tumor resection was satisfactory with the help of AR-navigation system. This concept made the navigation system simple and available without additional cost and time.

Poster 321 #2791799

THE EFFICACY OF INTRAOPERATIVE ANHYDROUS ETHANOL THERAPY AFTER CURETTAGE FOR ANEURYSMAL BONE CYSTS IN PEDIATRIC PATIENTS

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Objective: Aneurysmal bone cyst (ABC) is a bone tumor arising in pediatric patients frequently, and tumor curettage is performed commonly for a treatment. Although several intraoperative adjuvant therapies after curettage were reported, local recurrence occurs in 11-30% cases. Intraoperative anhydrous ethanol therapy has been reported to reduce recurrence rate in other bone tumors such as giant cell tumor of bone. However, reports of the efficacy of intraoperative anhydrous ethanol therapy for ABC are rare. The purposes of this study were to investigate the efficacy of intraoperative anhydrous ethanol therapy, and to examine potential risk factors of recurrence of ABC in pediatric patients.

Methods: ABCs of pediatric patients (under 16 years old) which were performed tumor curettage in Tohoku University Hospital between January 1998 – December 2015 were included in this study. Kaplan-Meier method was used with the log-rank tests to compare local control rates between subgroups of patients who had been performed the intraoperative anhydrous ethanol therapy (ethanol group) and had not been performed (non-adjuvant group). Cox proportional hazards analysis was conducted to calculate the hazard ratio (HR) and 95% confidence interval (CI) for tumor recurrence according to intraoperative anhydrous ethanol therapy and potential risk factors as follows: age, sex, tumor location, proximity to the growth plate, pathological fracture, experiences of recurrence, tumor length, tumor volume, and internal fixation.

Results: The final study population was comprised of 34 cases (aged 2 to 16 years old, male 64.7%). The follow up period was 1 to 107 months. Among them, 70.6% (n = 24) of patients were in the ethanol group and 29.4% (n = 10) of patients were in the non-adjuvant group. Tumor recurrence occurred in 41.2% (n = 14) cases (Table 1). The local control rate of 5 years after operation was 73.4% in ethanol group, and 33.3% in non-adjuvant group (Fig.1). In ethanol group, the recurrence rate decreased significantly (Sex, age-adjusted HR [95% CI]: 3.21 [1.04-9.93], p = 0.042). In cases without experiences of tumor recurrence, the recurrence rate decreased significantly (Sex, age-adjusted HR [95 CI]: 0.30 [0.09-0.93], p = 0.038) (Table 2).

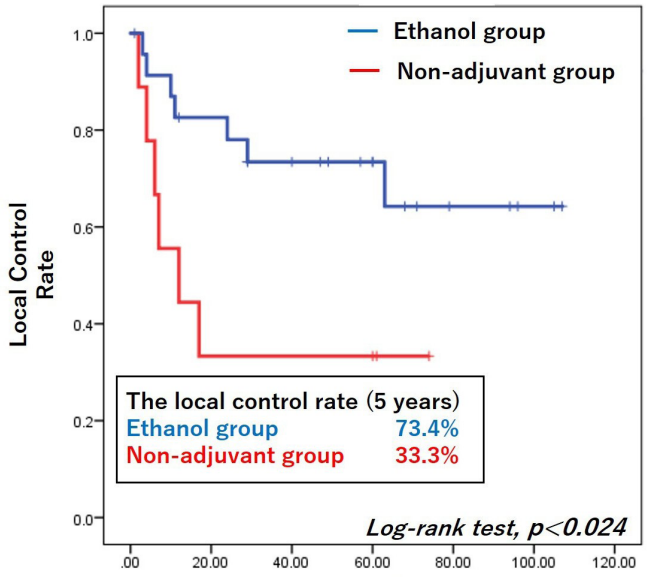

Figure 1

Conclusion: Intraoperative anhydrous ethanol therapy can reduce recurrence rate, and recurrent case would be a risk factor of recurrence for ABC in pediatric patients.

Table 1: Basic characteristics of aneurysmal bone cyst (ABC) in pediatric patients.

Variables	Categories	Median (IQR)	Persentage
Sex	Male		64.7
	Female		35.3
Age (years)		12.0 (7.0 - 13.0)	
Tumor location	Around hip lesion		67.6
	Extremity		32.4
Proximity to the growth plate	(+)		32.4
	(-)		67.6
Pathological fracture	(+)		23.5
	(-)		76.5
Experiences of tumor recurrence	(+)		67.6
	(-)		32.4
Tumor length (cm)		4.2 (3.3 - 8.4)	
Tumor volume (cm3)		37.6 (11.4 - 104.8)	
Internal fixation	(+)		29.4
	(-)		70.6
Intraoperative anhydrous ethanol therapy	(+)		70.6
	(-)		29.4
Tumor recurrence	(+)		41.2
	(-)		58.8

Table 2

Variables	Category	P value	Hazard ratio	95% CI
Age	Per 1y increase	0.911	0.911	0.853-1.153
Sex	Male	0.404	0.580	0.161-2.085
Tumor location	Around hip lesion	0.076	0.254	0.056-1.152
Proximity to the growth plate	+	0.876	1.131	0.240-5.325
Pathological fracture	+	0.932	1.066	0.247-4.600
Experiences of recurrence	+	0.038	0.301	0.097-0.933
Tumor length	Per 1mm increase	0.537	0.991	0.961-1.021
Tumor volume	Per 1mm3 increase	0.994	1.000	1.000-1.000
Internal fixation	+	0.437	1.713	0.440-6.667
Intraoperative anhydrous ethanol therapy	+	0.042	3.219	1.043-9.934

Poster 322 #2792913

RISK FACTORS FOR LOCAL RECURRENCE IN THE BENIGN VASCULAR TUMORS OF SOFT TISSUE

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Objective: Although biologically benign, treatment of benign vascular tumors of soft tissue is not always simple. Local recurrence is not rare, and they sometimes recur multiple times. Our goal was to evaluate risk factors for local recurrence in the benign vascular tumors of soft tissue.

Methods: Medical records of patients with synovial hemangioma, intramuscular angioma, venous hemangioma, arteriovenous malformation/hemangioma, and angiomatosis from 1999 to 2014 were retrospectively reviewed. Age, gender, location, symptom duration, multiplicity, angiomatosis, multi-layer involvement, main length, and surgical margin were considered as potential risk factors for recurrence.

Results: There were 92 males and 141 females with a median age of 29 years. Median follow-up was 24 months. Univariate analyses demonstrated that 5-year recurrence-free survival rates were 95.4% and 36.5% in patients with negative and positive surgical margin (P<0.001), 46.7% and 88.3% in those with and without angiomatosis (p=0.005), 36.8% and 86.2% in those with

and without multi-layer involvement (p=0.014). Multivariate analyses showed that surgical margin was a risk factor for recurrence (relative risk: 80.835, 95% confidence interval: 18.578-351.732, p<0.001).

Conclusion: Surgical margin was the only independent risk factor for local recurrence in the benign vascular tumors of soft tissue in this study. Extent of tumor such as vertical extension could be more important as a risk factor rather than the size, to achieve complete excision.

Poster 323 #2793417

RADIOGRAPHIC PARAMETERS AND DECISION TREE FOR ASSESSING MECHANICAL FAILURE AFTER COMPRESSIVE OSSEOINTREGRATION LIMB SALVAGE

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Objective: Compressive osseointegration is a newer form of fixation for endoprosthetic reconstruction that may be used for complex limb salvage. It can be difficult to determine if ingrowth has occurred, nor are there established parameters. Therefore we sought a reliable method of determining radiographic ingrowth of prostheses, and any radiographic parameters that show failure of fixation.

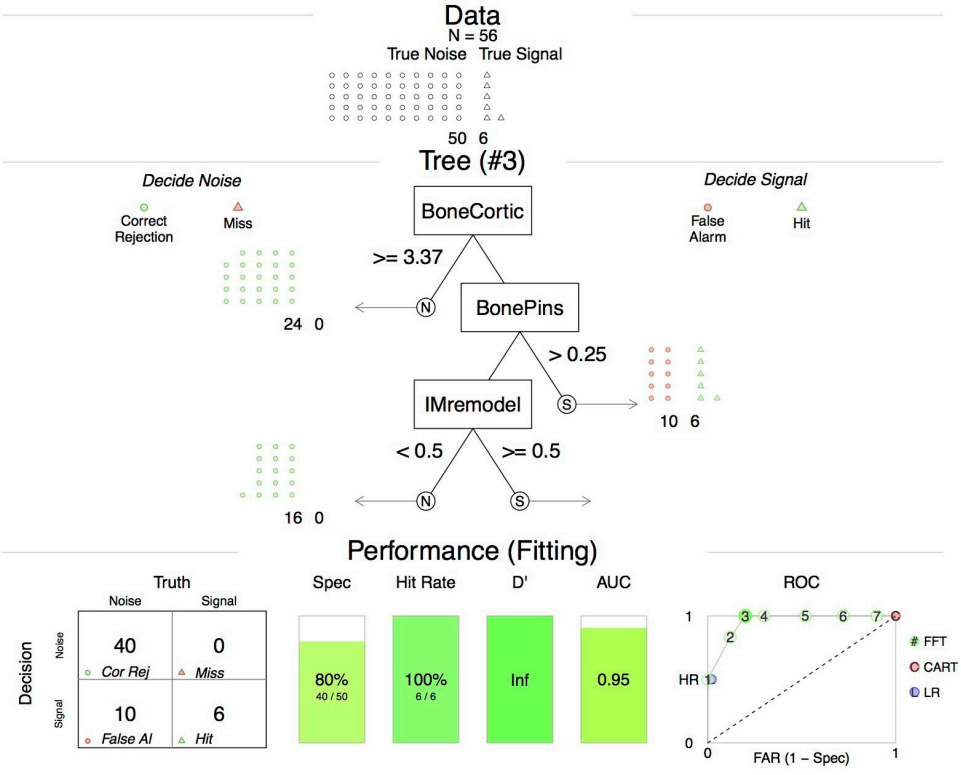
Methods: 29 sets of radiographs were evaluated by 8 reviewers of various training levels. Reviewers were blinded to patient, demographics, and outcomes. Three sets were known failures of fixation that required aseptic revision. For each set, the reviewers compared 2 time points. Radiographic markers assessed were varus/valgus alignment, flexion/extension alignment, evidence of bone hypertrophy at the implant and at the pins, evidence of bone osteolysis, evidence of intramedullary remodeling, number of cortices with bone hypertrophy, difference in bone width (delta hypertrophy), and difference in length between spindle and anchor plug (delta spindle length).
Intraclass correlation coefficients (ICCs) were calculated to assess test-retest and inter-rater reliability. Fisher exact and t-tests were utilized to compare proportions and means. A fast and frugal decision tree (FFT) was constructed to guide risk stratification based on radiographic parameters.

Results: The highest reliability was seen in measuring changes in the spindle difference (ICC=0.85, p<0.01 for all raters) and the number of bone cortices with bone hypertrophy (ICC=0.79, p<0.01 for all raters). Inter-rater reliabilities were all highly significant.

The FFT model selected BoneCortic (number of cortices at implant junction with hypertrophy), BonePins (presence or absence of hypertrophy at pin sites), and IMremodel (presence of absence of intramedullary remodeling at the level of the pins) to build a decision tree, which selected all failures with a specificity of 80% and area under the curve (AUC) of 0.95 (Figure 1).

Conclusion: Compressive osseointegration is an option for limb salvage, which modes of mechanical failure that present differently than stemmed implants. We found good intra-rater and inter-rater reliability for several parameters. A FFT based on three radiographic parameters classified mechanical failures with 100% sensitivity, 80% specificity, and an AUC of 95%. This decision tree provides a means for identifying patients at-risk for mechanical failure following compressive osseointegration reconstruction.

Figure 1: Fast and Frugal Decision Tree



Poster 324 #2804227

RESULTS OF PROMIS PHYSICAL FUNCTION AND PAIN INTERFERENCE SCORES IN SURGICALLY TREATED PATIENTS WITH METASTATIC BONE DISEASE: ANALYSIS AFTER EARLY PATIENT ENROLLMENT IN A MULTICENTER, PROSPECTIVE STUDY

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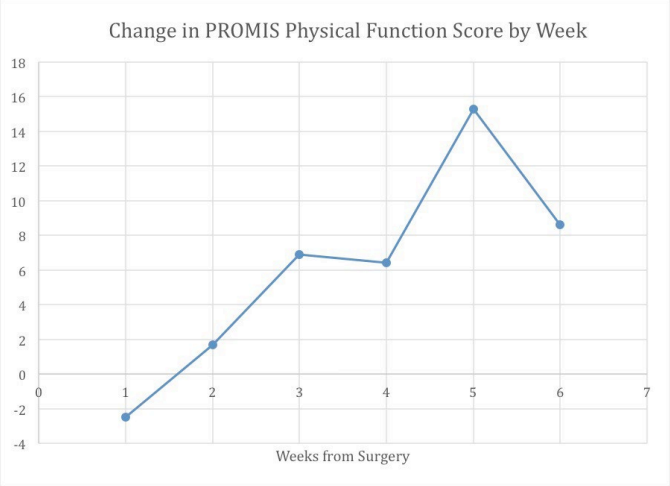
Objective: Approximately 20% of cancer related US health care dollars (12 billion $) are spent managing skeletal related events. Much has been published regarding the benefits of surgical treatment of metastatic bone disease(MBD) including improved function, decreased in hospital morbidity, and significant cost savings. Using PROMIS instruments, we sought to determine if patients' function and pain scores improve after surgical treatment for MBD.

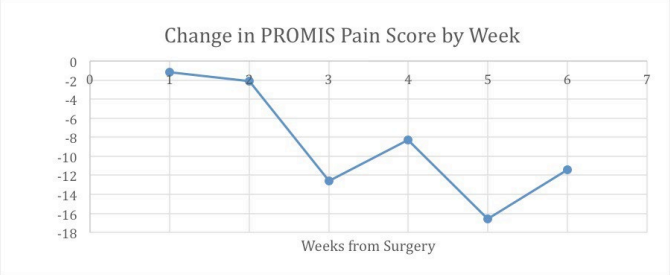
Methods: This is an IRB approved, multicenter, prospective study involving patients treated surgically for MBD. Basic demographic and disease related data were recorded as well as the PROMIS instruments for Pain Interference and Physical Function. Descriptive analysis of all data was performed. PROMIS scores were collected longitudinally and summarized at each point of time to evaluate average change in score over period of time.

Results: A total of 43 records of 13 patients at 9 possible periods of time were recorded: baseline, 1, 2, 4, 6, 10 weeks, 3, 5 and 6 months. Regarding change in physical function score from baseline, the average change at week 1 was -2.5 (SD=5.4), at 2 weeks 1.7 (SD=7.6), after 4 weeks 6.9 (SD=10), after 6 weeks 6.4 (SD =10.9), after 10 weeks 15.3 (SD=3.1), and after 3 months 8.6 (SD=7.6). Regarding change in pain inference score from baseline, the average change at week 1 was -1.2 (SD=7.3), at 2 weeks -2.1 (SD=9.5), after 4 weeks -12.6 (SD=4.5), after 6 weeks -8.3 (SD =10.2), after 10 weeks -16.6 (SD=4.3), and after 3 months -11.4 (SD=8.2).

Conclusion: This study demonstrated trends of increasing physical function and decreasing levels of pain interference after surgery for metastatic bone disease, demonstrating proof of concept that collecting PROMIS data on this population is feasible. Continuing our multicenter, prospective enrollment will hopefully elucidate more information regarding pain and function in surgically treated patients with metastatic bone disease.



PROMIS physicial function scores by weeks from surgery. Increasing score indicates improving function.



PROMIS pain scores by weeks from surgery. Decreasing scores indicate improving pain.

Poster 325 #2804231

ADJUVANT 90YTRRIUM RADIOSYNOVECTOMY IN PVNS DOES NOT IMPROVE LOCAL CONTROL

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Objective: Aims Intra-articular ^{90}Yttrium (^{90}Y) is an adjunct to surgical treatment by synovectomy for pigmented villonodular synovitis (PVNS) of the knee with variable success rates. Clinical information is sparse, and its value is unclear. We investigated the long-term outcome of patients who underwent synovectomy with and without adjuvant ^{90}Yttrium radiosynovectomy.

Methods: All patients with diffuse type PVNS of the knee joint and who underwent synovectomy between 1991-2014 were enrolled. Group A patients underwent synovectomy and intra-articular injection of ^{90}Yttrium 6-8 weeks after surgery and Group B patients underwent surgery alone.

Results: There were 34 patients in Group A and 22 pa-

tients in Group B. Recurrence of PVNS was identified by imaging findings and clinical symptoms of recurrent pain and/or swelling and impaired function. At final follow-up, residual disease was present in 15 Group A patients and 11 Group B patients ($p < 0.363$). The mean MSTS score at last follow-up was 85% and 83%, respectively ($p < 0.91$).

Conclusion: There were no significant differences in the examined parameters between the patients treated surgically for diffuse-type PVNS of the knee with or without adjuvant intra-articular injections of ^{90}Yttrium . We could not provide conclusive evidence of any benefits derived from the adjuvant treatment.

Poster 326 #2804315

VARIABILITY IN TECHNIQUE OF ISOLATED LIMB PERFUSION FOR ADVANCED SOFT TISSUE SARCOMA (ESTS): RESULTS FROM A WORLDWIDE SURVEY

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Objective: Isolated limb perfusion (ILP) is currently considered as an alternative limb sparing treatment option for patients with locally advanced or unresectable extremity soft tissue sarcomas (ESTS). However, ILP is performed at a limited number of referral centers worldwide. The technique is well described but a wide range of differences in techniques and protocol is reported. We hypothesized that significant technical variations exist for this procedure among referral centers.

Methods: Clinicians/surgeons who published institutional series of ILP for ESTS were contacted for a web-based survey. Pre-operative, intra-operative and post-operative management of patients undergoing ILP were assessed. Data collection was limited to STS, while data on ILP for melanoma or other indications were excluded.

Results: Fourteen centers from 11 countries in 4 continents responded. One routinely performs ILI while one routinely uses ILP for osteosarcoma and they were not included in the analyses. Volume of STS operations per year was <50, 50-100 and >100 in 3, 5 and 4 centers respectively. Volume of ILPs was <5, 6-10 and 11-20 in 4, 5 and 3 centers respectively. For desmoid type fibromatosis, 75% of the centers routinely used ILP. Of all centers, 67% repeated ILP in the same patient after recurrence or local progression, while 58% considered observation instead of post-ILP resection as an option. All used TNF, while 58% vs 25% tailor TNF-alpha dose according to tumor site or volume respectively A high variability of hyperthermia thresholds was found (range 38-40.5°C). Circulation time varied from 15' to 30' for TNF-alpha. At the end of perfusion, there was a wide range of volume of fluids used for limb wash out (median volume 4 l, range 0.5-6.0 l). Node dissection is performed only in case of macroscopic involvement or for specific histologies. Isotope leakage monitoring is routinely performed in 75% of centers. ICU admission is routinely used in 50% of centers. Length of hospital stay was uniformly <10 days.

Conclusion: There is a high variability in the ILP protocol for ESTS in the different international centers, suggesting that an update of the 20 years old protocol could be of value. An international cooperative effort may be of help to standardize the technique based on the available evidence and clinical experience, in order to maximize therapeutic benefits and minimize toxicity and costs.

Poster 327 #2804740

SOLVING PROBLEM IN SURGERY OF SARCOMA INVOLVING THE AORTA, SUPERIOR MESENTERIC ARTERY AND INFERIOR VENA CAVA

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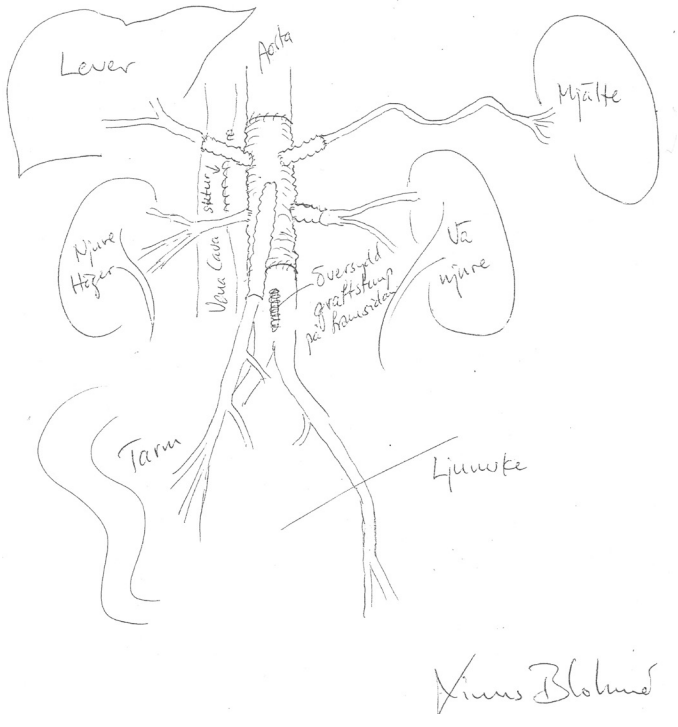
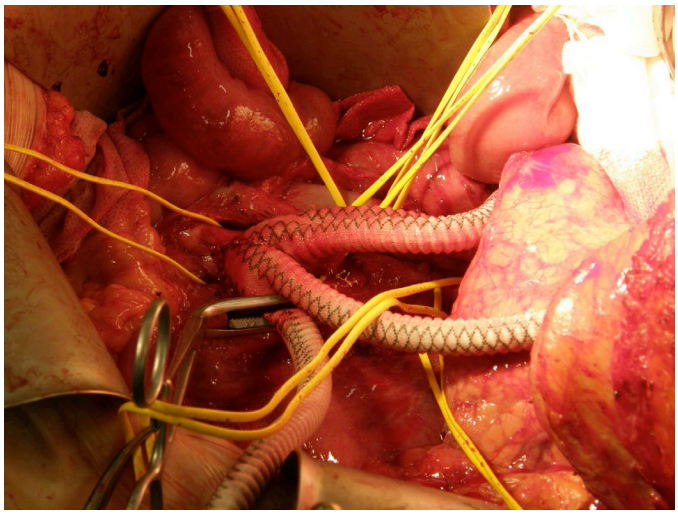
Objective: Sarcoma of the retroperitoneum (RPS) is rare and counts for 10-20% of all sarcoma. Liposarcoma and leiomyosarcoma is the most common types. RPS is often large at diagnosis. Standard treatment is complete resection with adequate margins as for sarcoma at other locations. RPS often implies proximity to and invasion of contiguous vital structures and organs, which makes complete resection with negative margins difficult. The survival is significantly lower than for sarcomas arising at other sites. The difference is assumed mainly due to the difficulty of obtaining adequate surgical margins because of large tumor size and difficult locations. Especially tumors involving aorta and v. cava, particularly if superior mesenteric artery (SMA) and celiac trunk is involved. These tumors is mostly regarded as not operable

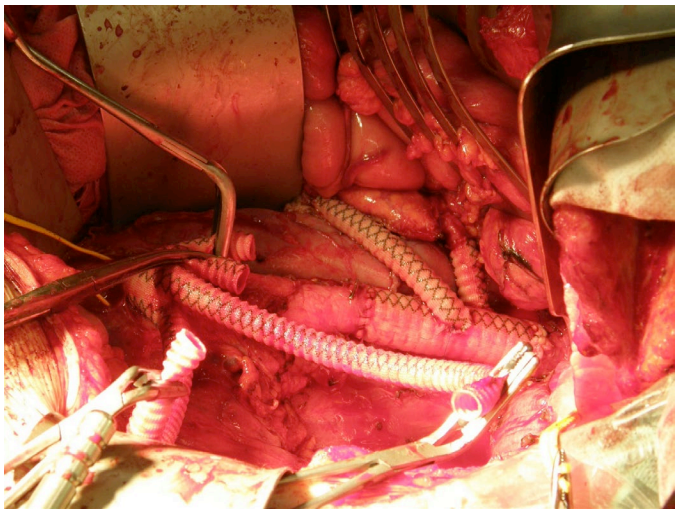
Methods: At the Karolinska Hospital have we operated five patients with sarcoma since 2008 using heart-lung machine in order to get time enough to make a complete resection and reconstruction of tumors involving aorta,

SMA and v. cava. We have also operated one patient with adrenocortical carcinoma with a tumor-thrombosis into vena cava.
Main principle has been that the heart-lung machine supports the lower part of the body by taken blood from inferior vena cava (Fig 1, Fig 2) and supply it to the aortic bifurcation through one leg of four that has been given by suturing two aortic graft together and where the base has been sutured to the aortic bifurcation. The other 3 legs have been sutured to SMA, liver artery and the renal artery. After resection of the tumor the resected part of descending aorta has been replaced by a straight graft and finally has the three “legs” been sutured into the straight graft. The remaining part of the grafts has thereafter been removed (Fig 3).
In the case of tumor thrombosis in the renal vein the main principle has been to go on heart-lung machine, cool down the patient and get cardiac arrest in order to exclude the inferior vena cava from blood supply, thereafter resect the malignant thrombosis together with the rest of the tumor.

Results: All patients except one are still alive. Three without any recurrence while the patient with adrenocortical carcinoma has developed lung metastasis. The patient, who died, was a young man with p53 mutation and he soon after surgery developed new tumors as well as recurrence.







Conclusion: Heart-lung machine makes it possible to resect tumors involving aorta and SMA.

Poster 328 #2804795

TECHNIQUE, COMPLICATIONS, AND FUNCTIONAL OUTCOMES OF GASTROCNEMIUS ROTATIONAL FLAP FOR SOFT TISSUE RECONSTRUCTION FOLLOWING PROIMAL TIBIAL SARCOMA RESECTIONS

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Objective: Proximal tibial sarcomas present a surgical challenge because of extensor mechanism disruption and limited soft tissue for coverage following wide resection. Rotational gastrocnemius flap can be used to augment and cover the patellar tendon reconstruction; however, little data exists regarding the complication rates and functional outcomes of patients following this procedure. Our purpose was to describe our technique of gastrocnemius flap reconstruction and to determine the overall rate of surgical complications; the rate of surgical complications related to the extensor mechanism; and the intermedi-

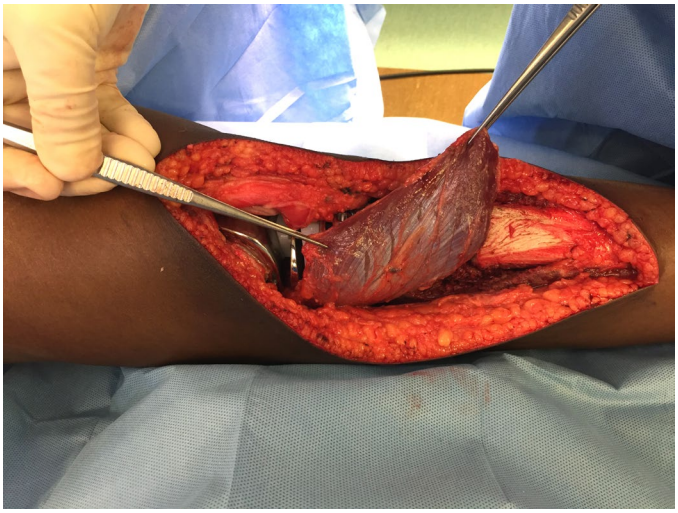
ate/long-term range of motion, extensor lag, and extensor-specific function following this procedure.

Methods: This retrospective case series examined 21 patients who were treated for primary bones sarcomas of the proximal tibia by a single orthopedic oncologist over a 23-year period. One was excluded for allograft reconstruction, and two were excluded for primary closure without a flap; all others underwent endoprosthetic proximal tibial replacement with medial or lateral gastrocnemius flap and split thickness skin graft for anterior knee coverage. (Figure 1) Of these 18 patients, four were excluded for less than two years of follow-up, leaving 14 available for study. Medical records were reviewed for patient demographics, diagnosis, complications related to the flap and extensor mechanism, other complications requiring operative intervention, follow-up range of motion, and follow-up extensor lag. Final outcomes were graded as excellent (flexion ≥110 and no lag), good (flexion 90-110, lag ≤10), fair (flexion <90 or lag>10), or poor (amputation secondary to complications). Extensor-specific function was assessed in terms of ability to rise from a seated position without assistance, climb stairs individually, and ambulate independently without a limp.

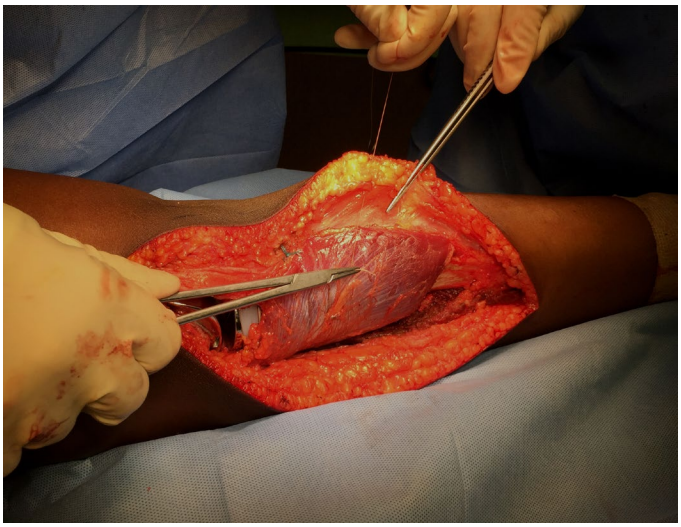
Results: At final follow-up (mean 106, range 28-260 months), 10 patients had undergone a major revision (four mechanical failures, six deep infections), and three experienced a complication related to the flap or extensor mechanism (two patellar tendon avulsions, one flap necrosis). Mean, median, mode, and range were 104, 110, 100, and 60-120 degrees for flexion; and 4, 0, 0, and 0-10 degrees for extensor lag, respectively. Extensor-specific functional outcomes of the reconstruction were excellent in eight patients, good in three, fair in one, and poor in two. All patients with good or excellent function (79% of the total study population and 92% of patients with limb salvage at final follow up) were able to rise from a seated position without assistance, climb stairs individually, and ambulate independently without a limp.

Figure 1. Operative technique for medial gastrocnemius rotational flap following proximal tibial resection and endoprosthetic reconstruction.

A) The patellar tendon remnant is sutured to the prosthesis with the knee in full extension.



B) The medial gastrocnemius flap is rotated anteriorly to cover the prosthesis, including the patellar tendon repair.



C) The flap is sutured to the patellar tendon superiorly and the tibialis anterior laterally to cover the soft tissue defect and augment the extensor mechanism reconstruction.

Conclusion: While general complications requiring major revisions were common, few were directly related to the extensor mechanism or flap, and the majority of patients achieved excellent range of motion and no extensor lag at final follow up. These findings support the use of gastrocnemius flap as a simple, safe, and effective method of soft tissue reconstruction following wide resection of proximal tibial sarcomas.

Poster 329 #2753798

EVALUATING TREATMENT STRATEGIES FOR SPINAL LESIONS IN MULTIPLE MYELOMA: A SYSTEMATIC REVIEW

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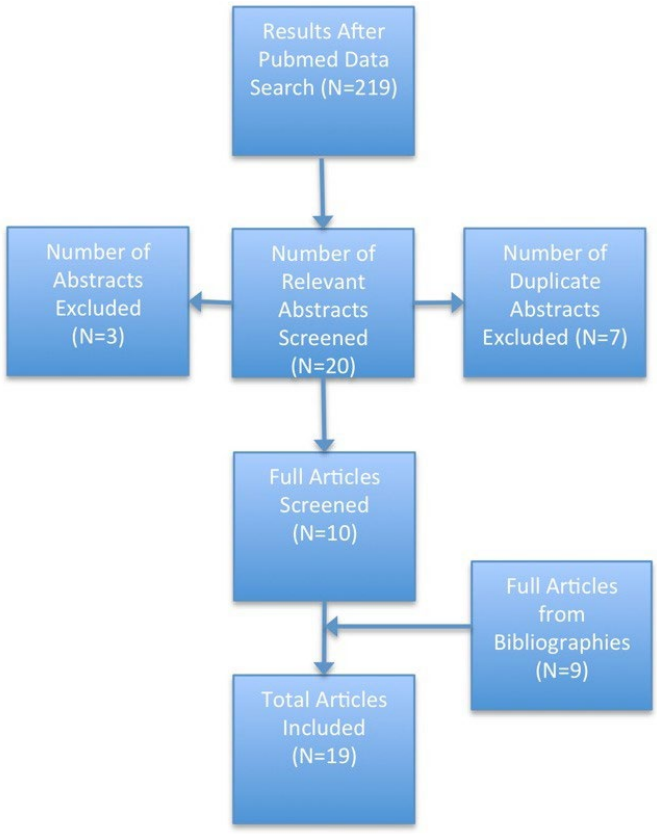
Objective: Vertebral disease is a major cause of morbidity in those with Multiple Myeloma (MM) and is known to cause debilitating pain, functional restrictions, worsening spinal deformity, and cord compression. Currently, various treatment modalities that have demonstrated clinical improvement include systemic therapy, radiotherapy, and cementoplasty (vertebroplasty/kyphoplasty). However a clearly defined superior treatment regimen has not been established. The objective of this systematic review is to report on the efficacy of the aforementioned treatment options and to determine if a logical standardized treatment algorithm for osteolytic vertebral lesions in MM has been described.

Methods: A systematic search of the PubMed database was performed for papers relevant to the treatment of vertebral disease in myeloma patients. A multitude of search terms in various combinations were utilized including but not limited to: “vertebroplasty”, “kyphoplasty”, “multiple myeloma”, “radiotherapy”. Study design inclusion criteria were constituted by English written randomized control trials, prospective, and retrospective cohort studies. Case reports, animal studies, studies without confirmation of MM diagnosis, and those that included spinal metastases but did not stratify by MM were excluded from the review.

Results: Our initial search resulted in 219 articles and was then reduced to 10 papers following full-text review. Further bibliography review yielded an additional 9 papers. Papers were then grouped by treatment modality: radiotherapy, cementoplasty, or combination therapy. The majority of reviewed literature was retrospective and showed improved pain, functional score and vertebral height outcome compared to control therapy across all treatment modalities. While complications of treatment occurred, particularly with cementoplasty, few complications were noted to be clinically significant.

Conclusion: The treatment options presented for vertebral lesions and pathologic fractures as a result of MM demonstrate significant radiographic and clinical improvement. However there is no consensus in the literature as to the best treatment modality as a result of few head to head comparisons. Moreover, the use of treatment options in combination with respect to amount, frequency, or order of delivery is not well characterized due to insufficient literature. Further prospective studies comparing treatment options in myeloma patients are required before implementation of a standardized treatment protocol may occur.



Poster 330 #2760003

A RETROSPECTIVE COMPARISON OF MINIMAL INVASIVE LAPAROSCOPIC PROCEDURES FOR GASTROINTESTINAL STROMAL TUMORS OF THE STOMACH

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Objective: Gastrointestinal stromal tumors (GISTs) are potentially malignant neoplasms, and surgical resection is recommended for the management of localized GISTs. Smaller GISTs, measuring less than 5 cm in diameter, have little risk for intra-operative rupture and thus are good candidates for undergoing laparoscopic surgery. However, the optimal surgical approach still remains controversial, as the technique used depends on not only the tumor size, but also the primary organ and growth pattern. The intra-luminal type often needs a particularly wide resection area, and inadequate surgery for that type is likely to result in the deformation of the rest of the stomach. The aim of this study was to compare the usefulness and difficulty of laparoscopic surgical techniques for the management of gastric GISTs measuring less than 5 cm in size.

Methods: This retrospective study consisted of 30 patients with gastric GIST who were treated from April 2002 to March 2017 at a single institution. The surgical procedures consisted of laparoscopic extra-luminal wedge

resection (ELWR) for 20, single-incision laparoscopic surgery (SILS) for 6, and laparoscopic and endoscopic cooperative surgery (LECS) for 4 patients. The surgical difficulty was evaluated based on the operating time and estimated blood loss. The usefulness was evaluated based on the postoperative complications, hospital stay, and resected non-tumor gastric area. The area was calculated as the resected area minus the tumor area.

Results: Median tumor size was 795 mm2in ELWR,637 mm2 in SILS, and 450mm2 in LECS (p=0.72). The patients with intra-luminal tumor underwent ELWR for 15, SILS for 6, ad LECS for 4. All the patients with extra-luminal type underwent ELWR(p=0.24). There was no statistically significant difference between the three groups in relation to estimated blood loss and operative time. The duration of hospital stay was 8 in ELWR, 8.5 in SILS, and 9 in LECS. One patient in ELWR group experienced grade II postoperative delayed gastric emptying, One patient in SILS group experienced SSI grade II. The patients with postoperative complications needed longer hospital stay as compared with the patients without complications. Resected non-tumor area was significantly smaller in LECS (1457mm2 in ELWR, 771mm2 in SILS, 367mm2 in LECS).

Conclusion: LECS was thus found to be useful for the minimal resection of intra-luminal gastric GISTs. However, the optimum procedure should be selected based on the characteristics of the tumor.

Poster 331 #2791407

THE OUTCOME OF PLUMONARY METASTASECTOMY FOR HIGHI GRADE BONE AND SOFT TISSUE SARCOMAS

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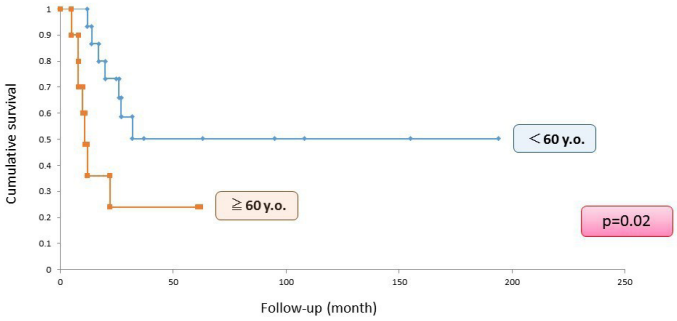
Objective: Sarcomas are a group of very uncommon malignant tumors. The lung is one of the most common organs targeted by sarcoma. Sarcoma with pulmonary metastases are so advanced that the prognoses of patients are unfavourable. Pulmonary metastasectomy for sarcoma is widely accepted as standard therapy and is associated with long-term survival. However, there are no clinical guidelines to optimize patient selection for pulmonary metastasectomy. The purposes of our study are to evaluate clinical parameters in patients who underwent pulmonary metastasectomy for high grade sarcoma metastases and to identify prognostic factors associated with improvement of survival.

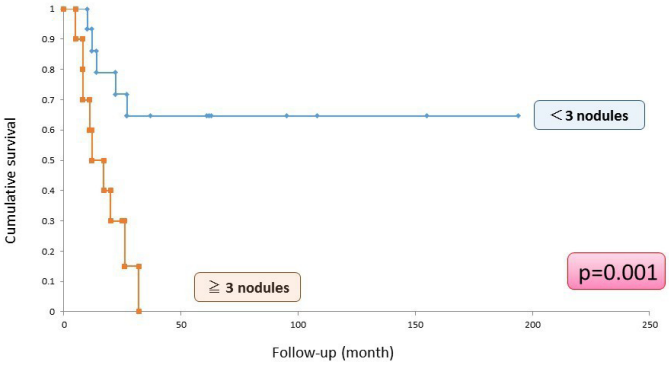
Methods: We performed a retrospective review of patients admitted in our hospital with lung metastases who underwent metasectomy following treatment of the primary sarcoma from June 2000 to November 2016. Prognostic factors, disease-free interval (DFI), age at first pulmonary metasetasectomy, number of pulmonary metastases, laterality of metastases (unilateral or bilateral), maximum size of nodules, associated with overall survival after the first pulmonary metastasectomy were evaluated using Kaplan-Meier method and log-rank test.

Results: Twenty-seven patients underwent pulmonary metastasectomy. The most common diagnosis was undifferentiated pleomorphic sarcoma. The survival rates were 56.0% and 31.8% at 2 years and 5 years, respectively. The age at first pulmonary metastasectomy (<60 y.o.), the number of pulmonary metastases (<3 nodules) and laterality of metastases (unilateral) were significant factors for overall survival. The DFI longer than 12 months tended to be associated with a better survival rate. However, there was no significant difference considering maximum size of nodules.

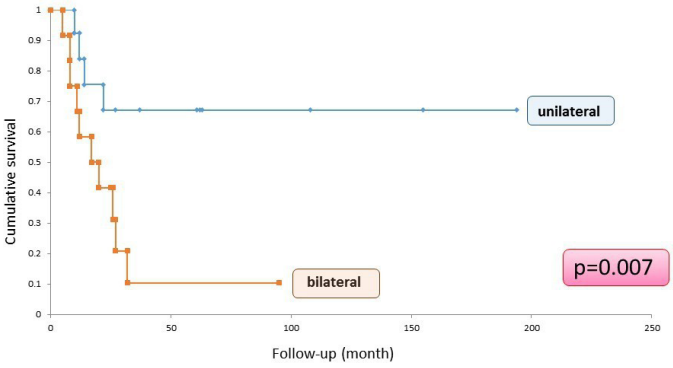
② ***Age at first pulmonary metastasectomy***



③ ***Number of pulmonary metastases***



④ ***Laterality of metastases(unilateral or bilateral)***



Conclusion: It was reported that the 5-year survival rate of pulmonary metastases of sarcoma was 35%. In this study, the 5-year survival rate was 31.8% similar to previous reports. And this study identified a group of patients who may benefit from pulmonary metastasectomy. Repeated pulmonary metastasectomy in select patients may improve survival despite recurrent disease.

Poster 332 #2753794

MULTI-DISCIPLINARY MANAGEMENT OF SPINAL METASTASIS AND VERTEBRAL INSTABILITY: A SYSTEMATIC REVIEW

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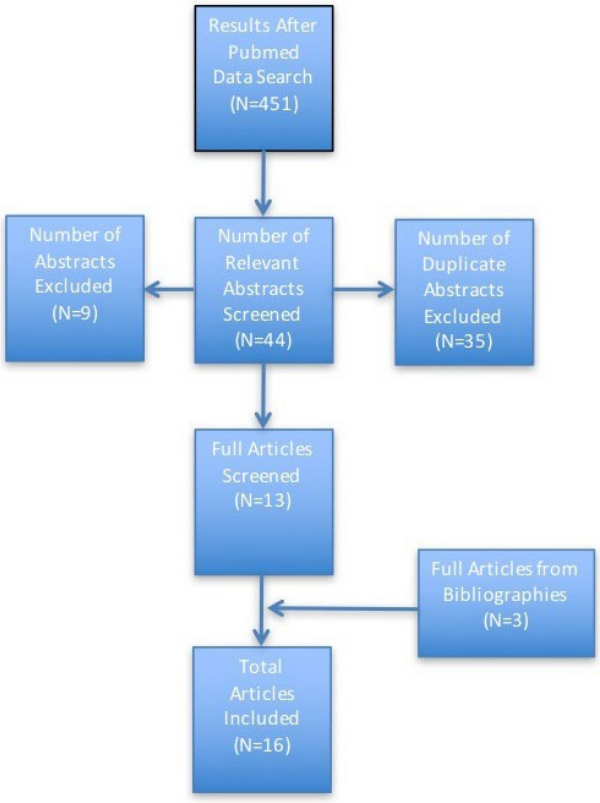
Objective: The aim of this systematic literature review is to evaluate recent attempts in creating a standardized multi-disciplinary approach combining tumor treatment with current vertebral stabilization techniques for palliative treatment of vertebral metastasis.

Methods: We performed a systematic literature search for studies using a tumor modality in conjunction with Kyphoplasty or Vertebroplasty. The following initial search term was used, but not limited to, on Pubmed: "Vertebral Kyphoplasty Metastatic Cancer". In addition, the bibliographies of selected articles were examined for additional studies not viewed in database searches.
Inclusion criteria included: English speaking randomized control trials (RCTs) and retrospective studies using a multi-disciplinary approach of tumor treatment and vertebral stabilization. Non-human studies, case reports, clinical reports without technical outcomes, studies involving patients with osteoporotic or traumatic vertebral compression fractures, and narrative reviews were excluded.

Results: A total of 451 papers were yielded after our database search, 16 of which fulfilled our inclusion criteria. Articles were then divided into categories based on combination and order of tumor modality such as Radiofrequency Ablation (RFA) versus Radiotherapy (includes radiosurgery, external beam radiation therapy, Iodine-125 and Samarium Seeding), PKP or Vertebroplasty. The final categories included: RFA followed by PKP (3), RFA followed by Vertebroplasty (4), Radiotherapy followed by PKP (1), Radiotherapy followed by Vertebroplasty (3), PKP followed by Radiotherapy (3), and Vertebroplasty followed by Radiotherapy (2). Multiple studies reported significant decreases in VAS scores after combined procedures with very low rates of symptomatic complications. Studies that compared their combination to control treatment groups demonstrated greater clinical efficacy.

Conclusion: While multi-disciplinary management of spinal metastasis using a combination of tumor ablation techniques with vertebral stabilization has been recommended in previous literature, this review demonstrates that there is no consensus supporting any specific combination. In addition, there is no consensus of standardized variables used to evaluate efficacy of treatment, limiting the efficacy of treatment results for the analyzed studies. Therefore, further study is needed to try to create a standardized protocol that describes or recommends a combination of approaches that provides maximal effect.



Poster 333 #2792565

RADICAL NEPHRECTOMY FOR PRIMARY RETROPERITONEAL LIPOSARCOMA NEAR THE KIDNEY HAS A BENEFICIAL EFFECT ON DISEASE-FREE SURVIVAL

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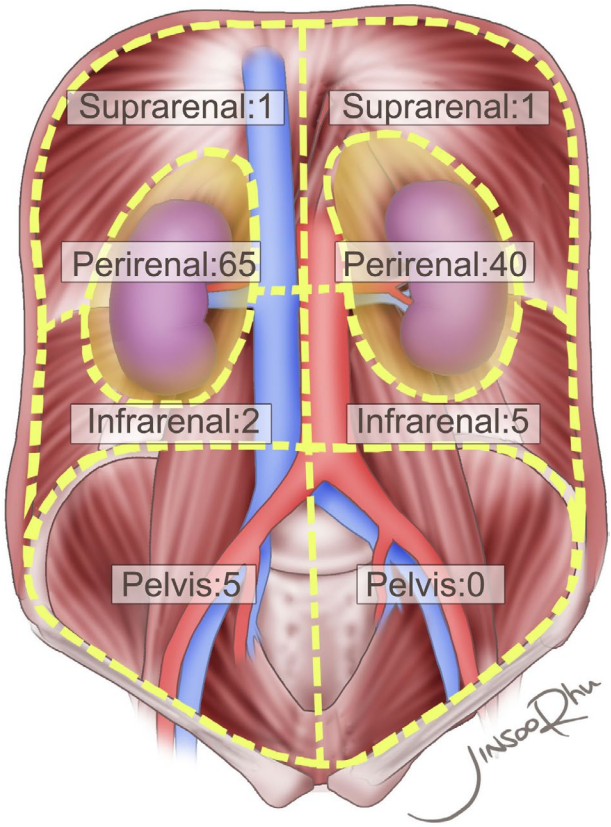
Objective: The purpose of this study is to analyze the clinical impact of radical nephrectomy on retroperitoneal liposarcoma near the kidney.

Methods: Data of patients who underwent surgery for unilateral primary retroperitoneal liposarcoma near the kidney were retrospectively collected. Patients were divided into four groups according to whether they underwent nephrectomy and combined resection of other organs. Kaplan-Meier survival analysis was used to estimate 1-, 3-, and 5-year disease-free survival and overall survival. Multivariable Cox analysis was used to analyze factors related to disease-free survival and overall survival.

Results: The 1-, 3-, and 5-year disease-free survival rates were 70.4%, 56.3%, and 44.6%, and overall survival rates were 95.9%, 79.9%, and 71.8%, respectively. Operation method (p=0.007), and FNCLCC grade (p<0.001; G2, HR=1.833, CI=0.684-4.915, p=0.228; G3, HR=9.190, CI=3.351-25.199, p<0.001) were significant factors for disease-free survival. While combined organ resection without nephrectomy group (HR=1.604, CI=0.167-15.370, p=0.682) and radical nephrectomy with combined organ resection group (HR=1.309, CI=0.448-3.825, p=0.622) did not show significant difference in disease-free survival from the mass excision only group, radical nephrectomy without combined organ resection group (HR=0.279, CI=0.078-0.991, p=0.048) showed superior disease-free survival.



Conclusion: Radical excision with nephrectomy of retroperitoneal liposarcoma near the kidney has a beneficial effect on disease-free survival.

Poster 334 #2804234

A NOVEL METHOD TO PREVENT TERMINAL APPOSITIONAL OVERGROWTH FOLLOWING PEDIATRIC BELOW KNEE AMPUTATIONS

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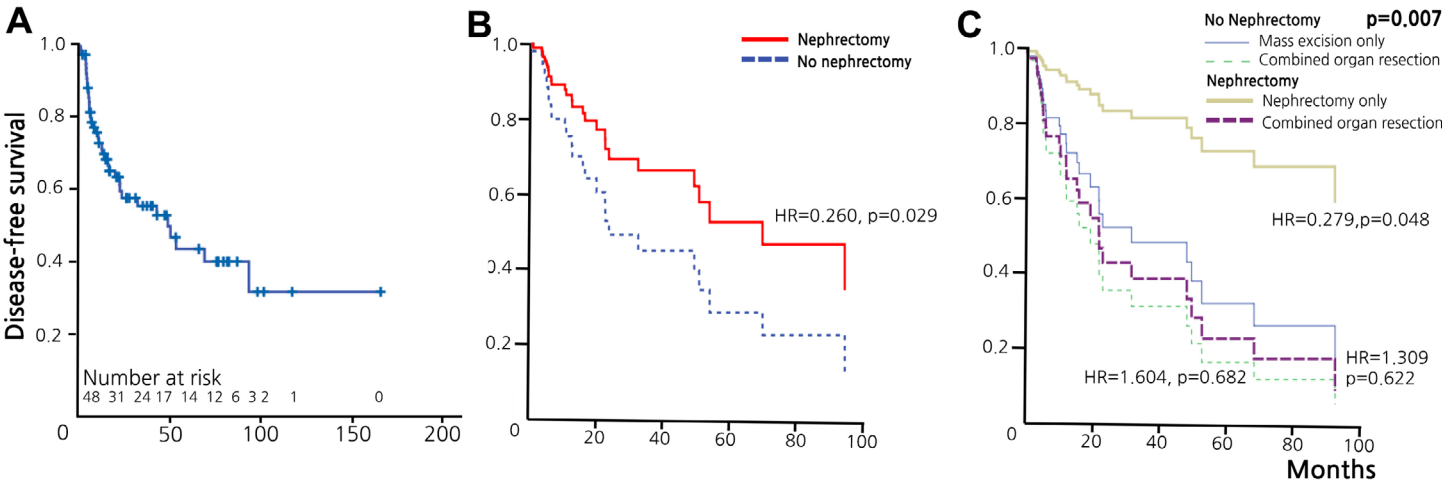
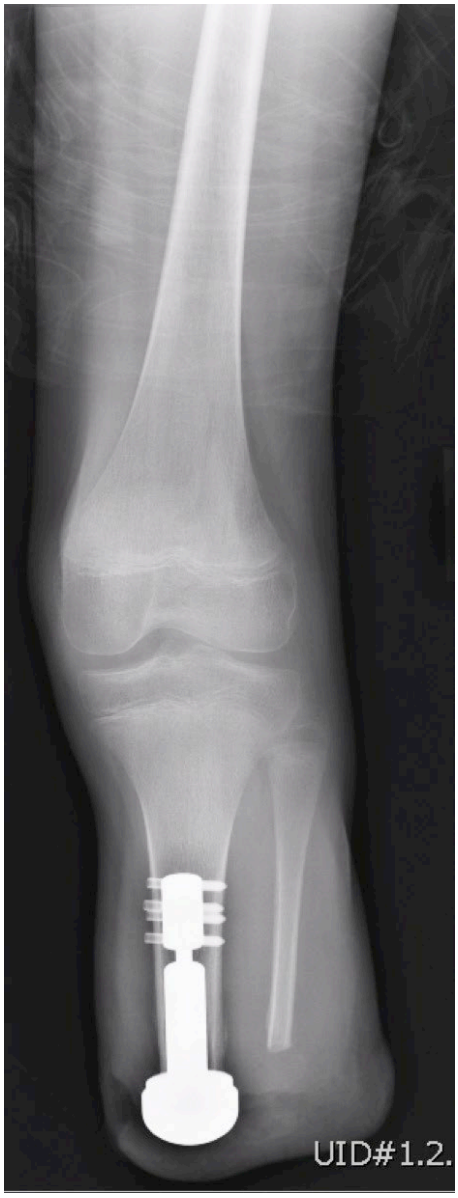
Objective: Terminal appositional overgrowth is a common adverse outcome following trans-osseous amputations in the pediatric population. While surgical resection of the overgrown segment is often performed and well tolerated, recurrence is frequently observed. Previous attempts to inhibit bone overgrowth with implantable devices have resulted in unsatisfactory outcomes. We sought to determine if the use of a compressive osteointegration device with a custom metal cap is a safe and effective method to prevent overgrowth in pediatric amputations.

Methods: We present three cases of pediatric below knee amputations in which custom cobalt alloy end-caps were implanted with compressive osseointegration in an attempt to prevent terminal bone overgrowth and decrease the number of revision procedures required following a trans-tibial amputation in skeletally immature patients.

Results: At short-term follow up, two patients had excellent functional outcomes—engaged in physical activities as desired and accomplished academically. Neither of these patients demonstrated any radiographic boney overgrowth. Both patients did experience superficial wound complications requiring a return to the operating room, however there have not been any complications related to implant durability. Complete inhibition of termi-



nal bony overgrowth has been observed. The third patient did experience a wound dehiscence after an acute traumatic event one month postoperatively and underwent irrigation, debridement and primary wound closure. His wound has subsequently healed and he will soon be fit for a prosthetic.



AP radiograph of the compress cap device in the tibia following below knee amputation.

Conclusion: The application of an end-cap implant utilizing compressive osseo-integration fixation can prevent terminal bone overgrowth in pediatric trans-tibial amputations. It is unclear if wound-healing issues are inherent to this procedure with such a small number of patients; however, short-term evaluations are encouranging. Further follow-up is required to ensure the durability of our results.

Poster 335 #2804370

COMPARISON OF OUTCOMES OF YOUNG ADULT AND PEDIATRIC PATIENTS UNDERGOING THORACOTOMY FOR LUNG METASTASES

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Objective: Adolescents and young adults (AYAs) with cancer have unique medical concerns compared to pediatric counterparts and their surgical management may have unique requirements. AYA patients are known to have improved survival on pediatric chemotherapeutic protocols. However, little is known about the impact of pediatric environment for surgical care of young adults.

Purpose: To compare young adults and children undergoing primary thoracotomy for resection of lung metastases.

Methods: A retrospective institutional review of oncologic patients who underwent thoracotomy between 2012-2017. Demographics, surgical procedural factors, cost and post-operative course were analyzed.

Results: 45 procedures were performed in 34 patients, 21 patients were under 18 years old and 13 were >18. Primary diagnoses and data are listed in Table 1. No significant differences were noted between the 2 groups in operative time, duration of chest tube, length of stay. Although without significant difference, analgesia by epidural was more frequent in adult population.
In 30 day follow up no complications were noted in either group. There were no significant differences for surgical cost and hospital stay for both groups.

Results

Primary Diagnosis	Pediatric (n=21)	Adult (n=13)	
Hepatoblastoma	9	0	
Sarcoma	9	12	
Wilm	2	1	
Hepatocellular Carcinoma	1	0	
Total Procedures	Pediatric (n=30)	Adult (n=15)	p-value
Surgery Length (minutes), median (Q1, Q3)	174.5 (114, 197)	188 (136, 231.5)	0.32
No. Resections, median (Q1, Q3)	4 (3, 6)	4 (1, 7)	0.54
Any PICU days, % (n)	23.3% (7)	6.6% (1)	0.16
No. C-tube days, median (Q1, Q3)	2 (2, 3)	2 (1, 4)	0.89
No. Surgery days, median (Q1, Q3)	4 (3, 5)	4 (3, 5)	0.78
Any Epidural days, % (n)	46.7% (14)	66.7% (10)	0.20
Any PCA days, % (n)	53.3% (16)	33.3% (5)	0.20

Conclusion: AYA patients have unique developmental and emotional challenges compared to their younger and older counterparts, Surgical intervention in AYA patients cared for within a pediatric environment shows no significant differences when compared with pediatric patients undergoing the same procedure. AYA patients can safely undergo multi-disciplinary care including surgical treatment within a single pediatric environment without need to fragment care.

– SURVIVORSHIP/LATE EFFECTS –

Poster 336 #2797454

TREATMENT OF SOFT TISSUE SARCOMA IN PATIENTS AGE 80 YEARS OR OLDER

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Objective: Because of the demographic changes, the proportion of elderly patients is rapidly increasing in Japan; by 2060, 40% will be older than 65 years compared to 26.7% in the current population. It is estimated that 1/3 will be comprised by 80 years or older. Due to the increased incidence of cancer with advanced age, elderly patients with soft tissue sarcoma (STS) will likely increase. Elderly patients are more likely to have various comorbidities and decreased performance status which pose significant problems for an effective treatment. In this study, we analyzed our management and clinical outcome of STS in patients older than 80 years of age.

Methods: Between 1991 and 2017, 19 STS in patients older than 80 years of age were treated at our institutes (15 male and 4 female). The average age was 84.3 years (range 80-89), and the median follow up period was 37.8 months (range 6-146). Tumors were localized in the upper extremity (n=5), lower extremity (n=7), and trunk (n=7). Histological diagnosis included undifferentiated pleomorphic sarcoma (n=6), myxofibrosarcoma (n=6), liposarcoma (n=4), and others (n=3). 8 cases were locally recurrent cases referred to our institutes for further treatment.

Results: Wide resection was performed in 12 cases (including 2 amputations), marginal resection in 4 cases, and intralesional resection in 3 cases. 6 cases underwent plastic reconstruction and 1 case underwent post-operative radiation. There were 5 local recurrences and 3 distant metastases. Oncological outcomes were 8 CDF, 8 NED and 3 DOD, and 5-year disease specific survival was 63.3 %.

Conclusion: Generally, STS patients older than 80 years receive surgery when feasible and rarely receive chemotherapy. In order to maintain as much pretreatment ADL as possible, less aggressive treatment might be implemented, but could lead to multiple operations like our 2 cases who had to undergo amputation. There were no peri-operative deaths, and although there is a possibility of higher complication rate, aggressive surgery should be indicated when feasible and can be performed safely. There have been several reports of risk stratification tools for surgery in elderly patients, but there are still unknown factors that need to be elucidated. Further accumulation of data including prospective studies are needed to refine the treatment for elderly patients.

Poster 337 #2804669

THE LONG-TERM SURVIVAL OF MEGA-ENDOPROSTHETIC RECONSTRUCTIONS AFTER TWO-STAGE REVISION SURGERY FOR PERIPROSTHETIC JOINT INFECTION

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Objective: Mega-endoprosthetic reconstructive surgery offers both oncologic and non-oncologic patients an important treatment option for limb salvage. Periprosthetic joint infections (PJI) are a devastating complication that affect between 2-10% of patients and commonly result in additional invasive procedures, amputation, and sometimes death. The difficulty in dealing with these infections is attributed to the elusive nature of its diagnosis and complexity of treatment. Despite this risk, mega-endoprosthetics remain a preferred treatment option. However, there is little published data evaluating the survival of mega-endoprosthetic reconstructions after two-stage revision surgery with cement spacers for the treatment of periprosthetic joint infections. We investigated the following questions:

1. What is the survival of mega-endoprosthetic reconstructions after re-implantation following two-stage revision surgery with a cement spacer for the treatment of a PJI?
2. How does the length of the bony defect (i.e. the size of the cement spacer) affect survival of the reconstruction or future complications?
3. What is the functional status of patients following re-implantation of mega-endoprosthetics as evaluated by validated questionnaires?

Methods: This study evaluates mega-endoprosthetic reconstruction survival after PJI and two-staged reconstruction using a cement spacer. We retrospectively reviewed the charts of 22 patients (23 limbs) treated for mega-endoprosthesis infection with cement spacer between 1990 and 2017 by a group of orthopedic surgeons at a single

institution. We analyzed the effect of spacer length on the survival of the prosthesis and number of associated complications. Complications included recurrent periprosthetic joint infection, prosthesis failure due to loosening or separation, and amputation. For the evaluation of functional outcomes we used patient-reported quality of life surveys EQ-5D and Lower Extremity Functional Scale Questionnaire.

Results:

1. After the two-stage revision and re-implantation there was a 43% chance of complication, including eight patients treated for recurrent PJI and two patients treated for mechanical failure of the reconstruction. In this series there was a 17% chance of amputation following two-stage revision surgery.
2. Spacers of greater than 10 cm yielded 90% (9/10) of the complicated surgeries and 38% (5/13) of the non-complicated surgeries. Spacers of less than 10 cm yielded 10% (1/10) of the complicated surgeries and 62% (8/13) of the non-complicated surgeries.
3. The average LEFS was 35.5 out of 80. For the EQ-5D mobility averaged 1.9, looking after myself averaged 1.6, activities of daily life averaged 1.6, pain or discomfort averaged 1.9, and feeling worried/sad/unhappy averaged 1.5.

Conclusion: In our series 83% of patients in the study retained their limb at a minimum of two years post-operative follow up. The data confirmed that as the size of the bony defect increases, which directly correlates to the size of the cement spacer, the patient had a higher probability of undergoing more surgeries in the future. Additionally, those limbs with complications were more likely to eventually result in an amputation. The validated questionnaires suggested moderate functionality despite the severity and invasiveness of limb salvage surgery. This information leads us to believe that a mega-endoprosthetic PJI can be successfully managed using a two-stage revision with cement spacer though the complication rate remains high and the surgeon must be mindful of how much bone is resected before re-implantation.

PO 001 #2791875

L-TYPE AMINO ACID TRANSPORTER 1 (LAT1) EXPRESSION IN PROXIMAL-TYPE EPITHELIOID SARCOMA: A CASE REPORT

S. Yahiro[1], *T. Fujimoto*[1], *T. Sudo*[2], *I. Fujita*[1], *T. Sakuma*[3], *T. Takai*[4], *N. Fukase*[5], *M. Morishita*[1], *T. Kawamoto*[5], *H. Hara*[5], *T. Akisue*[6], *R. Kuroda*[5], *T. Hirose*[3]

[1]Department of Orthopaedic Surgery, Hyogo Cancer Center, Akashi, JAPAN; [2]Section of Translational Research, Hyogo Cancer Center, Akashi, JAPAN; [3]Department of Pathology, Hyogo Cancer Center, Akashi, JAPAN; [4]Department of Dermatology, Hyogo Cancer Center, Akashi, JAPAN; [5]Department of Orthopaedic Surgery, Kobe University Graduate School of Medicine, Kobe, JAPAN; [6]Division of Rehabilitation Medicine, Kobe University Graduate School of Medicine, Kobe, JAPAN

Objective: Proximal/axial type of epithelioid sarcoma (PES), a rare malignant tumor in adults, was described as a variant of epithelioid sarcoma (ES) by Guillou in 1997. Different from conventional ES that commonly involves distal parts of upper extremities, PES is seen primarily in axial locations such as pelvic or genital regions with a relatively more aggressive behavior and poor prognosis, and, presently, there is no effective treatment other than wide surgical resection. Described here is a case of PES expressing LAT1, and discussed is the potentiality of new treatment methods for PES.

Methods: Case report.

Results: A 24 year-old woman presenting with a 10cm painful tumor in the right inguinal region was referred to our hospital, where imaging studies showed a subcutaneous well-defined solid mass near the right side of the genital region, but no metastatic area. Histological examination revealed that the tumor was predominantly composed of round epithelioid cells including cells showing rhabdoid features. Immunohistochemically, tumor cells were positive for cytokeratin and EMA, but lacked expression of INI1. Furthermore LAT1 was focally detected in tumor cells. Although, the patient underwent wide local excision of the primary tumor, follow-up MRI showed local recurrence two month after the surgery, but no metastasis. A second wide local excision was, therefore, carried out, and postoperative radiation therapy was administered. Nonetheless, local recurrence and abdominal metastasis were subsequently observed; the patient declined further treatment and died three months after the second surgery.

Conclusion: The present highly aggressive case of PES, with no effective treatment as reported to date, expressed LAT1, however (Fig. 1). LAT1 strongly expressed in the membranes of many malignant tumors, transports not only large neutral amino acids, especially essential amino acids needed for cell proliferation, but also a boron compound used in boron neutron capture therapy (BNCT). Since BNCT is based on the atomic interaction between boron, which selectively accumulates in tumor cells, and low-energy thermal neutrons, it destroys individual tumor cells. Therefore, LAT1 expression in PES is of clinical interest in that it is a target of LAT1 inhibitors and BNCT, and may potentially be a new and effective therapy. Only one clinical case is described here; therefore, further, larger studies are warranted.

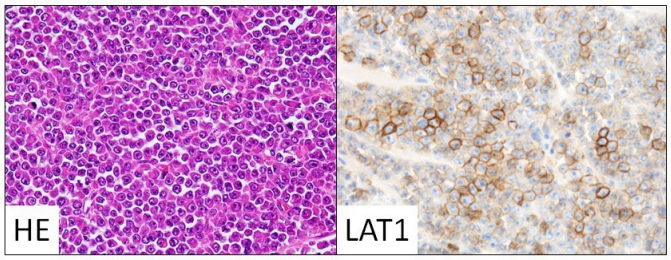

Fig.1 Diffuse proliferation of round epithelioid tumor cells including rhabdoid cells. (HE staining, X200). LAT1 is expressed on cell membranes of many tumor cells. (LAT1 immunohistochemistry, X200)

PO 002 #2791880

A PHASE 2 MULTI-CENTER INVESTIGATION OF THE EFFICACY OF ABI-009 (NAB-RAPAMYCIN) IN PATIENTS WITH ADVANCED MALIGNANT PERIVASCULAR EPITHELIOID CELL TUMORS (PECOMA)

A. J. Wagner[1], *R. Riedel*[2], *B. A. Van Tine*[3], *R. Chugh*[4], *K. Ganjoo*[5], *L. D. Cranmer*[6], *S. M. Pollack*[6], *K. Sankhala*[7], *V. Ravi*[8], *J. Hornick*[9], *D. Kwiatkowski*[9], *B. Grigorian*[10], *N. Desai*[10], *M. Dickson*[11]

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Objective: PEComa is a rare subset of soft tissue sarcomas with a strong female predominance and a median age of ~43 years. Most PEComas are benign and treated with surgery, but there are no therapies approved for the treatment of unresectable or metastatic malignant PEComas. This patient subset has a poor prognosis, with median survival estimated at 12-17 months. Recent case studies have shown mTOR pathway activation often through

TSC2 mutations or deletion, making advanced PEComas a promising target for mTOR inhibitors. This prospective study will assess the safety and efficacy of ABI-009, a nanoparticle albumin-bound rapamycin (nab-rapamycin), a novel mTOR inhibitor, in patients with advanced malignant PEComa.

Methods: The study is currently enrolling patients. Approximately 35 patients without prior mTOR inhibitor treatment will be enrolled. ABI-009 100 mg/m2 is given intravenously, weekly for 2 weeks followed by a week of rest until disease progression or unacceptable toxicity. Cycles are repeated every 21 days. The primary endpoint is overall response rate, as determined by independent radiologic assessment using RECIST v1.1. CT/MRI scans will be performed every 6 weeks for the first year, followed by every 12 weeks thereafter until disease progression. Secondary endpoints are duration of response, progression-free survival (PFS) rate at 6 months, median PFS, median overall survival, and safety. Exploratory endpoints include pharmacokinetic/pharmacodynamic relationships for safety and/or efficacy endpoints, as well as correlative studies including mutations in the primary tumor sample (exome sequencing/300 genes), cell free plasma DNA analysis (next-generation sequencing), FISH analysis for translocations of TFE3, immunohistochemistry of relevant pathway markers, and analysis of post-treatment (progression) biopsies for causes of resistance. An external data monitoring committee will assess safety data when 1/3 of patients have enrolled and received at least 2 cycles of therapy. ClinicalTrials.gov: (NCT02494570).

Results: The study is ongoing.

Conclusion: Currently there are no results available.

PO 003 #2793097

TRABECTEDIN IN ELDERLY PATIENT WITH RETROPERITONEAL LIPOSARCOMA: A CASE REPORT

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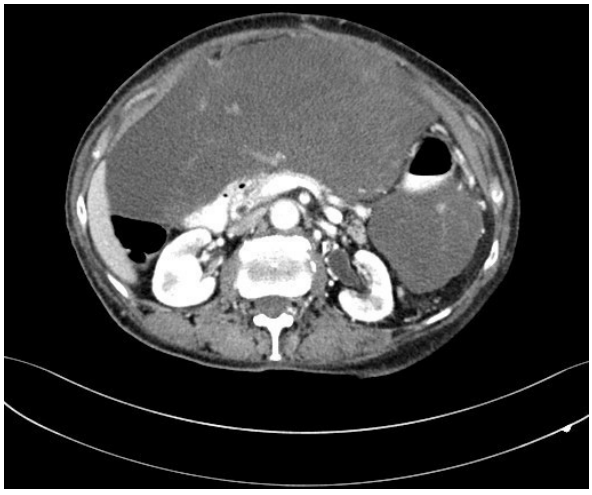
Objective: The definition of elderly is evolving due to longer life expectancy and improved general health. However there is some skepticism as to palliative chemotherapy for elderly patients. We present a case report of an eighty-three years old female with rapidly relapsed retroperitoneal liposarcoma treated with trabectedin as the first line of chemotherapy.

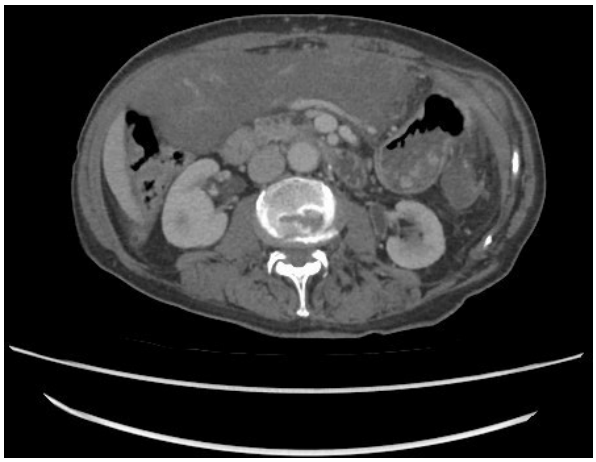
Methods: The patient presented with 2 months' history of increased abdominal girth, vomiting and dyspnea. CT revealed contrast enhancing abdominal tumors. The patient was in PS ECOG 1. In June 2015 the R1 tumor resection was performed. The histopathology revealed multifocal well-differentiated diffuse infiltrating liposarcoma, FNCLCC grade 1, mitoses 2/10 HPF, and necrosis <50 %. A multifocal intraperitoneal relapse was shown 3 months later. CT scan in October 2015 confirmed rapid tumor growth, indicating malignant transformation. Chemotherapy with Trabectedin was initiated in October 2015. During the next 6.5 months the patient received 9 cycles, with no hematological toxicity and transient elevation of ALP and ALT.

Results: CT scan after the 3rd cycle of chemotherapy showed SD, however the patient reported symptom relief. Next CT scans after the 6th cycle revealed partial response and minor volume reduction after 9th cycle. After disease progression in June 2016 the patient received low dose doxorubicin weekly as a second line of therapy with SD for 6 months as best response.

Despite inclusion of elderly patients in clinical trials of Trabectedin, there are few reports on efficacy and tolerability of the treatment in this patient group. The PubMed search gave 95 hits on "sarcoma" and "elderly" and "trabectedin". After discarding publications, where the oldest patients were less than 65 years as well as pre-clinical studies, the number was reduced to 56. Still only few report therapy tolerance and efficacy in patients in the 9th life decade. Despite increasing expected lifespan and relatively high incidence of liposarcoma in older population there is a paucity of literature on chemotherapy response in older patients. Here we present a case of a patient diagnosed with aggressive, rapidly progressing liposarcoma and ralatively long lasting effect of chemotherapy with preserved quality of life in the 9th decade of life.



CT scan before initiation of Trabectedin



CT scan after 4 months of treatment with Trabectedin

Conclusion: We conclude that palliative chemotherapy of elderly patients is feasible and patients in their 8th and even 9th decade with good performance status and limited comorbidity should be considered for the treatment.

PO 004 #2796188

CLONAL DYNAMICS IN LIPOSARCOMAS FOLLOWED FOR UP TO 25 YEARS

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Objective: While intercellular genetic heterogeneity among cancer cells has been amply demonstrated, less is known about how evolution acts on such variation. We evaluated the waxing and waning of mutations in two pathogenetically distinct types of liposarcoma: gene fusion-driven myxoid liposarcoma (MLS) and amplicon-driven well-differentiated liposarcoma (WDLS).

Methods: Whole Exome Sequencing
TSCA-Sequencing
SNP-Array
Cytogenetic analysis

Results: Some surprising observations were made when the chromosome and nucleotide level mutations in primary tumors (PT) were compared with those in local recurrences (LR) and/or metastases (Met) occurring 1-25 years later. First, MLS displays few mutations other than the FUS-DDIT3 fusion, and the PT is genetically sometimes much more complex than its LR or Met. Second, although WDLS displays extreme intercellular variation at the cytogenetic level, this has only minor impact on the structure of core amplicons in chromosome arm 12q.

Conclusion: Thus, some sarcomas seem to obtain a genetic fitness maximum early in tumor development.

PO 005 #2798851

CHRONICE OSTEOMYELITIS MIMICKING OSTEOSARCOMA: A CASE REPORT

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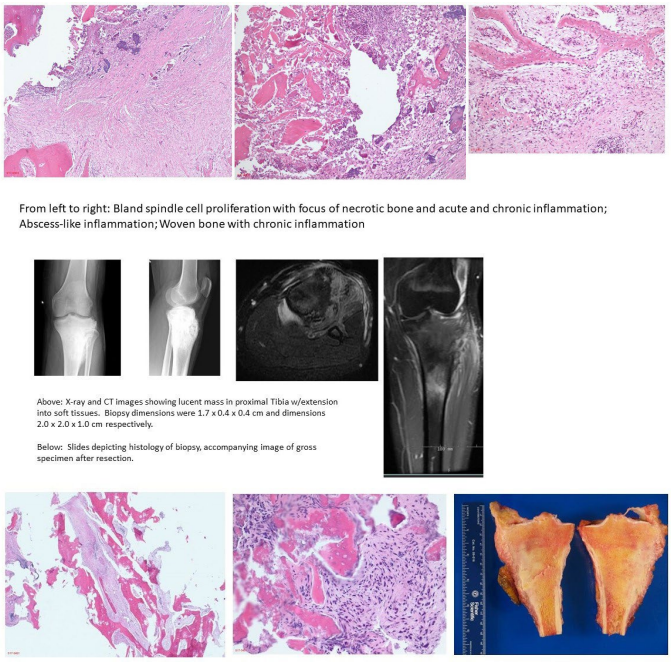
Objective: Chronic osteomyelitis is a deep bone infection that can present with medullary and periosteal features and may be radiographically indistinguishable from low-grade Osteosarcoma (OST) (World J Surg Onc 11:283). As the gold standard of diagnosis, biopsy with histologic analysis and culture helps discriminate between the two (Phys Sportsmed 36:1). There is no standard protocol in cases where biopsy fails to definitively eliminate OST. Wide excision is indicated for OST while chronic infection may be treated with a variety of surgical approaches depending on extent of disease. In cases where the diagnosis is unclear, the surgeon may be compelled to treat the lesion more aggressively with wide margin surgery (JCO 2699:12). We present such a clinical dilemma.

Methods: A literature review was conducted in Pubmed, Scopus, and Google Scholar using 'Osteomyelitis', 'Osteosarcoma', and 'Differential Diagnosis'.

Results: A 22-year-old female with unremarkable medical history presented to our clinic with three weeks of knee pain and swelling. Similar symptoms had been present intermittently dating back 5 years. The patient was physically active, but had no history of trauma. She had received no treatment aside from occasional use of NSAIDs. Radiographs revealed a hyperdense non-geographic mass within the left proximal tibia. MRI imaging demonstrated a soft tissue component with abnormal enhancement involving the proximal calf musculature, favoring low-grade osteosarcoma given the radiographic appearance and the patient's age, but other neoplastic and infectious entities remained on the differential. Both initial core trephine biopsy and a repeat open biopsy were suggestive but not definitive for low-grade OST. An expert second opinion of the histology was obtained, which concurred with our impression that low-grade OST was the most likely diagnosis. All findings, imaging, and opinions were reviewed by our multidisciplinary tumor board and a wide resection was recommended. Wide en bloc resection followed by mod-onc reconstruction was performed. Pathological examination of the final specimen revealed focal areas of woven bone surrounding dense scar-like fibrosis with chronic inflammation that was not previously evident on

either biopsy, supporting low-grade sclerosing osteomyelitis.



From left to right: Bland spindle cell proliferation with focus of necrotic bone and acute and chronic inflammation; Abscess-like inflammation; Woven bone with chronic inflammation

Above: X-ray and CT images showing lucent mass in proximal Tibia w/extension into soft tissues. Biopsy dimensions were 1.7 x 0.4 x 0.4 cm and dimensions 2.0 x 2.0 x 1.0 cm respectively.

Below: Slides depicting histology of biopsy, accompanying image of gross specimen after resection.

Conclusion: The reported case demonstrates a clinical dilemma: when diagnosis of osteomyelitis and osteosarcoma are equivocal, there is no standard procedure to eliminate one of these diseases. In this case, surgical intervention with means of debridement less invasive than wide resection would have been unlikely to eliminate the disease due to chronicity and extent. A novel potential solution for this dilemma may be to employ emerging bacterial RT-PCR testing to detect the presence of prokaryotic (bacterial) DNA (JCM 1072: 53). More definite diagnostic tools are needed.

PO 006 #2804278

PROBLEMS WITH MALIGNANT PERIPHERAL NERVE SHEATH TUMOR ASSOCIATED WITH NEUROFIBROMATOSIS-1 SYNDROME

H. Koyanagi[1], *K. Ae*[2], *S. Matsumoto*[2], *J. Manabe*[3], *T. Shimoji*[3], *T. Tanizawa*[2], *T. Gokita*[3], *S. Sato*[1], *K. Hayakawa*[2], *Y. Funauchi*[2], *A. Okawa*[1]
[1]*Orthopaedic, Tokyo Medical and Dental University, Tokyo, JAPAN;* [2]*Orthopaedic, Cancer Institute Hospital, Tokyo, JAPAN;* [3]*Orthopaedic, Saitama Cancer Center, Tokyo, JAPAN*

Objective: The clinical management of malignant peripheral nerve sheath tumor (MPNST) arising in neurofibromatosis-1 (NF-1) patients is very difficult, because of its aggressiveness, the difficulty of diagnosing it as a malignant transformation of neurofibromas, and the limited therapeutic options. We retrospectively investigated cases of MPNST in NF-1 patients with the aim of improving diagnoses and the prognosis for patients of this disease.

Methods: We studied 18 cases of MPNST associated with NF-1 from 1994 to 2016 at the Cancer Institute Hospital in Tokyo and Saitama Cancer Center in Saitama prefecture in Japan.

Results: Ten male and eight female patients with a median age of 45 years formed the sample group. The average tumor size was 10.9 (6–17) cm, and 12 were located in the trunk and six in a limb. Biopsy was performed in all cases. However, the pathological findings of four cases indicated benign neurofibromas on the first biopsy. Recurrence was found in three out of the 16 cases in which radical resection was performed. The average follow-up period was 3 years and 7 months, and the five-year survival rate was 27%.

Conclusion: MPNST is one of the most progressive cancers, and it occurs sporadically or in association with the NF-1 syndrome. Especially, MPNST associated with NF-1 syndrome has a very poor prognosis, with a five-year survival of approximately 20%. There are some reasons for this poor prognosis of the disease, such as the relatively low diagnostic accuracy of using needle biopsy, the difficulty of radical resection of MPNST originating from important nerves, and no effective medicine being specified yet. PET-CT has the potential of being useful for finding the malignant transformation area in neurofibromas for needle biopsy. A large portion of peripheral nerves associated with MPNST should be removed around the tumor, because malignant cells sometimes invade inside the nerve far from the tumor. As for systemic treatment, we need to evaluate the efficacy of some new medicines adopted for soft-tissue sarcomas such as pazopanib, trabectedin, and eribulin. Furthermore, currently basic research is in progress on the therapeutic target of BMP2 and MEK-ERK pathways for NF1-associated MPNST. It is expected to result in new effective medicines for this poor prognostic tumor.

PO 007 #2804351

RETROPERITONEAL SARCOMAS (RS): A DESCRIPTIVE ANALYSIS OF THE CLINICAL PRACTISE IN RAMÓN Y CAJAL HOSPITAL OF MADRID

O. Martínez-Saez[1], *C. Saavedra Serrano*[1], *M. Reguero*[1], *J. Cabañas*[1], *J. Serrano Domingo*[1], *R. Martín-Huertas*[1], *E. Corral*[1], *V. Pachón*[1], *R. Ferreiro*[1], *F. Longo*[1], *M. Rodríguez-Garrote*[1], *C. Guillén Ponce*[1], *A. Carrato*[1], *M. Vaz Salgado*[1]
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Objective: RS are only a 10-15% of all soft tissues sarcomas. The mean age at diagnosis is 50 years old, without differences between sexes. Usually, RS are large at diagnosis, with an average size of 15 cm, and they can invade locally, but it is not common to find metastases at diagnosis.

There are different histological types. The most frequent are liposarcoma (LPS) and leiomyosarcoma (LMS). They have different behaviors: LPS are usually of low-grade, and they tend to local failure but rarely metastasize, while in LMS are common the distant relapses (mostly in lung).

The main treatment is surgery but, instead a complete resection, RS have high rate of local relapse. Adjuvant treatments, radiotherapy (RT) or chemotherapy (CT), are employed but the evidence about their benefit in terms of disease-free survival (DFS) and overall survival (OS) is limited.

Methods: We retrospectively analyzed the data of patients diagnosed with primary localized RS resected between 1995 and 2016 in Ramón y Cajal Hospital. We studied patient, tumor and treatment variables including survival status. Stata 14.1 was used to analyze the data.

Results: A 55% cases were women and the mean age was 57 years old (range 19-78). The mean tumor size was 18 cm, with a wide range (3,5 - 40 cm). The most frequent histological type was LPS, followed by LMS and undifferenciated pleomorphic sarcoma. We found the same percentage of low-grade and high-grade in LPS, while LMS were mostly intermediate-grade.
All patients were operated. Fifty-five percent of tumor resections included adjacent organs, but only in two cases they were infiltrated. 28% of patients received adjuvant RT, 28% intraoperative radiotherapy (IORT), and 31% adjuvant CT. At the time of the analysis, the rate of relapse was 60%, 77% as local failures. LPS tend to relapse locally (82%) and LMS do it at distance (75%).
DFS and OS were 47.6 and 77.1 months respectively.

Conclusion: Data obtained in our study are similar to them described in the literature: middle-aged patients with large tumors, mostly LPS or LMS, which relapse locally. Randomized clinical trials are need in or order to establish a standardized treatment.

PO 008 #2804441

TREATMENT CONSIDERATIONS IN A PATIENT WITH NICKEL ALLERGY UNDERGOING LIMB-SALVAGE SURGERY AND JOINT RECONSTRUCTION FOR OSTEOSARCOMA

P. Hogan[1], *S. J. Dvorak*[1], *A. Trenga*[1], *A. Logan*[1], *S. Gitelis*[1], *P. Kent*[1]
[1]*Rush University Medical Center, Chicago, IL, USA*

Objective: Extensive research on metal hypersensitivity has been performed on implants for traditional total joint replacement, but no reports describe metal hypersensitivity in the context of limb-salvage surgery or orthopaedic oncology. We present treatment considerations and surgical technique for limb-salvage surgery in a patient with osteosarcoma (OST) and documented nickel allergy, using a whole osteoarticular allograft (OAG) with multiligament knee reconstruction (MKR).

Methods: The patient is a 17-year-old female with OST of the proximal tibia (Fig 1) referred for limb salvage surgery following chemotherapy. She reported a severe nickel allergy later confirmed by laboratory testing. Traditional nickel-containing endoprostheses and ModOnc prostheses containing cobalt-chrome were therefore not considered. Ceramic APC arthroplasty was rejected due its decreased stability, the patient's age, and other factors. Ultimately, we chose OAG of the proximal tibia and fibula with MKR.

An allograft was selected and sized, with soft tissue attachments left intact. Resection of the OST was performed and the graft cut to match the resected bone, preserving attachments between the allograft tibia and fibula (Fig 2,3). The allograft tibia was plated to the native tibia, and the extensor mechanism and joint ligaments reconstructed. Figure 4 shows the final construct. X-rays at 4 months show good healing (Fig 5).

Results: Metal hypersensitivity is seen in 10-15% of the population, with nickel allergy most common [1-3]. Although metal hypersensitivity has been implicated in joint implant complications and failure, causality is unproven and controversy remains over its role [1,2]. Nonetheless, in a patient undergoing oncologic resection and joint reconstruction, confirmed metal sensitivity presents orthopaedic surgeons with several considerations. While ModOnc endoprostheses offer faster recovery, fewer immediate complications, and are less challenging, medium to long-term outcomes when compared with OAG are similar [4-7]. Given this, avoidance of nickel-containing prostheses and potential metal ion contamination is in the best interest of patients with concern for metal hypersensitivity. Furthermore, OAG is superior to APC in younger patients.

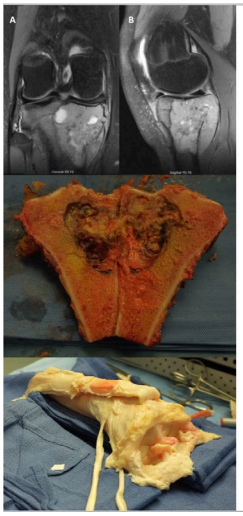

Figure 1. MRI of the right knee. A. Coronal PD FS MRI of the R proximal tibia demonstrating a lytic tumor consistent with osteosarcoma in the medial tibial plateau. B. Sagittal PD FS MRI of the R proximal tibia demonstrating tumor invasion into the posterior soft tissues.

Figure 2. The bisected tibial specimen grossly demonstrating wide distal margins.

Figure 3. The prepared osteoarticular allograft.

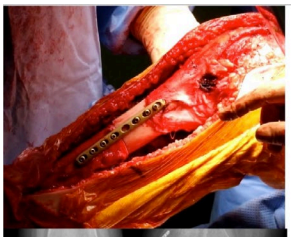

Figure 4. Final construct with compression bridge plating and reconstruction of the extensor mechanism. The previous biopsy site is ablated with plasma cautery.

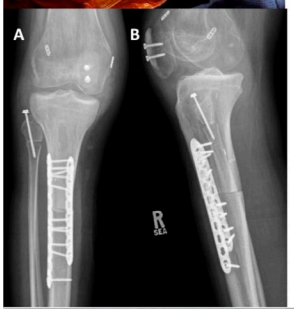

Figure 5. Radiographs 4 months post-operatively. A. AP x-ray of R knee. B. Lateral x-ray of R knee.

Works cited:
1. Lachiewicz PF, Watters TS, Jacobs JJ. Metal hypersensitivity and total knee arthroplasty. J Am Acad Orthop Surg. 2016;24(2).
2. Granchi D, Cenni E, Giunti A, Baldini N. Metal hypersensitivity testing in patients undergoing joint replacement. J Bone Joint Surg Br. 2012;94-B(8):1126-1134.
3. Basko-Plluska JL, Thyssen JP, Schalock PC. Cutaneous and systemic hypersensitivity reactions to metallic implants. Dermatitis. 2011;22(2):65-79.
4. Brigman BE, Hornicek FJ, Gebhardt MC, Mankin HJ. Allografts about the knee in young patients with high-grade sarcoma. Clin Orthop Relat Res. 2004;421:232-239.
5. Albergo JI, Gaston CL, Aponte-Tinao L, et al. Proximal tibia reconstruction after bone tumor resection: Are survivorship and outcomes of endoprosthetic replacement and osteoarticular allograft similar? Clin Orthop Relat Res. 2017;475(3):676-682.
6. Muscolo DL, Ayerza MA, Farfalli G, Aponte-Tinao L. Proximal tibia osteoarticular allografts in tumor limb salvage surgery. Clin Orthop Relat Res. 2010;468(5):1396-1404.
7. Muscolo DL, Ayerza MA, Aponte-Tinao LA. Survivorship and radiographic analysis of knee osteoarticular allografts. Clin Orthop Relat Res. 2000;373:73-79.

Conclusion: Osteoarticular allograft is a viable option in patients with metal hypersensitivity undergoing joint reconstruction. Further research is needed to describe the importance of metal sensitivity in the context of limb-salvage surgery and orthopaedic oncology.

PO 009 #2804646

RECURRENCE RATE OF PRIMARY BONE AND SOFT TISSUE NEOPLASMS OF THE FINGERS

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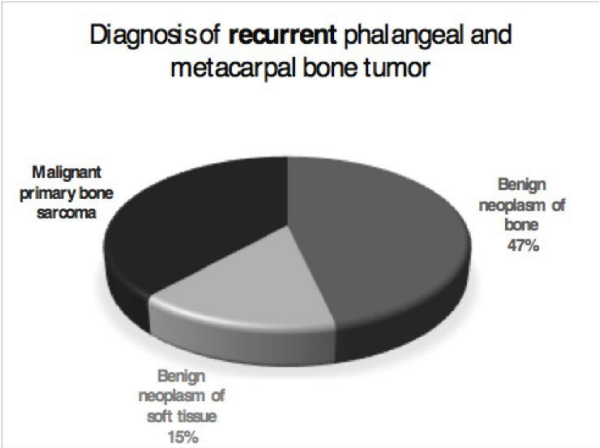
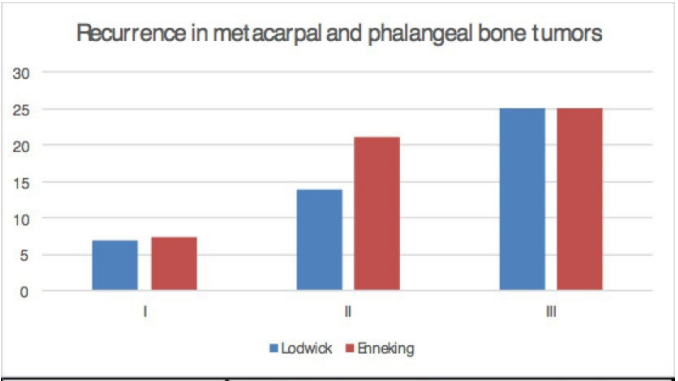
Objective: The goal of this study was to identify if pathologic fractures, along with other factors were associated with tumor recurrence in primary neoplasms of bone and of the soft tissues of the hand.

Methods: We retrospectively identified 123 patients with primary neoplasms of bone of the metarcarpals or phalanges or primary neoplasms of soft tissues of the fingers that visited one of our two urban hospitals between 1992 and 2015. The average age at presentation was 45±15 years, and 57% were female. Benign neoplasms were present in 85% of the patients. The most common treatment was intralesional curettage (62%) followed by excision (35%) and amputation (2.4%). One patient did not have oncological treatment and only underwent open reduction and fixation for a pathologic fracture. Patient demographics, tumor characteristics, and presence of a pathologic fracture were gathered from the medical records. Tumors were assessed on radiographs according to the Enneking and Lodwick-Madewell classifications. A bivariate analysis was performed to identify factors associated with tumor recurrence.

Results: The overall recurrence rate of neoplasms in the fingers was 11% of which 11/13 recurred within two years. Malignant tumors had a higher recurrence rate compared to benign tumors, 28% versus 8% (p=0.023). There was a trend of increased recurrence rates with increasing Enneking and Lodwick-Madewell stage for primary bone tumors (p=0.066 and p=0.10, respectively). We failed to show a statistically significant association between pathologic fractures and tumor recurrence.





	Total	Recurrent tumors		P-value
	n	n	%	
Lodwick stage, n (%)				0.10*
I	29	2	6.9	
II	22	3	14	
III	16	4	25	
Enneking stage, n (%)				0.066*
I	41	3	7.3	
II	14	3	21	
III	12	3	25	

*Calculated with two-sample Wilcoxon rank-sum test

Conclusion: Our findings support that the most important factor for recurrence is the biologic aggressiveness of ma-

lignant tumors of bone or soft-tissues. Furthermore, the Enneking and Lodwick-Madewell classifications proved to be useful means to estimate tumor aggressiveness and inherent risk of recurrence. Our data showed no significant association between pathologic fractures and tumor recurrence; this is in line with studies that have investigated this in other tumors and locations. However, if patients present with a pathologic fracture, we recommend simultaneous oncologic and fracture treatment, specially if there is a suspicion of a malignancy.

PO 010 #2783359

EFFICACY OF PAZOPANIB FOR RECURRENT DESMOID TUMORS IN FAMILIAL ADENOMATOUS POLYPOSIS PATIENTS

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Objective: Desmoid tumor is a rare invasive soft-tissue neoplasm characterized by high recurrence rate and post-treatment morbidity. When occurring in familial adenomatous polyposis (FAP) patient, it is especially troublesome since it often localizes in the abdominal cavity causing morbidity and even mortality. When surgery is not feasible, only a few drugs have shown activity. In this study, we analyzed the effect of pazopanib in desmoid tumor associated with FAP.

Methods: Case 1 is a 44-year-old female with 15-year history of desmoid tumor treatment. She has undergone 6 operations, but presented with multiple desmoid tumors in the nape of neck through the lower back. 7 courses of ADR (50mg/m2) and 8 courses of MTX (30mg/m2) + VBL (6mg/m2) were performed, but had to abort due to CTCAE grade 3 liver dysfunction. Case 2 is a 32-year-old male with 3 prior operations for intra-abdominal desmoid tumors in the last 7 years. Past history included gastrointestinal perforation from desmoid tumor and peritonitis. Additionally, there were multiple desmoid tumors in the back. Several courses each of ADR (20mg/m2) + DTIC (150mg/m2), MTX (30mg/m2) + VBL (6mg/m2) and tamoxifen (40mg) + sulindac (300mg) were ineffective for local control. Pazopanib was initiated in both cases, and clinical outcomes and complications were analyzed.

Results: 3 weeks of 200mg once daily (od) pazopanib was effective in alleviating pain and the dosage was increased to 400mg in case 1. MRI at 8 weeks showed stable disease (SD) with cystic change in the mass; however, due to grade 4 pancreatitis, medication was discontinued. Sporadic grade 2-3 hematological toxicities have been observed with 600-800 mg in case 2, but at the final follow-up after 18 months, tumors are in SD.

Conclusion: Imatinib and sorafenib have been shown to have some activity in desmoid tumor in several phase 2 studies. Pazopanib is the only drug that has shown success in soft-tissue sarcomas, and our results suggest that pazopanib is also active in desmoid tumor. Although further accumulation of data is necessary, pazopanib is a promising option for desmoid tumor refractory to conventional chemotherapy.

PO 011 #2741802

CLINICAL CHARACTERISTICS AND OUTCOMES OF RESECTED EXTREMITY SOFT TISSUE SARCOMA: 10-YEAR OF SINGLE INSTITUTE EXPERIENCE

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Objective: This study evaluated the clinical characteristic, prognostic factors, survival outcome and outcome of treatment in high-risk extremity soft tissue sarcoma patients who were undergone complete extremity resection for soft tissue sarcoma in Siriraj hospital.

Methods: Medical records of patients who were diagnosed with extremity soft tissue sarcoma with tumor size larger than 5cm. or any size grade3 and undergone extremity resection procedure in Siriraj hospital from January 2007 to November 2016 were reviewed. Data including clinical characteristic (e.g. age, gender), operation procedure, pathological results, and treatment were collected and evaluated. For those who received chemotherapy, regimen, numbers of cycles and toxicities were recorded. Outcomes of disease-free survival (DFS) and overall survival (OS) were calculated using survival analysis, Kaplan-Meier method.

Results: A total of 58 patients with extremity sarcoma were included in this study. Of those, the median age was 53.5 years and 43.1% were male. There were 13 patients received adjuvant chemotherapy. A significant difference for worse DFS was tumor grade 3 with a size larger than 10 cm. ($p < 0.001$). Median DFS was 56.2 months in chemotherapy group and 20.5 months in the non-chemotherapy group ($p = 0.29$). Recurrence of the disease occurred in 43% of the patients. Median OS was 77.2 months in chemotherapy group and 66.6 months in the non-chemotherapy group ($p = 0.24$). No benefit of adjuvant chemotherapy was observed in any subgroup. Twenty percent developed grade3-4 hematologic toxicity and 15.4% developed febrile neutropenia in patients received chemotherapy. Two patients experienced non-hematologic toxicities from chemotherapy leading to dose reduction or treatment discontinuation.

Conclusion: The results showed that high-grade tumor larger than 10cm was a significant prognostic factor of

DFS. There was an inconclusive benefit of adjuvant chemotherapy related to DFS and OS in the patients with high-risk extremities soft tissue sarcoma.

PO 012 #2746162

EXERCISE IMPACTS TUMOR VASCULATURE AND METASTASIS IN EWING SARCOMA

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Objective: Exercise (Exer) improves chemotherapy efficacy in primary tumor mouse models and is a growing part of care for cancer patients. Improved chemotherapy efficacy in primary tumors is due to tumor vessel normalization (increased vessel function and decreased leakiness). Vessel normalization may prevent tumor cell extravasation, reducing metastasis, or increase chemotherapy delivery to established metastases. We aim to determine whether moderate exercise decreases Ewing Sarcoma (ES) metastatic rate and improves chemotherapy efficacy against established metastases in mice (Fig 1).

Methods: Luciferase (Luc)+GFP+ A673 cells were injected into gastrocnemius of nude mice. When tumors were detected (Fig 2A), mice were divided into groups: Control, Doxorubicin (Doxo; 2 mg/kg, 2x/wk), Exer (45min treadmill x 5d/wk), or Exer+Doxo. Primary tumors were resected by amputation after 2 weeks and treatment was discontinued. Metastatic rate is being monitored by bioluminescent imaging.

To evaluate established metastases, Luc+GFP++ A673 ES cells were injected intravenously. After tumors were detected (Fig 2B), mice were divided into Control, Doxo, Exer, or Exer+Doxo groups as above. Once tumor burden caused symptoms (~2 days after completion of treatment), mice were injected with lectin and dextran and euthanized.

In both models, micrometastases will be quantified by GFP immunostaining. To evaluate vessel function and leak, lectin and dextran localization, respectively, will be compared to CD31 (endothelial cells). Microvessel density, vessel quantity, length, open lumens, and γH2Ax, a surrogate marker of doxorubicin delivery, will also be evaluated.

Results: The orthotopic metastasis model is ongoing. Primary tumors are being evaluated and lungs will be harvested once metastases are visualized. We expect combination Exer+Doxo to reduce metastasis due to improved chemotherapy delivery and reduced leakiness allowing for less tumor cell escape.

There was no difference between Control and Exer groups of mice that received tail vein Luc+GFP+ A673 cells at macroscopic exam (Fig 3). Doxo and Exer+Doxo mice did not complete experiment due to Doxo toxicity. Evaluation of vasculature and microscopic tumor burden is underway.

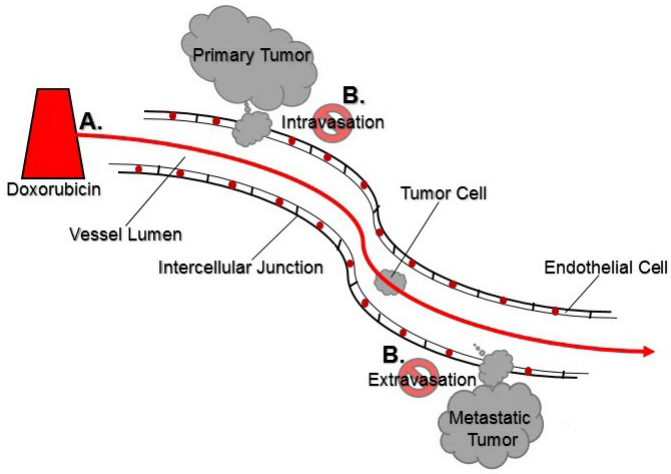

Fig 1. Moderate aerobic exercise potentially inhibits metastasis in 2 ways. A) Exercise promotes vessel normalization and increases drug delivery to primary tumor and metastases. B) Exercise inhibits tumor cell entry into circulation and metastasis by creation of tighter junctions between endothelial cells, hindering tumor cell intravasation and extravasation.

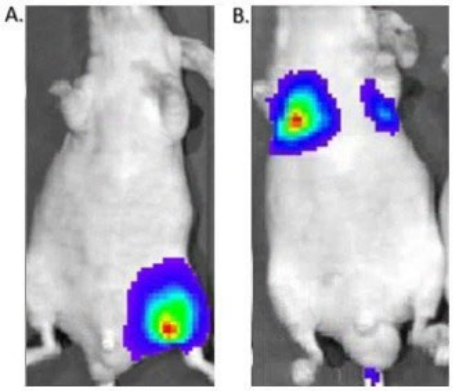

Fig 2. Bioluminescence of mouse models for the development of A673 Ewing sarcoma metastasis. A) gastrocnemius tumor, Day 7 after intramuscular inoculation. B) metastatic lung tumor, Day 7 after intravenous inoculation.

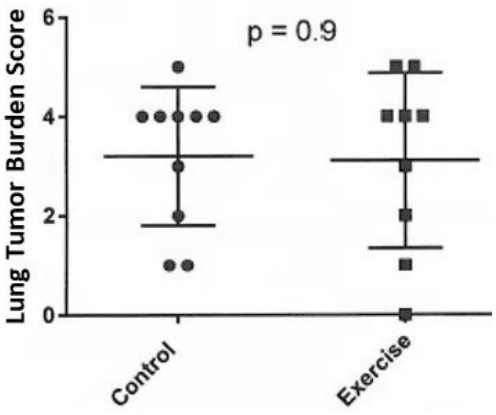

Fig 3. Lung Tumor Burden Score. Lungs scored on scale of 1 – 5 based on percentage of lung covered in tumor (0 = no lung tumors, 1 = countable # of nodules, 2 = <50% lungs covered by tumor, 3 = 50%, 4 = >50%, 5 = lung deformed by tumor).

Conclusion: We aim to identify the role of exercise in chemotherapy efficacy against metastases and rate of metastasis. Given the growing use of exercise for patients undergoing chemotherapy it is important to know whether exercise impacts metastasis.

PO 013 #2764921

L-TYPE AMINO ACID TRANSPORTER 1 (LAT1) EXPRESSES IN CLEAR CELL SARCOMA AND ITS INHIBITOR BLOCKS INCORPORATION OF ESSENTIAL AMINO ACIDS

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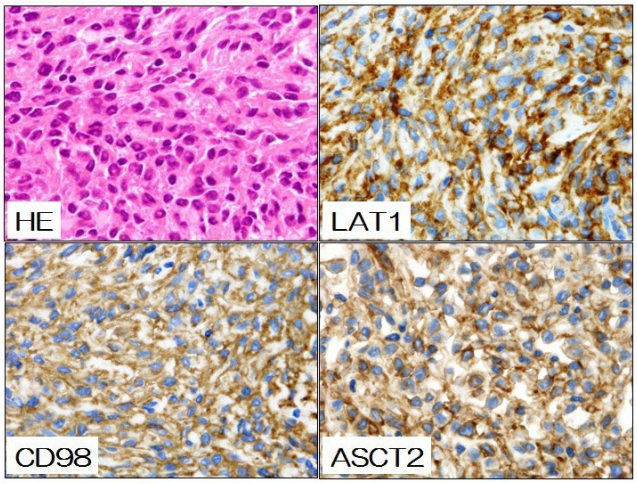
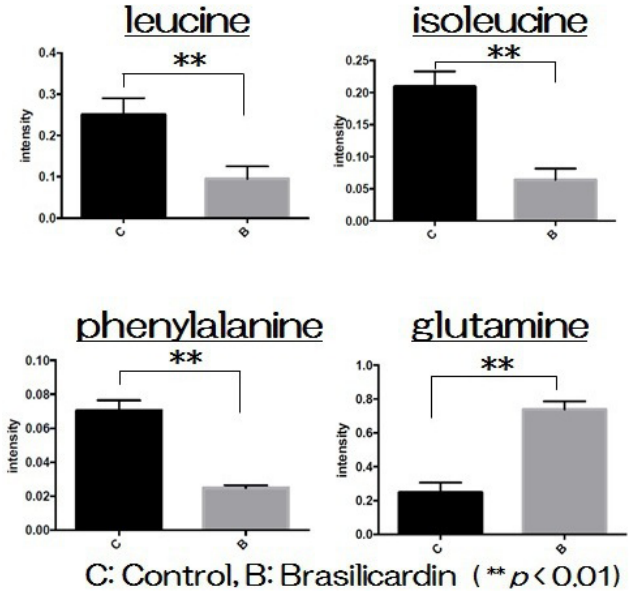
Objective: There is no effective treatment other than surgery for clear cell sarcoma (CCS). We have previously demonstrated that Boron Neutron Capture Therapy (BNCT) is very effective in the treatment of CCS-bearing animal models. In BNCT, the tumor is irradiated with thermal neutrons after its selective accumulation of a boron compound (BPA) through L-type amino acid transporter 1 (LAT1). LAT1, in association with CD98, is expressed in tumor cell membranes and mainly incorporates essential amino acids (EAA), such as leucine, into tumor cells for their proliferation by replacing the complimentarily glutamine taken into cells by the alanine-serine-cysteine amino acid transporter-2 (ASCT2). The aim of this study is to reveal the expression of amino acid transporters in clinical cases of CCS through immunohistochemical analysis, and to develop a new method for diagnosing and treating the disease.

Methods: Tumor tissue collected from 5 cases of clinical CCS, including original tissue of cell line MP-CCS-SY, was analyzed by immunohistochemistry with the use of anti-LAT1, anti-CD98 and anti-ASCT2 antibodies. To evaluate the uptake of essential amino acids (EAA), MP-CCS-SY cells were cultured with LAT1 inhibitor brasilicardin A (Bra-A). Subsequently, inhibition of the uptake was evaluated by gas chromatography mass spectrometry (GC-MS), and the inhibition by Bra-A on the growth of MP-CCS-SY cells was analyzed.

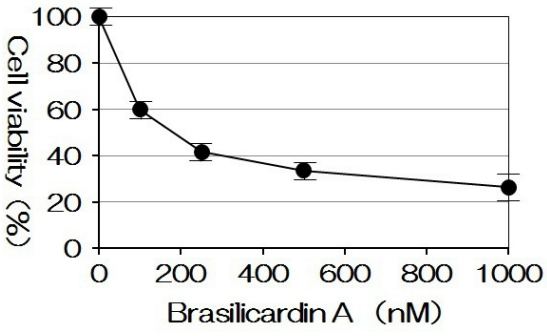
Results: Immunohistochemical analyses revealed strong and diffuse expression of LAT1, CD98 and ASCT2 in all 5 clinical cases of CCS [Fig. 1]. Also, the uptake of EAA into CCS cells was inhibited by Bra-A; on the other hand, intracellular glutamine, which is not an EAA, increased [Fig. 2]. Furthermore, Bra-A reduced the proliferation of CCS cells [Fig. 3].



[Fig. 1] Expression of amino acid transporters in the original tissue of cell line MP-CCS-SY. Strong and diffuse expression of LAT1, CD98 and ASCT2 was detected in tumor cell membranes as well as in other clinical cases of clear cell sarcoma (CCS).



[Fig. 2] Measurement of amino acid uptake by clear cell sarcoma (CCS). The uptake of essential amino acids (EAA) by CCS cells was analyzed by gas-chromatography mass spectrometry (GC-MS) (n=3) after adding Brasilicardin A (Bra A) to cell line MP-CCS-SY. Bra A suppressed the uptake of EAA by CCS cells and increased glutamine in tumor cells.



[Fig. 3] Brasilicardin A (Bra A) proliferation inhibition assay for clear cell sarcoma (CCS). The inhibition of MP-CCS-SY cell proliferation by Bra A was measured with the WST-8 Cell Proliferation Assay (n=3). Bra A suppressed the proliferation of CCS cells dose-dependently.

Conclusion: The same result of LAT1, CD98 and ASCT2 immunostaining in all clinical cases suggested that such immunostaining results play a very important role in the pathological diagnosis of CCS. Also, since BNCT has been very effective in the destruction of tumor cells that selectively uptake BPA, cases of clinical CCS are expected to be similarly affected by BNCT. Furthermore, the inhibition of the uptake of EAA into tumor cells and the suppression of cell proliferation by Bra-A indicate that LAT1 inhibitor may also exert an anti-tumor effect on clinical cases of CCS. Thus, this study suggests the possibility of not only applying histopathological diagnosis, but also developing a new method for the treatment of CCS. Further study is warranted.

PO 014 #2771964

INCIDENCE OF GIANT CELL TUMOR OF BONE IN THE CHINESE POPULATION

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Objective: To estimate incidence of giant cell tumor (GCT) of bone in 2017 in China using a direct (registry-based) approach.

Methods: The registry-based approach utilized the most recent age- and sex-specific incidence rates of GCT recorded by the Bone Tumor Registry in Japan (2006-2015), and applied these to the age- and sex-matched populations in China in 2017 as projected by the United Nations. Estimates were adjusted based on Chinese Bone Tumor Registry data (1957–1988) (Guo, 1999) for differences between Japan and China.

Results: Annual GCT incidence was estimated to be 1.51 per million or 2,102 new cases in China for 2017. A comparison of this incidence rate with Japan and the United States is shown in the table. Under the assumption that GCT represents a greater proportion of bone tumors in China (16.6%) than in Japan (9.6%) (Guo, 1999), the adjusted GCT incidence in China increased by approximately 73% to 2.62 per million or 3,641 new cases in 2017.

Conclusion: Quantifying the incidence of GCT is challenging because it is a rare, histologically benign bone tumor that is not recorded at the population level in most countries. Leveraging unique population-based registry data, we estimated that GCT is a rare disease in the Chinese population with an incidence ranging between 1.51 and 2.62 cases per million persons per year. Possible differences in diagnostic classification of GCT, urban-rural demographics, and the younger demographic distribution of the Chinese population may underlie observations that GCT, a condition that primarily affects young individuals (20-40 years of age), accounts for a higher proportion of skeletal tumors in China.

Registry-Based Approach Used to Estimate GCT Incidence in 2017

Country	Population 2017 (United Nations)	Incidence	Incidence Rate per Million
China	1,388,232,693	2,102*	1.51*
Japan	126,045,211	160	1.27
United States	326,474,013	454	1.39

*3,641 new cases in 2017 or 2.62 per million accounting for proportionally higher incidence of GCT in China per Guo et al (1999

PO 015 #2772528

THE EFFICACY OF GEMCITABINE AND DOCETAXEL COMBINATION CHEMOTHERAPY IN SOFT TISSUE SARCOMA

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Objective: The activities of gemcitabine (G) and docetaxel (D) combination chemotherapy in bone and soft tissue sarcoma have been suggested recently. We retrospectively evaluated the efficacy of GD after operation in patients with soft tissue sarcoma.

Methods: The patients, receiving GD at our hospital since May 2009 to December 2016, were eligible. They basically received G 900 mg/m2 d1, 8; D 75 mg/m2 d8, every month.

Results: Fifteen patients were included, with a median age of 52 years (16-66). Tumor location was mainly divided into limb (eight cases) and trunk (seven cases). The final diagnosis are as follows; leiomyosarcoma (n=6), un-

differentiated pleomorphic sarcoma (UPS, n=3), myxoid liposarcoma (n=3), and each one cases of dedifferentiated liposarcoma, rhabdomyosarcoma and synovial sarcoma. Eight (53 %) patients had metastases to lungs, and four (27 %) patients had those of multiple sites. The patients have received GD 3.5 times on average (1-8 courses). We used GD as first-line in five, second-line in seven, and third-or-greater line in three patients. GD was carried out as an adjuvant setting in two cases, and the others including all second-or-greater line were carried out as a salvage chemotherapy. No patients were assessed as complete response (CR), and two were partial response (PR), three were stable disease (SD), 10 were progressive disease (PD). Three first-line settings exhibited no CR, one PR, so the response rate (RR) was 33 % (1/3). On the other hand, the patients treated as second-or-greater line had one PR, resulting in RR of 10% (1/10). Eventually, 10 patients were alive (four CDF five AWD and one NED) and five patients were dead. While the average progression-free survival (PFS) in progressive cases (PD cases) was 5.4 months, that of non-progressive cases (SD and PR cases) was 20.8 months. In addition, the median PFS for the first-line was 19.2 months, that of second-or-greater line was 6.2 months. Moreover, the average overall survival (OS) was 28.9 months in progressive cases and 49.4 months in non-progressive cases, while the median OS was 49.4 months in first-line, and 28.9 months in second-or-greater line respectively.

Conclusion: The efficacy of GD in soft tissue sarcoma isn't always good. However, because of its simplicity as being able to administer in outpatient section and relatively moderate survival rate, we should consider to use GD in soft tissue sarcoma.

PO 016 #2784535

A CASE OF A PATIENT WITH AN ADENOCARCINOMA OF THE DISTAL FEMUR - IS IT TRULY A METASTATIC BONE TUMOR FROM UNKOWN ORIGIN?

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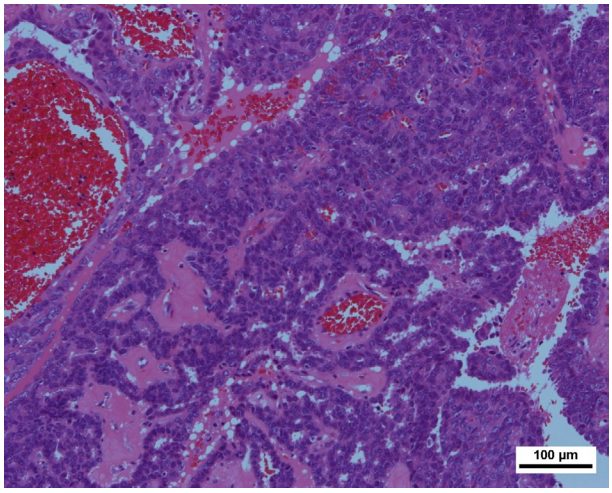
Objective: There are often cases of patients who have a metastatic bone tumor from unknown origin and that is the first symptomatic lesion for them. In most of the cases, the primary cancer, and in some cases, other metastatic lesions are detected by detailed examinations. Even if the primary cancer is not found initially, it usually becomes apparent within at least one year. It is very rare that not only the primary cancer stays occult and undetected, but also no other metastatic lesion emerges for more than one year after a solitary metastatic bone tumor is surgically resected. Here we report a case of a patient with an adenocarcinoma of the distal femur that has remained silent for more than 41 months after surgical resection.

Methods: Case: A 76-year-old male complaining of a pain on his right knee for one month was diagnosed with a bone tumor of his right distal femur by X-ray examination and MRI. After referral to us, he was examined generally by PET-CT and other tests, but no other tumor lesion was detected than the tumor of his right femur. He underwent surgical resection of the distal femur with endoprosthetic reconstruction.

Results: Histopathological examination of the resected specimen revealed the tumor as a well-differentiated adenocarcinoma (Fig.). Therefore, his disease was strongly suspected of a metastatic bone tumor from an unknown cancer. The primary lesion, however, has not been detected in spite of multimodal and repeated examinations post-operatively including PET-CT and fiberscopy of the upper and lower digestive organs. He is alive with no evidence of disease without any additional chemo- or radiotherapy after a follow-up period of 41 months. There was no local recurrence and no other distant metastasis. At a final follow-up, he is able to walk without any aid.



Conclusion: No case of a patient with an adenocarcinoma originated from the bone has been reported within our retrievals. Therefor, his tumor is considered as metastasis from unknown origin. It means that his primary cancer remains silent and occult for more than three years, or spontaneously disappeared after a metastatic lesion was treated. Further investigation and follow-up are required to elucidate the origin of his bone tumor.

PO 017 #2784634

THE REASONS OF POOR PROGNOSIS IN PATIENTS WITH PELVIC OSTEOSARCOMA

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Objective: The probability of survival for patients with extremity osteosarcoma (OS) has improved with an expected five-year survival rate between 60% and 80%, whereas pelvic OS has still been difficult to treat with an expected five-year survival rate between 18% and 38%. The reasons of the poor prognosis in patients with pelvic OS are unclear. We reviewed our cases with pelvic OS in comparison with extremity OS to identify the reasons of the poor prognosis and to figure out how to improve it.

Methods: We reviewed fourteen patients with high-grade pelvic OS who were treated at our hospital or two other affiliated centers and forty-three patients with high-grade extremity OS who were treated at our hospital between 1999 and 2015. We assessed patient survival using Kaplan-Meier method with log-rank test. Differences between pelvic OS and extremity OS were assessed Fisher's exact test.

Results: The observed differences between pelvic OS and extremity OS were patient age, tumor size, and the ratio of the patients who had metastasis at presentation, and underwent chemotherapy or surgical resection. The proportion of the patients who had secondary osteosarcoma was not significantly different between pelvic OS and extremity OS.

Pelvic osteosarcoma was one of the poor prognostic factors as well as presence of metastasis at presentation, older patient age, lack of surgery, and lack of chemotherapy but not large tumor size or secondary osteosarcoma. Overall survival rate at five years (OSR-5) for patients with pelvic OS was 32.1%, while it was 91.8% for patients with extremity OS. In pelvic OS, the patients who underwent surgical resection had significantly better prognosis than those without surgical resection. Overall survival was not different between pelvic OS and extremity OS in the younger patients (under 39 years old) without metastasis at presentation (M0), or in the older patients (over 40 years old) with metastasis (M1). The difference of the overall survival between pelvic OS and extremity OS was observed in the younger M1 patients and in the older M0 patients.

Conclusion: The patients with pelvic OS have significantly poor outcome compared with the patients with extremity OS. The poor prognosis of pelvic OS is attributed not only to older patient age and metastasis at presentation but also to the lack of surgery. To improve the prognosis of pelvic osteosarcoma, we should try surgical resection.

Table1. Differences between pelvic OS and extremity OS

		Pelvic OS N=14	Extremity OS N=43	P value*
Tumor size (2 cases N.A)	< 10 cm	4	30	0.005
	10 cm ≦	10	11	
	< 8 cm	2	22	0.013
	8 cm ≦	12	19	
Metastasis at presentation	No	8	36	0.049
	Yes	6	7	
Patient age	≦ 39	7	30	0.209
	40≦	7	13	
	≦ 49	7	34	0.047
	50 ≦	7	9	
Secondary osteosarcoma	No	10	39	0.091
	Yes	4	4	
Chemotherapy	Yes	9	41	0.008
	No	5	2	
Surgery	Yes	7	43	<0.001
	No	7	0	

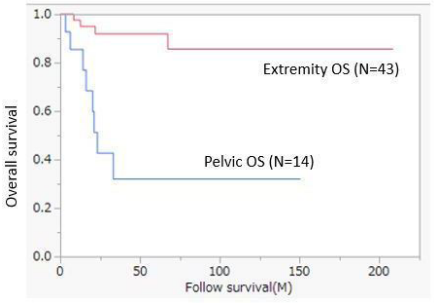
* Fisher's exact test

Table2. Prognostic factors of Osteosarcoma

		N	OSR-5(%)	p*
Tumor location	Pelvis	14	32.1	<0.001
	Extremity	43	91.8	
Tumor size	< 10 cm	34	82.1	0.265
	10 cm ≦	21	64.0	
	< 8 cm	24	80.3	0.363
	8 cm ≦	31	71.4	
Metastasis at presentation	No	44	89.6	<0.001
	Yes	13	37.0	
Patient age	≦ 39	37	87.3	0.005
	40 ≦	20	54.5	
	≦ 49	41	88.2	<0.001
	50 ≦	16	N.A	
Secondary osteosarcoma	No	49	78.8	0.571
	Yes	8	60.0	
Chemotherapy	Yes	50	81.2	<0.001
	No	7	N.A	
Surgery	Yes	50	85.1	<0.001
	No	7	N.A	

* log rank test
OSR-5: overall survival rate at 5 years

Fig1. Poor prognosis in patients with pelvic osteosarcoma



PO 018 #2786260

CLINICAL OUTCOME OF SURGICAL TREATMENT FOR RETROPERITONEAL SARCOMA AT A HIGH VOLUME CANCER CENTER IN JAPAN

A. Maejima[1], *M. Komiyama*[1], *Y. Shinoda*[1], *E. Kobayashi*[2], *A. Yoshida*[3], *A. Kawai*[2], *H. Chuuman*[2], *H. Fujimoto*[1]

[1]*Department of Urology, National Cancer Center Hospital, Tokyo, JAPAN;* [2]*Department of Musculoskeletal Oncology and Rehabilitation, National Cancer Center Hospital, Tokyo, JAPAN;* [3]*Department of Pathology and Clinical Laboratories, National Cancer Center Hospital, Tokyo, JAPAN*

Objective: The management of retroperitoneal sarcomas (RPS) is complex and many patients experience a severe clinical course, even after radical multidisciplinary treatment. Tumor resection appears to be the only promising strategy associated with survival benefit.
This study evaluated the impact of surgical treatment for RPS in a high-volume center in Japan.

Methods: We retrospectively examined 108 patients with primary retroperitoneal sarcoma who underwent initial surgery at the National Cancer Center Hospital between April 2011 and December 2016. Overall survival (OS) and disease free survival (DFS) were analyzed using the Kaplan-Meier method.

Results: Median follow-up time was 22 months [range: 3–80 months]. Median age at diagnosis was 59 years [range: 14–82 years] and 57% (n=61) of patients were male. The histological subtypes included de-differentiated liposarcoma (n=49; 45.3%), well-differentiated liposarcoma (n=30; 27.8%), leiomyosarcoma (n=10; 9.3%), and other (n=19; 17.6%).
Median operation time was 306 minutes [range: 51–720 minutes] and median blood loss volume was 1283 ml [range: 4–9524 ml]. R0/1 resections were performed on 29 patients (26.9%), while 79 patients (73.1%) underwent R2 resection. In 63 cases (58.3%), other organs were resected en bloc with the tumor, with nephrectomy being the most common surgery.
Except for well-differentiated liposarcoma, median OS was 67.0 months [HR 15.66, 95%CI: 36.3–97.6]. The 2-year and 5-year survival rates were 77.1% and 58.6%, respectively.
Tumor recurrence occurred in 49 cases (45.4%) after initial surgery and median DFS was 11.0 months [range: 2–54 months, HR 2.08, 95%CI: 6.90–15.09]. Among recurrent cases, median OS was 67.0 months [HR 19.8, 95%CI: 28.1–105.8]. The major strategy for recurrence was also surgical resection (n=20). Compared to surgery, salvage chemotherapy (n=12) did not show a greater survival benefit and OS in the chemotherapy group was 25.0 months [HR 11.2, 95%CI: 3.0–46.9].

Conclusion: Overall survival of patients with RPS is acceptable, although the recurrence rate is high. It is crucial to develop effective treatment strategies during the perioperative period and following relapse.

PO 019 #2793361

PATTERNS OF CARE WITH PROPHYLACTIC STABILIZATION OF METASTATIC DISEASE TO THE FEMUR IN THE VA HEALTHCARE SYSTEM

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Objective: Metastatic bone disease is a major cause of morbidity and healthcare cost, and the femur is the most common site of metastatic disease and pathologic fracture in the appendicular skeleton. Predictive tools for estimating the risk of pathologic fracture are available, yet little is known regarding national rates of prophylactic stabilization, or regional variations in practice. We asked the following questions: What is the rate of prophylactic femoral nailing in the Veterans Healthcare Administration nationally, and has it changed over time? Are there regional differences in the rate of prophylactic stabilization of the femur?

Methods: Through the Veterans Affairs Informatics and Computing Infrastructure (VINCI) Corporate Data Warehouse, all patients undergoing prophylactic stabilization of the femur between October 2010 through September 2015 were retrospectively identified. Patients receiving care at VA hospitals and via purchased care outside the VA system were included. Demographic variables were abstracted; date of procedure was coded by year, and by location via the United States Census Bureau designation into four regions. Change in the annual rate was analyzed via Spearman rank correlation; for regional variations a generalized linear model (GLM) with Poisson distribution was constructed for count data and rate ratios computed with the Delta method.

Results: A total of 940 prophylactic femur stabilization procedures were performed during the study period. Median age was 65 years (interquartile range 59-71) and 93% were men. Annual rates of prophylactic stabilization did not change in absolute terms (p=0.68) nor when adjusted for population (0.70). The GLM for regional differences showed significant differences among the four regions (p<0.001): with the Midwest as the reference, rates of prophylactic stabilization were lower in the Northeast (relative rate 0.53) and the West (0.65) and higher in the South (1.2).

Conclusion: In a large, national retrospective study of patients covered through the Veterans Healthcare Administration, a stable rate of prophylactic femur stabilization over 5 years was identified despite an aging population

and increasing incidence of metastatic disease. However, there was significant regional variation in practice patterns, with a greater than two-fold increase in rates in some regions over others. These regional differences suggest that there is variability in surgical indications for prophylactic stabilization of impending fractures.

PO 020 #2803252

RADIATION-INDUCED DEDIFFERENTIATED CHONDROSARCOMA OF THE LEFT PUBIS: A CASE REPORT

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Objective: To report a rare case of dedifferentiated chondrosarcoma arose in the left pubis that was diagnosed after combined surgical resection and radiotherapy for rectal cancer and its remarkably unusual clinical presentation.

Methods: Retrospective analysis of medical records of a 70-year-old man with a post radiation pubic chondrosarcoma with review of literatures.

Results: The patient developed a mass in the left pubis 4 years after external beam radiation therapy followed by surgical resection for rectal cancer. The patient underwent preoperative chemotherapy and after two courses, the tumor was resected with wide margin using CT-navigation system. Histology of resected specimen showed atypical chondrogenic tumor cells, continuing to different component of spindle to pleomorphic sarcoma cells, suggesting this tumor is dedifferentiated chondrosarcoma.

Conclusion: We experienced a rare case of radiation-induced chondrosarcoma. This case highlights the risk of secondary chondrosarcoma in patients following radiotherapy and the importance of lifetime monitoring.

PO 021 #2803253

WELL-DIFFERENTIATED LIPOSARCOMA WITH HIBERNOMA-LIKE COMPONENT:A CASE REPORT

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Objective: Hibernoma is a rare benign fat-forming soft tissue tumor that differentiates similar to brown fat. There are unusual variants of hibernoma including myxoid, spindle cell and lipoma-like morphology. Well- differentiated liposarcoma(WDL) can show a morphologic spectrum, including lipoma-like, sclerosing and inflammatory subtypes. However, hibernoma-like morphology as part of WDL variant is not well recognized, since it is very rare.

Methods: We report a rare case of trunk well- differentiated liposarcoma that showed hibernoma-like morphology. The clinicopathologic and immunohistochemical features are presented.

Results: The patient was a 48-years-old woman who presented with a slowly growing, painless mass. Tumor location was the right chest between pectoralis muscles, sized 69 mm. Preoperative diagnosis through a percutaneous core needle biopsy was ordinary lipoma. The patient underwent tumor resection with marginal margin. Histological examination showed areas of typical WDL, with mature fat intersected by fibrous septa containing atypical enlarged spindle cells. Focally, tumor contained hibernoma –like area with multivacuolated adipocytes. Immunohistochemistry for CDK4 was positive,MDM2 was unclear.

Conclusion: We experienced a rare case of WDL with hibernoma-like morphology. Recognition of this variant is important in treatment of adipocytic tumors and its prognostication.

PO 022 #2803549

ABDOMINAL WALL RECONSTRUCTION AFTER ONCOLOGIC RESECTION: A SYSTEMATIC REVIEW

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Objective: Management of tumours involving the abdominal wall often requires full-thickness resection and restoring integrity can be challenging. Available reconstruction options include synthetic and biologic meshes, and autologous tissue grafts. However, no consensus exists regarding which reconstructive method should be used. This systematic review synthesizes the current literature describing outcomes of different approaches for full-thickness abdominal wall reconstruction after oncologic resection.

Methods: A systematic review of articles involving abdominal wall reconstruction after resection of abdominal wall neoplasms was completed. Databases including MEDLINE and EMBASE were searched through June 2016. Two reviewers independently screened citations, extracted data and assessed quality using the checklist for Case

Series Studies by the Institute of Health Economics. A narrative synthesis is presented for early wound complications and incidence of hernias.

Results: Thirty-three of 529 records were included. None were comparative. Eight studies used synthetic mesh, 3 biologic mesh, 10 myocutaneous flaps, and 7 mixed reconstruction (myocutaneous flaps and mesh), Desmoid tumor was the most frequent indication for full-thickness abdominal wall resection. For synthetic mesh, early wound complications were rare (0-2%) with no hernias observed. However, early wound complications were more common with concomitant visceral resection. Biologic mesh alone was infrequently described and the rate of seroma was reported as high as 33%, with no hernias at follow-up. For myocutaneous flaps, partial flap necrosis was frequent (5-75%) with hernias in 3 of 67 patients, and wound infections in 8-33% of patients.

Conclusion: Hernia rates are low with all reconstruction methods. Early wound complications were more common among patients reconstructed with synthetic mesh after concomitant visceral resection and those with myocutaneous flaps. These conclusions must be confirmed with direct comparative studies.

PO 023 #2804185

GROWTH MODULATION RATE IN L-SARCOMA PATIENTS TREATED WITH TRABECTEDIN

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Objective: The growth modulation index (GMI) is the ratio of time to progression measured in patients receiving two successive treatments (GMI = TTP2/TTP1). A GMI >1.33 is considered as a sign of treatment efficacy. The aim of this retrospective single center analysis is the evaluation of GMI in leiomyosaroma- and liposarcoma- patients (L-sarcoma) treated with Trabectedin (T).

Methods: In this retrospective analysis we evaluated the GMI in 55 advanced L-sarcoma patients treated with T 1.5 mg x square meter (24-h infusion every 3 weeks). We included all L-sarcoma patients treated at the Campus Bio-Medico University from the date of the drug approval in Italy since June 31th 2016. All cases were reviewed by an expert radiologist and a medical oncologist. The radiological evaluation was performed combining RECIST and Choi criteria.

Results: The population was represented by 34 (61.8%) leiomyosarcoma patients and 21 liposarcoma patients. 22 patients received T as second line therapy after doxorubicin-based first line chemotherapy and 33 as further line treatment. The median TTP with T was 4.8 months (range 0.5-19.8), whereas the median TTP1 was 5.3 months (0.4-25.5). The median GMI was 0.91 (0.3-9.9). However, in patients who recieved more than one previous treatment, the GMI was 1.61, supporting the activity of T in subsequent lines of therapy. Overall, 25 patients (45.5%) had a GMI <1, 12 (21.8%) a GMI equal to 1-1.33 and 18 (32.7%) a GMI >1.33, which correlated with the median overall survival in those patients (P=0.02). A high concordance rate between the GMI and response rate (P=0.01), and GMI and progression-free survival (P=0.004) was observed.

Conclusion: GMI is associated with efficacy outcomes in L-sarcoma patients treated with T. In the setting of patients treated in third line, our data support a strong activity of T in L-sarcoma patients. As expected, considering we included L-sarcoma patients only, GMI in our analysis was higher in comparison to previous published results in an unrestricted sarcoma patients' population.

PO 024 #2804220

IS MALNUTRITION ASSOCIATED WITH POSTOPERATIVE COMPLICATIONS IN PATIENTS WITH PRIMARY BONE SARCOMAS?

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Objective: Postoperative wound complications remain some of the most challenging problems following limb salvage surgery for bone sarcomas. Whether modifiable risk factors can be optimized to decrease postoperative complications following surgeries for bone sarcomas is unknown. The purpose of this study is to evaluate whether malnutrition is associated with a higher rate of postoperative complications in patients with primary bone sarcomas requiring surgical therapy.

Methods: We retrospectively identified 275 patients aged 18 and older who underwent surgery for primary bone sarcomas between 1992 and 2014. We included patients who had serum albumin values recorded within 4 weeks prior to surgery. A postoperative complication was defined as an infection, hematoma, need for additional surgery, or wound complication. Preoperative serum albumin level, total lymphocyte count (TLC), patient characteristics, tumor characteristics, and treatments were recorded. We performed a bivariate analysis to evaluate if the aforementioned factors were associated with postoperative complications. For variables with $P < 0.1$, we performed logistic regression for multivariate analysis with $P < 0.05$ considered to be statistically significant.

Results: Of the 275 patients, there were 173 patients with osteosarcoma, 66 with chondrosarcoma, 15 with Ewing's

sarcoma, and 21 with other types of sarcomas. In the bivariate analysis, age, TLC < 1000 cells/mm3, albumin < 2.7 g/dL, neoadjuvant chemotherapy, neoadjuvant radiotherapy, and location in the pelvis were associated with postoperative complications (P < 0.05). In the multivariate analysis, age (P = 0.04), pelvic location (P = 0.04), and neoadjuvant radiotherapy (P = 0.008) were independently associated with postoperative complications. We then performed a sub-analysis of patients without a pelvic tumor or history of neoadjuvant radiotherapy (n = 178). In this population, albumin < 2.7 g/dL was found to be independently associated with postoperative complications (odds ratio = 4.69, 95% confidence interval = [1.03-21.34], P = 0.04).

Conclusion: This study demonstrates that hypoalbuminemia is independently associated with postoperative complications in patients with extremity bone sarcomas who do not receive neoadjuvant radiotherapy. Future studies may show that nutritional status is a modifiable risk factor that can be optimized to improve the outcome of surgery for primary bone sarcomas.

Bivariate Analysis of Postoperative Complications

	All Complications		p-value
Variable	Yes (n = 70)	No (n = 205)	
Age, median (IQR)	29 (16-53)	39 (23-54)	0.0099
Diagnosis			0.78
Osteosarcoma	47 (27.2)	126 (72.8)	
Chondrosarcoma	13 (19.7)	53 (80.3)	
Soft tissue sarcoma	4 (36.4)	7 (63.6)	
Ewing Sarcoma	4 (26.7)	11 (73.3)	
MFH	2 (22.2)	7 (77.8)	
Metastasis	0 (0)	1 (100)	
Albumin < 2.7	7 (50.0)	7 (50.0)	0.030
TLC < 1000	31 (33.7)	61 (66.3)	0.26
Treatment related factors			
Location			0.035
Femur	20 (19.6)	82 (80.4)	
Pelvis	25 (41.0)	36 (59.0)	
Tibia	9 (25.0)	27 (75.0)	
Vertebra	7 (33.3)	15 (66.7)	
Humerus	5 (29.4)	12 (70.6)	
Scapula	1 (10.0)	9 (90.0)	
Below the knee	2 (14.3)	12 (85.7)	
Other	1 (7.1)	13 (92.9)	
Neoadjuvant chemotherapy	49 (31.0)	21 (18.0)	0.014
Neoadjuvant radiotherapy	22 (50.0)	48 (20.8)	<0.001

Logistic Regression for Postoperative Complications in Patients without Radiotherapy or Pelvic Tumors

Variable	Odds ratio	Standard error	95% confidence interval	p-value
Age	0.97	0.013	[0.95, 1.0]	0.058
TLC < 1000	1.50	0.64	[0.65, 3.46]	0.34
Albumin < 2.7	4.69	3.62	[1.03, 21.34]	0.045
Neoadjuvant chemotherapy	1.54	0.83	[0.54, 4.41]	0.42
Adjuvant chemotherapy	1.46	0.78	[0.52, 4.09]	0.47

PO 025 #2804238

NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN) GUIDELINES COMPLIANCE IN A SINGLE CENTER MULTIDISCIPLINARY SARCOMA SERVICE: A RETROSPECTIVE REVIEW OF 35 PATIENTS

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Objective: Sarcoma is diagnosed in approximately 13,000 patients annually in the United States. Nearly 5,500 patients die each year from sarcoma related causes. Clinical workup and treatment guidelines have been published by the NCCN to ensure that patients are treated in a uniform and appropriate manner. This study sought to retrospectively review patients with a new diagnosis of sarcoma who were treated in a National Cancer Institute Designated Cancer Institute (NCIDCI) and determine compliance rates with the guidelines.

Methods: Data was collected prospectively on 35 newly diagnosed patients treated by a sarcoma division within an NCIDCI. Patients who obtained any significant workup or treatment for their diagnoses prior to presenting to this sarcoma service were excluded from the study. All included patients had biopsy proven pathology, which could be treated using one of the NCCN guidelines for either soft tissue sarcoma (STS) or bone sarcoma.

Results: Thirty-five patients met inclusion criteria for the study from August of 2016 to January of 2017. The most common diagnoses were Giant Cell Tumor (GCT) of Bone (7 cases, 20%), Undifferentiated pleomorphic sarcoma (4 cases, 11%) and Liposarcoma (3 cases, 9%). The most commonly used NCCN guidelines protocols included STS extremity guidelines (51%) and GCT of bone guidelines (20%). Primary site imaging was obtained in 100% of cases. Chest imaging was obtained in 97% of cases. Full body imaging was obtained in 100% of indicated cases. Tissue was obtained preoperatively in 97% of cases. Imaging was reviewed at multidisciplinary Treatment Planning Conference (TPC) in 97% of cases. Pathology was reviewed in 94% of cases in TPC. TNM staging was reviewed in 100% of cases in TPC. Plan of care was re-

viewed in 100% of cases at TPC. Surgery was recommended in 68%, radiation in 32%, and systemic therapy was recommended 29% of cases. Treatment guidelines were followed in 94% of all cases reviewed.

Diagnosis	# of cases	% of Total
Giant cell tumor of Bone	7	20%
Soft Tissue leiomyosarcoma	3	11%
undifferentiated Pleomorphic Sarcoma	4	9%
Liposarcoma	3	9%
Scalp soft tissue Sarcoma	2	9%
Extremity Synovial Sarcoma	3	9%
Chondrosarcoma	3	9%
Desmoid	3	6%
low grade soft tissue sarcoma	2	6%
Angiosarcoma	1	6%
myxofibrosarcoma	1	3%
high grade soft tissue sarcoma	2	3%
epithelioid sarcoma	1	3%
STS Extremity Guidelines	18	51%
Bone - GCT of Bone Guidelines	7	20%
Bone - Chondrosarcoma Guidelines	3	9%
STS Head Guidelines	2	6%
STS Desmoid	4	9%
STS Trunk Guidelines	2	6%
IA	3	9%
IB	4	11%
IIA	3	9%
IIB	5	14%
III	4	11%
IV	5	14%
IVA	1	3%
no staging necessary	10	29%

Numeric and percent makeup of cases by diagnosis, NCCN guideline used and stage of disease.

Conclusion: This study evaluated the workup and treatment provided by a single NCIDCI sarcoma service to a series of patients with pathologies defined with the NCCN sarcoma treatment guidelines. Overall rates of obtaining appropriate imaging and biopsy were 97-100%, as was the rate of reviewing all pertinent information in a multidisciplinary TPC (94-100%). NCCN guidelines were followed appropriately in 94% of cases overall. By following these NCCN guidelines we believe that patient care can be optimized and each case treated on an individually appropriate manner.

PO 026 #2804353

RETROPERITONEAL SARCOMAS: HOW CAN WE ESTIMATE THE RISK? VALIDATION OF A PROGNOSIS NOMOGRAM

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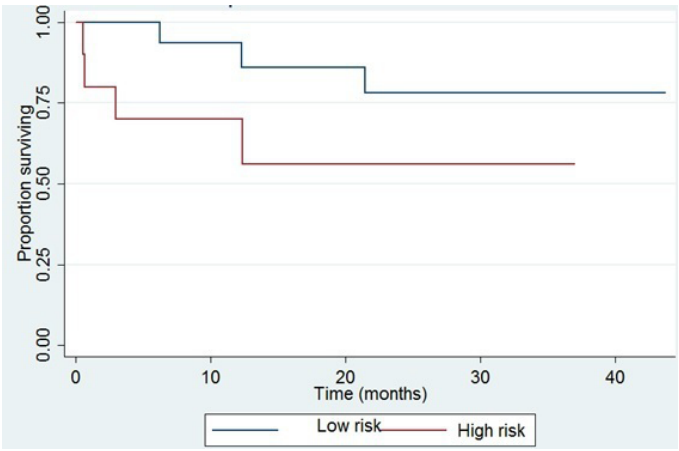
Objective: Integration of numerous prognostic variables not included in the conventional staging of retroperitoneal soft tissue sarcomas (RPS) is essential to establish an accurate risk of recurrence. The current AJCC staging algorithm for resectable RPS is inadequate. Recently, Gronchi et al have established a reliable new prognostic tool, a nomogram that estimates 7 year overall survival (OS) according to a score assigned to age, tumor size, grade, histological subtype, presence of multifocality and the extent of the resection. This nomogram has been validated externally. Our objective was to analyze if Gronchi's nomogram was able to establish two different groups of risk.

Methods: We retrospectively included patients with primary localized RPS resected between 1995 and 2016 in Universitary Ramón y Cajal Hospital. Stata 14.1 was used to analyze the data. Kaplan and Meier plots and log rank analyses were carried out.

Results: 32 patients were identified. The median follow-up was 30.1 months. The median recurrence free survival (RFS) was 47.67 months and the median OS was 77.18 months. We established 2 groups of risk according to the score obtained with the nomogram: low risk (less than 150 points) and high risk (150 points or more). The median RFS in the low risk group was 47.67 months (IC 95%) and 20.2 months in the high risk group, although long rank test showed not statistically significant differences (p: 0.21). The median OS in our low risk was 74.81 months and 31.37 months in the high risk group, long rank test showed no statistically significant differences (p: 0.13).



Conclusion: Although our sample is small, we could observe that the nomogram correctly classifies patients in two different groups of risk of recurrence and survival. The implementation of this nomogram in the daily clinical practice could be used to accurately assess individual patient risk, leading to improved prognosis-based decision making and enhanced clinical trial stratification.

PO 027 #2804639

PATHOLOGIC FRACTURES IN PRIMARY BONE NEOPLASMS OF THE FINGERS

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Objective: The goal of this study was to identify predictors for pathological fractures and recurrence in neoplasms affecting the bones of the fingers. Secondarily, we tried to identify if fracture per se is a predictor for tumor recurrence.

Methods: We retrospectively identified 131 histologically confirmed neoplasms affecting the bone, 97 phalanges and 34 metacarpals, over a 13-year period. The mean age at presentation was 42 years and 57% of the patients were female. Most tumors (84%) were benign bone neoplasms and the remainder were primary bone sarcomas. Tumors were located most frequently in the long finger (27%), ring finger (23%) and small finger (23%). Predictors evaluated included demographics, clinical information, tumor size, Enneking and Lodwick-Madewell classifications. A bivariate analysis was performed to identify factors associated with pathologic fractures. Variables with a p-value of <0.10 in the bivariate analysis were analyzed using a multivariable logistic regression models to identify factors independently associated with pathologic fractures. The same bivariate analysis was performed to test pathologic fracture as a predictor of recurrence.

Results: Forty-two percent of the tumors presented as a pathologic fracture. The small finger was independently associated with pathologic fractures, having 4.8 times the odds compared to the other fingers (p=0.0050). Fractures of the small finger were caused by no or minor trauma in >50%. Compared to the proximal phalanx, tumors in the metacarpal bone were less likely to fracture (OR=0.21, p=0.0070). We were not able to prove pathologic fractures as predictor of primary bone tumor recurrence.

Conclusion: Primary benign or malignant bone tumors located in the small finger are at risk for pathologic fractures. Therefore, they should be addressed surgically in an early stage, independent of patient symptoms, in order to prevent pathologic fracturing. Tumors of the metacarpals have a lower risk for a pathologic fracture, solely requiring monitoring as far as the patient is asymptomatic.

Table 1: Patient Characteristics and Factors Associated with Pathologic Finger Fractures

Characteristic	All phalangeal bone tumors (n=131)	Pathologic Fractures No (n=76)	Pathologic Fractures Yes (n=55)	P Value
Affected finger, n(%)				**0.014**
Thumb	13 (9.9)	10 (13)	3 (5.4)	
Index	21 (16)	15 (20)	6 (11)	
Long	36 (27)	25 (33)	11 (20)	
Ring	30 (23)	15 (20)	15 (27)	
Small	31 (23)	11 (14)	20 (36)	
Benign tumor, n(%)				0.23
No	21 (16)	15 (20)	6 (11)	
Yes	110 (84)	61 (80)	49 (89)	
Affected bone, n(%)				**0.0030**
Metacarpal	34 (26)	28 (37)	6 (11)	
Proximal phalanx	49 (37)	26 (34)	23 (42)	
Middle phalanx	28 (21)	15 (20)	13 (24)	
Distal phalanx	20 (16)	7 (9.2)	13 (24)	

Table 2: Factors Independently Associated with Pathologic Phalangeal Fractures (n=131)

Characteristic	Odds ratio	Lower (95% CI)	Upper (95% CI)	P-value
Digit (ref: Long)				
Thumb	1.4	0.28	7.3	0.66
Index	1.1	0.31	3.7	0.90
Ring	2.8	0.96	8.3	0.060
Small	**4.8**	**1.6**	**14**	**0.0050**
Phalanx (ref: Proximal)				
Metacarpal	**0.21**	**0.070**	**0.66**	**0.0070**
Middle	0.79	.029	2.2	0.65
Distal	1.9	0.59	5.8	0.29

Area under the ROC= 0.74; P value for Hosmer–Lemeshow test (goodness-of-fit test) = 0.94

PO 028 #2804710

AN OBSERVATIONAL ANALYSIS ABOUT RELAPSES PATTERN IN RETROPERITONEAL SARCOMAS (RS): OUR EXPERIENCE IN RAMÓN Y CAJAL HOSPITAL

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Objective: RS are uncommon tumor, around 1% of all tumors and 15% of soft tissues sarcomas. They are diagnosed mostly located and the main treatment is surgery. However, the five-year relapse-free survival (RFS) is 40-50% and the five-year overall survival (OS) is 50-60%. Local failure is the most usual pattern of recurrence, but distant metastases are possible too, especially in the lung and liver. Relapses used to appear in the first 2-3 years but they can appear even 10-15 years later.

Methods: We retrospectively analyzed the data of patients diagnosed with primary localized RS resected between 1995 and 2016 in a single institution (Ramón y Cajal Hospital University). Our objective was to study the patients that had relapses, and their main prognostic variables. Stata 14.1 has been used for the analysis.

Results: A 55% cases were women and the mean age was 56 years old. The mean tumor size was 17 cm. The most frequently were liposarcoma (LPS) and leiomyosarcoma (LMS). A 60% cases relapses: 16 (84%) were local relapses and 3 (15%) were at distance. Most of the RS which relapses locally were LPS. Tumors with distance relapses were LPS in two cases and one LMS. Two were intermediate-grade and the other high-grade. Two were state III (AJCC staging scale) and the third was state I. The tumor sizes were greater than 10 cm in all cases. The main organ affected were lungs (in the three cases) and liver (one case). The treatment in two of the three cases was surgery exclusively, and in the other case, the patient received neoadjuvant chemotherapy (CT). None received radiotherapy (RT). Median DFS for local relapses patients was 20,7 months and 13,6months in distant relapse. Median OS were75 and 21.5 months, respectively.

Conclusion: According to the literature, all cases progressed with pulmonary metastases, and the DFS and OS seem less in tumors which relapse at distance. However, some cases present an unexpected behavior, because probably we do not know yet all factors which define RS evolution. Our study population is not enough to establish conclusions and larger studies to improve our knowledge about the behavior and prognostic of RS are necessary.

PO 029 #2804767

A CASE REPORT OF A POORLY DIFFERENTIATED ESTHESIONEUROBLASTOMA IN A YOUNG ADULT

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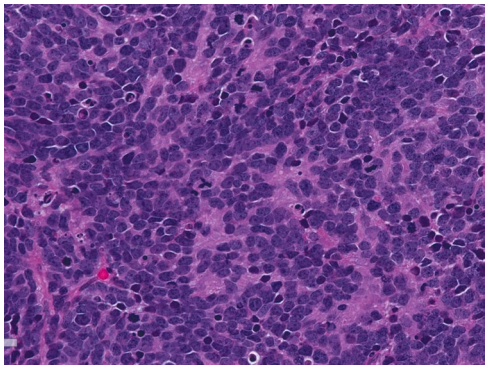
Objective: Esthesioneuroblastoma (ENB) is a neuroendocrine tumor that is fairly uncommon and can occur in a wide age range. It typically involves the upper portion of the nasal cavity, and its growth ranges from indolent to extremely rapid. It is more common in middle aged and older adults and accounts for 6% of nasal cavity and paranasal sinus neoplasms, and 0.3% of upper aero-digestive tract malignancies. It is far less common in the pediatric population. Approximately 10% of the patient's with ENB have neck metastases at time of diagnosis. Treatment options include surgical resection, radiation for the primary lesions, and chemotherapy for recurrent or metastatic lesions. Here, we report a rare case of poorly differentiated ENB in a young adult.

Methods: A 19 year old, previously healthy, female presented to her primary care physician with a 1 month history of weight loss, fatigue, night sweats, and right-sided facial pain and swelling. She also had a 3 week history of blurry vision in her right eye. She was initially diagnosed with a sinus infection and was treated with antibiotics. Despite antibiotic treatment, her facial swelling and right eye vison worsened. A CT scan of her head showed a large, right-sided ethmoid lesion that extended into the anterior skull base with bony erosion. Evaluation was completed by otolaryngology (ENT) and neurosurgery, after which a bilateral endoscopic surgery with nasal biopsy was obtained. Fresh frozen section showed small round blue cells. PET scan showed hyper-metabolism in the right ethmoid region and cervical lymph nodes. Pathologic diagnosis proved difficult and her specimen was reviewed by several pathologists at various institutions with a final diagnosis of poorly differentiated ENB (Kadish stage D). A week from her initial diagnosis, she had worsening right eye vision with a repeat head and neck MRI that showed aggressive and rapidly progressive disease. She was treated per a modified version of the protocol report by the North American Neuroendocrine Tumor Society (NANETS) Consensus Guidelines and received etoposide and cisplatin. She also received a prolonged course of decadron to help control tumor-related edema. Excellent response to two cycles of chemotherapy was noted. Approximately, 3 months after her initial diagnosis, she underwent a gross total resection of the sinonasal mass. Post-operative imaging did not show any nodular enhancement to suggest residual disease.

Results: She is now about three and a half months from initial diagnosis and is clinically doing well. Her right eye vision has been severely compromised, but she currently does not have any other deficits. Adjuvant chemotherapy, in addition to proton radiotherapy for local control, will be administered after surgical recovery. Of note, she had a strong family history of cancer with a maternal aunt who died from breast cancer, paternal great-grandmother who died from lung cancer, and paternal great-grandfather who died from pancreatic cancer. The patient's P53 mutation status was negative.



This shows a solid tumor nodule composed of small round blue cells with scanty cytoplasm, fine dusty nuclear chromatin pattern, a very high mitotitc rate and abundant karyorrhexis. The tumor is arranged in sheets, forms vague pseudorosettes with central fibrillary stroma reminiscent of neuropil in some areas.

Immunohistochemical profile: Positive for synaptophysin, calretinin, p63 and CD56. There is patchy weak/equivocal positive staining for pan-

keratin AE1/AE3 in a focally membranous and focally paranuclear dot pattern.The tumor is negative for Epithelial Membrane Antigen (EMA), chromograninin, tyrosine hydroxylase, S100, PHOX2B and GFAP.

Conclusion: ENB is a extremely rare diagnosis in the pediatric and adolescent population. Poorly differentiated ENB is often rapidly progressive and difficult to treat and diagnose. Despite the rapid growth and difficulty with diagnosis of our patient's tumor, aggressive multimodal treatments can help achieve positive outcomes.

PO 030 #2804778

USE OF INTENSITY MODULATED RADIOTHERAPY IN EXTREMITY SOFT-TISSUE SARCOMA: ANALSYSIS OF THE NATIONAL CANCER DATABASE

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Objective: Intensity modulated radiotherapy (IMRT) is a form of radiotherapy that can decrease radiation dose to normal tissues. Retrospective studies have suggested that when compared to conventional 3D conformal radiotherapy, IMRT may improve toxicity and local control. We aimed to determine the influence of demographic and clinical factors on IMRT use, and the impact of IMRT on overall survival (OS), utilizing the National Cancer Database.

Methods: Patients diagnosed with a soft tissue sarcoma of the extremity between years 2004 and 2012 were included in the cohort. Least squares linear regression determined the significance of the change in IMRT use over time. Univariate and multivariate logistic and Cox regression modeling was used to identify demographic and clinical factors predictive of IMRT use and OS, respectively.

Results: A total of 29,990 patients were included for analysis. During the study period, IMRT usage among patients receiving radiation increased from 5.9% in 2004 to 36.0% in 2012 (P<0.001). Factors predictive of IMRT use included year of diagnosis (Odds ratio [OR] 1.22, 95% Confidence Interval [CI] 1.20-1.24), treatment at an academic facility (OR 1.20, 95% CI 1.11-1.30), and tumor size > 5 cm (OR 1.29, 95% CI 1.18-1.41). In contrast, factors predictive of IMRT omission included black race (OR 0.78, 95% CI 0.68-0.90), treatment in a rural location (OR 0.75, 95% CI 0.62-0.91), and radiation dose greater than 64 Gy (OR 0.89, 95% CI 0.82-0.98). There was significant variation in practice in the United States, with the Northeast being the region most likely to use IMRT (P<0.01). No survival benefit with IMRT was noted on univariate (HR 0.98, 95% CI 0.93-1.04) or multivariate (HR 1.00, 95% CI 0.94-1.07) analysis.

Conclusion: The use of IMRT for soft tissue extremity sarcoma has increased significantly over time, with utilization being subject to multiple demographic and clinical factors. However, IMRT use was not associated with an OS benefit.

PO 031 #2804856

EVIDENCE MAPPING BASE ON SYSTEMATIC REVIEWS OF THERAPEUTIC INTERVENTIONS FOR GASTROINTESTINAL STROMAL TUMORS (GIST)

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Objective: The purpose of this evidence mapping project is to identify, describe and organise the current available evidence about therapeutic interventions on sarcomas. This approach aims to determine the clinical questions assessed in the scientific literature and the corresponding quality of the supporting evidence, as well as to give general information about their claimed effectiveness.

Methods: We followed the methodology of Global Evidence Mapping (GEM). We searched Pubmed, EMBASE, The Cochrane Library and Epistemonikos in order to identify systematic reviews (SRs) with or without meta-analyses published between 1990 and March 2016. Two authors assessed eligibility and extracted data. Methodological quality of the included systematic reviews was assessed using AMSTAR. We organised the results according to identified PICO questions and presented the evidence map in tables and a bubble plot.

Results: A total of 17 SRs met eligibility criteria. These reviews included 66 individual studies, of which three quarters were either observational or uncontrolled clinical trials. Overall, the quality of the included SRs was moderate or high. In total, we extracted 14 PICO questions from them and the corresponding results mostly favoured the intervention arm.

Conclusion: The most common type of study used to evaluate therapeutic interventions in GIST sarcomas has been non-experimental studies. However, the majority of the interventions are reported as beneficial or probably beneficial by the respective authors of SRs. The evidence mapping is a useful and reliable methodology to identify and present the existing evidence about therapeutic interventions.

PO 032 #2804390

PROGNOSTIC FACTORS OF LEIOMYOSARCOMAS IN A TERTIARY CENTER

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Objective: Leiomysarcomas arise from smooth muscle including blood vessels. Retroperitoneal leiomyosarcoma often involve major vessels. The aim of our study is to present our series of leiomyosarcomas and to examine whether vascular origin is associated with prognosis.

Methods: A retrospective analysis of all Leiomyosarcomas referred to our institution between 2005-2016 was performed. Visceral and dermal leiomyosarcomas were excluded. Demographic data, site of disease, tumour size and grade, extent of operation performed and the blood vessel that the tumour originated from were recorded. The origin of the Leiomyosarcoma was categorized as small/no named vessel, medium (e.g. gonadal or saphenous) or large sized (e.g. Inferior vena cava). The follow up was retrieved from the patient's medical notes and the Disease Specific Survival (DSS), the Distant Metastasis (DM) and the local recurrence (LR) rates were calculated.

Results: One hundred and eleven patients underwent surgery for resection of a Leiomyosarcoma over a 10-year period. The mean patient's age was 58 (±1.7 SEM) years and the majority were females (N=61, 55%). Most of the Leiomyosarcomas were located in the abdomen (N=72, 64.5%) with the second most common site being the lower limb (N=30, 27%). Regarding abdominal Leiomyosarcomas, 31 cases originated from the IVC (43%) and the median number of organs excised was 1 (N=31, 43%). There was a statistically significant association between the vascular origin of the Leiomyosarcoma and the number of organs excised. There was no association between vascular origin and DSS or DM (Table1). The median follow up was 47 months (2-118 months) and the 10-year DSS, DM and LR were 54.3%, 65% and 25% respectively. High grade tumours and abdominal site were associated with a worse DSS and DM and LR in the multivariate analysis.

Table 1. Origin of abdominal Leiomyosarcoma and the number of organs excised

	Organs Resected			
	0	1	>2	p value
Vascular Origin				
Small/No named vessel	5 (20%)	7 (22%)	10 (62%)	
Medium sized	9 (36%)	7 (22.6%)	3 (18.8%)	<0.021>
Large	11 (44%)	17 (54.8%)	3 (18.8%)	

Conclusion: Surgery remains the gold standard in the treatment of Leiomyosarcomas. The site of the disease and the grade of the tumour seem to be the only prognostic factors associated with survival.

PO 033 #2804393

BONE METASTASES IN PATIENTS WITH BREAST CANCER: EARLY VERSUS LATE ONSET AND THEIR IMPACT ON SURVIVAL. A SINGLE-INSTITUTION RETROSPECTIVE COHORT STUDY

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Objective: The aim of the present study was to further explore the impact of late-onset bone metastases (BMs) on the overall prognosis of patients with breast cancer.

Methods: We performed a retrospective analysis of medical records of 251 patients with histologically confirmed breast cancer, diagnosed and treated in the Gil medical center, between January 2010 and December 2014. For analytical purposes, patients were divided into 2 groups: the early bone metastases (EBM) group, who experienced bone metastasis less than 5 years from primary diagnosis, or the late bone metastases (LBM) group, who confirmed bone metastases later than 5 years from primary diagnosis and in whom the presence of bone metastases was not identified during the treatment. Demographic and clinicopathological features, including BMs and their time point of development (early onset/at diagnosis versus late onset/at a subsequent time point) were analyzed. Survival analysis was performed using the Kaplan–Meier method, log-rank tests, and Cox regression analysis.

Results: The median disease-free intervals were 24.6 months (range 6-55 months) in EBM group and 92.8 months (range 61-171) in LBM group. The median follow-up periods after BM were 37.4 months (range 10-115) in EBM and 120 months (range 68–295) in LBM. Median survival after bone metastases was significantly longer in LBM group than in EBM group (31months vs 5months, $p<0.001$). Patients with early-onset BMs had a reduced OS [Hazard ratio (HR) 11.9; 95 % Confidence interval (CI) 3.03–47.3; $p < 0.001$) as compared to those with late-onset BMs. (Fig 1)

Among the clinical characteristics, the age at primary breast cancer diagnosis was older in the EBM group than that in the LBM group ($p = 0.026$) (Table 1). Primary tumor size was significantly large in the EBM group ($p = 0.011$). The EBM group presented higher T-categories than the LBM group ($p < 0.001$).

Histological subtype analysis revealed that presence of hormone receptor is significantly higher in LBM group. 54% of patients with luminal A or luminal B and 20% with TNBC or HER-2 overexpressing tumors experienced late

bone metastases (p=0.007). Survival from the date of BM is longer in patients with luminal A or luminal B than in those with TNBC or HER-2 overexpression (p=0.026).

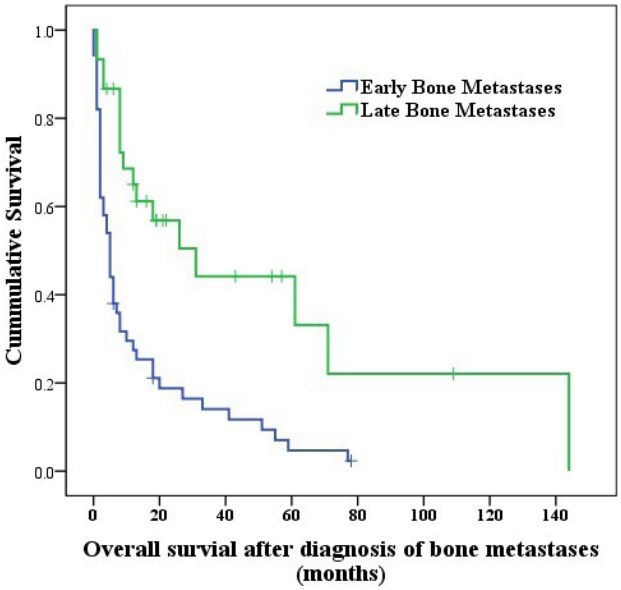

Fig. 1. Overall survival of EBM and LBM groups after diagnosis of bone metastases

Conclusion: The results of our single-institution study suggest that the development of early-onset BMs may represent an independent predictor of a worse prognosis among patients with breast cancer.

PO 034 #2804734

β_{III}-SPECTRIN STAINING AS A BIOMARK FOR DIAGNOSIS OF MPNST

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Objective: The most common malignancy affecting adults with the neurofibromatosis type 1 (NF1) cancer predisposition syndrome is the malignant peripheral nerve sheath tumor (MPNST), a highly aggressive sarcoma that typically develops from benign plexiform neurofibromas. Given the lack of specific morphological criteria and ancillary immunohistochemical/molecular tests, MPNSTs can be difficult to distinguish from their benign counterparts as well as from other sarcomas. Prior work from our laboratory suggested that bIII-spectrin was highly expressed in MPNST and thus we hypothesized that β_{III}-spectrin immunostaining could be used as a potential marker to aid in classification of these tumors.

Methods: β_{III}-spectrin immunostaining was performed on formalin-fixed paraffin embedded sections encompassing a collection of nerve sheath tumor specimens, including atypical neurofibromas, low grade MPNSTs, high grade MPNSTs, and other soft tissue sarcomas.

Results: While strong expression of β_{III}-spectrin was observed in 100% of high grade MPNSTs, only 47% of low grade MPNSTs or atypical neurofibromas exhibited β_{III}-spectrin staining and 7% of other sarcomas expressed β_{III}-spectrin. A 2 x 2 frequency table was used to estimate sensitivity and specificity for β_{III}-spectrin IHC. A linear logistic regression model was used to plot ROC curves and calculate AUC. In this regard, there was sensitivity of 100% and a specificity =97.56% in distinguishing high grade MPNSTs from other sarcomas (AUC=0.9878, c-index=0.988); there was a sensitivity of 100% and a specificity =100% (AUC=1.0 c-index=1.0) in distinguishing high grade MPNSTs from atypical neurofibromas; and a sensitivity of 100% and a specificity of 75%, (AUC=0.875, c-index= 0.875) in distinguishing high grade MPNSTs from the group of low grade MPNSTs and atypical neurofibromas combined.

Conclusion: Collectively, these data suggest that β_{III}-spectrin staining is specific to MPNSTs and may serve as a marker to aid in classification and diagnosis of these tumors.

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