2019 CTOS Annual Meeting

November 13-16, 2019

Tokyo, Japan

Final Program

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Bringing together the world's sarcoma specialists®

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Akira Kawai, MD

2019 CTOS Program Committee
Robin Jones, MD Takafumi Ueda, MD - Program Co-Chairs
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The Connective Tissue Oncology Society
greatly appreciates your support of the 2019 Annual Meeting. Your funding is vital and will advance the medical science and care of patients with bone and soft tissue tumors.

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CTOS Annual Meeting

November 13-16, 2019

Tokyo, Japan

Dear Colleagues,

We are delighted to invite you to join us in Tokyo for the 24th Annual Meeting of the Connective Tissue Oncology Society, November 13-16, 2019. The meeting will be held at the Hilton Tokyo.

The Annual Meeting continues to grow in attendance as well as the number of abstracts submitted. We will build on the excellent meeting in Rome last year. This year's meeting will provide the ideal venue for debate and connecting with old friends. This is the first time the meeting has been in Japan and we would like this to be an opportunity to have further collaboration between 'East and West'. There will be a special session for mentoring young researchers. CTOS is unique in bringing to together an international community of scientists, clinicians, patients and families.

Desmoplastic small round cell sarcoma is the "Sarcoma of the Year" and there will be a special session focusing on the challenges of diagnosing and treating this rare subtype. In addition, there will be a number of focused sessions with a multi-disciplinary theme, incorporating new data from basic science to outcomes research. Further highlights this year will include the Herman Suit Lecture which will be delivered by Jay Wunder and the Nina Axelrad Lecture by Richard Gorlick.

There will also be the opportunity to enjoy the amazing history and culture of Tokyo, we are delighted to provide complimentary tours of the city. The Gala Reception will be at the traditional Japanese beautiful garden of Happo En.

We look forward to seeing you in Tokyo!

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CTOS 2019 Board of Directors

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2019 Annual Meeting
Program At-a-Glance

Wednesday, 13 November, 2019

12:00 pm - 6:00 pm	Registration	*Kiku Lobby, 4th Floor*
12:00 pm - 6:00 pm	Poster Set Up	*3rd Floor*
2:00 pm - 6:00 pm	TARPSWG Semiannual Meeting	*Ran Room, 3rd Floor*
5:30 pm - 7:30 pm	Welcome Reception	*Kiku Ballroom*

Thursday, 14 November, 2019

6:00 am - 5:30 pm	Registration	*Kiku Lobby, 4th Floor*
6:15 am - 7:30 am	Sunrise in Tokyo	*Kiku Ballroom*
8:00 am - 4:30 pm	5th Annual International Sarcoma Nurse and Allied Professionals Meeting (iSNAP) "Strides in Sarcoma Care"	*Hinoki Room*
8:30 am - 9:00 am	Opening Remarks	*Kiku Ballroom*
9:00 am - 10:00 am	SESSION 1 – New WHO Classification WHO Classification of Bone Tumors: *Judith Bovee* WHO Classification of Soft Tissue Sarcomas: *Paolo Dei Tos* Clinical Implications of the New WHO Classification: *Jean-Yves Blay*	*Kiku Ballroom*
10:00 am - 10:30 am	Morning Break & Poster Viewing	*3rd Floor*
10:30 am - 12:00 pm	SESSION 2 – Novel Therapeutic Targets	*Kiku Ballroom*
12:00 pm - 1:00 pm	Lunch	*Second Floor*
12:00 pm - 1:00 pm	Board of Directors Meeting	*Ran Room, 3rd Floor*
1:00 pm - 3:00 pm	SESSION 3 – Clinical Trials + Precision Medicine	*Kiku Ballroom*
3:00 pm - 3:30 pm	Afternoon Break & Poster Viewing	*3rd Floor*
3:30 pm - 5:30 pm	SESSION 4 – Bone Sarcomas	*Kiku Ballroom*
5:30 pm - 6:30 pm	Poster Viewing Reception	*3rd Floor*

Friday, 15 November, 2019

6:00 am - 5:30 pm	Registration	*Kiku Lobby, 4th Floor*
6:15 am - 7:30 am	Sunrise in Tokyo	*Kiku Ballroom*
7:00 am - 8:00 am	Executive Committee Meeting	*Ran Room, 3rd Floor*
8:00 am - 8:30 am	SESSION 5 – Sarcoma of the Year: DSRCT	*Kiku Ballroom*
8:30 am - 9:30 am	SESSION 6 – Multi-Disciplinary Care	*Kiku Ballroom*
9:30 am - 10:00 am	Morning Break	*3rd Floor*
10:00 am - 11:00 am	SESSION 7 – Radiation Oncology	*Kiku Ballroom*
11:00 am - 12:00 pm	SESSION 8 – East Meets West in Sarcoma Care	*Kiku Ballroom*
12:00 pm - 1:00 pm	Lunch	*Second Floor*
12:00 pm - 1:00 pm	Board of Directors Meeting	*Ran Room, 3rd Floor*
1:00 pm - 2:00 pm	SESSION 9 – GIST	*Kiku Ballroom*
2:00 pm - 3:00 pm	Herman Suit Lecture – *Jay Wunder*	*Kiku Ballroom*
3:00 pm - 3:30 pm	Afternoon Break	*3rd Floor*
3:30 pm - 5:30 pm	SESSION 10 – Retroperitoneal / Pelvic Sarcomas	*Kiku Ballroom*
6:30 pm – 10:30 pm	GALA - Reception and Dinner at Happo En Cocktail Attire Buses will depart at 6:00 pm from the Hilton Tokyo Hotel. *(Badges are required)*	*Happo En*

Saturday, 16 November, 2019

6:00 am - 6:00 pm	Registration	*Kiku Lobby, 4th Floor*
6:15 am - 7:30 am	Sunrise in Tokyo	*Kiku Ballroom*
8:00 am - 10:00 am	SESSION 11 – Paediatric Sarcomas	*Kiku Ballroom*
10:00 am - 10:30 am	Morning Break	*3rd Floor*
10:30 am - 11:30 am	Nina Axelrad Lecture – *Richard Gorlick*	*Kiku Ballroom*
11:30 am - 12:00 pm	SESSION 12 – Young Investigator Awards	*Kiku Ballroom*
12:00 pm - 1:00 pm	Lunch	*Second Floor*
1:00 pm - 1:30 pm	LSERA Award	*Kiku Ballroom*
1:30 pm - 3:30 pm	SESSION 13 – Soft Tissue Sarcomas: Biology	*Kiku Ballroom*
3:30 pm - 4:00 pm	Afternoon Break	*3rd Floor*
4:00 pm - 5:00 pm	SESSION 14 – Sarcomas: Novel Therapy	*Kiku Ballroom*
5:00 pm - 6:00 pm	SESSION 15 – Challenges in MPNST and NF1	*Kiku Ballroom*
6:00 pm - 6:30 pm	Members Business Meeting	*Kiku Ballroom*
6:30 pm	ADJOURN	*Kiku Ballroom*

TARPSWG Semiannual Meeting

Wednesday, November 13th
2:00 to 6:00 pm

Hilton Tokyo
Ran Room, 3rd Floor

Agenda

2:00 pm - 2:15 pm	Welcome Introduction *(A. Gronchi)*
2:15 pm - 3:00 pm	RESAR Update • Update on Inclusion of Patients with Persistent Disease, Recruitment, Sites and Funding *(D. Gyorki)* • Status of Centralized RESAR Data Collection/Registry *(A. Trama)* • Recommendation of New RESAR Project o Complexity Score Project for Post-op Morbidity *(M. Fairweather)* o Biopsy Project *(A. Gronchi)* o Correlation between Anticipated Resection vs Actual Resection o Variation in Pattern of Care *(H. Snow)* • Pathology Guidelines Consensus Meeting *(B. Dickson)* • Survey on the Impact of STRASS on Routine Use of Preop RT *(C. Roland)*
3:00 pm - 3.30 pm	Update Consensus Guidelines on Primary RPS *(C. Swallow – D. Strauss)*
3:30 pm - 3:50 pm	Dynamic Prediction in Primary RPS *(D. Callegaro)*
3:50 pm - 4:20 pm	Strass vs Strexit Projects *(C. Raut)*
4:20 pm - 4:30 pm	Post-nephrectomy Outcomes Project *(M. Fairweather)*
4:30 pm - 5:00 pm	REC Committee Update *(C. Nessim)* • Presentation of Left Pancreatectomy Project *(S. Bagaria)* • Presentation of Neo-Adjuvant Chemo Project *(W. Tseng)* • Presentation of the Primary Mesenteric Sarcoma Project *(S. Ford)* • Presentation of the Myxoid LPS Project *(C. Nessim)* • Proposal Ganglioneuroma Project *(J. Siclick)*
5:00 pm - 5:30 pm	Recurrent RPS Series: • Morbidity Post Resection of Recurrence *(G. Lahat)* • Outcomes of Patients after a Second Recurrence *(R. Gladdy)* • Change in Grade between the Primary and the Recurrence *(C. Nessim and S. Bagaria)* • Any New Recommendations of Ideas for this Dataset?
5:30 pm - 5:50 pm	Update STRASS 2 *(W. van Houdt)*
5:50 pm - 6:00 pm	TARPSWG: Time to Brainstorm Beyond RPS? *(All)*
6:00 pm	AOB and Adjournment *(A. Gronchi)*

RETHINK THE BIOLOGY FUELING RESISTANCE AND PROGRESSION IN GIST

Resistance in GIST is driven by a myriad of mutations and demands a different therapeutic approach[1]

Nearly all patients with GIST will eventually develop clinical resistance to imatinib[1-3]

GIST exhibits broad intra- and inter-tumor heterogeneity, with multiple mutations fueling resistance and progression[1,3]

A novel approach to kinase inhibition against a broad spectrum of KIT and PDGFRα mutations may potentially transform treatment in GIST[4]

Could broader mutational coverage translate to sustained disease control?

Deciphera is committed to uncovering scientific insights around resistance and progression, in order to develop novel approaches for patients with GIST. Learn more at **RethinkGIST.com**

GIST=gastrointestinal stromal tumor; TKI=tyrosine kinase inhibitor.

References: 1. Ordog T, Zörnig M, Hayashi Y. Targeting disease persistence in gastrointestinal stromal tumors. *Stem Cells Transl Med.* 2015;4(7):702-707. **2.** Serrano C, George S. Recent advances in the treatment of gastrointestinal stromal tumors. *Ther Adv Med Oncol.* 2014;6(3):115-27. **3.** Li K, Cheng H, Li Z, et al. Genetic progression in gastrointestinal stromal tumors: mechanisms and molecular interventions. *Oncotarget.* 2017;8(36):60589-60604. **4.** Hemming ML, Heinrich MC, Bauer S, George S. Translational insights into gastrointestinal stromal tumor and current clinical advances. *Ann Oncol.* 2018;29(10):2037-2045.

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Wednesday, 13 November, 2019

12:00 pm - 6:00 pm	Registration	*Kiku Lobby, 4th Floor*
12:00 pm - 6:00 pm	Poster Set Up	*3rd Floor*
2:00 pm - 6:00 pm	**TARPSWG Semiannual Meeting**	*Ran Room, 3rd Floor*
5:30 pm - 7:30 pm	**Welcome Reception**	*Kiku Ballroom*

Thursday, 14 November, 2019

6:00 am - 5:30 pm	Registration	*Kiku Lobby, 4th Floor*
6:15 am - 7:30 am	Sunrise in Tokyo	*Kiku Ballroom*
6:15 am - 6:20 am	Case Introduction: Localized High-grade STS *Herbert Loong*	
6:20 am - 6:35 am	The Role of Radiation in High-grade STS *Rick Haas*	
6:35 am - 6:50 am	Surgical Approaches and Resection Margins in High-grade STS *Makoto Endo*	
6:50 am - 7:05 am	Role of Systemic Therapy in Localized Disease *Sebastian Bauer*	
7:05 am - 7:20 am	Pathology and Overview of High-grade STS *Akihiko Yoshida*	
7:20 am - 7:30 am	Wrap-up and What's New in High-grade STS @ CTOS 2019? *Taka Ueda*	
8:00 am - 4:30 pm	**5th Annual International Sarcoma Nurse and Allied Professionals Meeting (iSNAP) "Strides in Sarcoma Care"**	*Hinoki Room*
8:30 am - 9:00 am	**Opening Remarks**	*Kiku Ballroom*

Thursday, 14 November, 2019

9:00 am - 10:00 am — – SESSION 1 – — *Kiku Ballroom*

New WHO Classification

Chairs: **Akihiko Yoshida** and **Liz Demicco**

9:00 am - 9:20 am — **WHO Classification of Bone Tumors**
Judith Bovee

9:20 am - 9:40 am — **WHO Classification of Soft Tissue Sarcomas**
Paolo Dei Tos

9:40 am - 9:50 am — **Clinical Implications of the New WHO Classification**
Jean-Yves Blay

9:50 am - 10:00 am — Discussion

10:00 am - 10:30 am — Morning Break & Poster Viewing — *3rd Floor*

10:30 am - 12:00 pm — – SESSION 2 – — *Kiku Ballroom*

Novel Therapeutic Targets

Chairs: **Peter Grimison** and **Mark Agulnik**

Paper #01
10:30 am - 10:45 am — 3329872

TARGET: OSTEOSARCOMA
THE GENOMIC LANDSCAPE OF OSTEOSARCOMA: A TARGET REPORT

Ching C. Lau[1,2,3]*; Aaron Taylor*[1,3]*; Monika J.Y. Sun*[3]*; Alex Yu*[3]*; Jianhe Shen*[3]*; Lisa Teot*[4]*; Don Barkauskus*[5]*; Mark Krailo*[5]*; Richard Gorlick*[6]*; Timothy Triche*[7]*; Shintaro Iwata*[8,9]*; Miki Ohira*[8,10]*; Jay Wunder*[11]*; Irene Andrulis*[11]*; Silvia Regina Caminada de Toledo*[12]*; Antonio Sergio Petrilli*[12]*; Lisa Mirabello*[13]*; Sharon Savage*[13]*; Robert L. Walker*[13]*; Marbin Pineda*[13]*; Yuan Jiang*[13]*; Sven Bilke*[13]*; Jack Zhu*[13]*; Yonghong Wang*[13]*; Joshua Waterfall*[13]*; Chris T.K. Man*[3]*; Sean Davis*[13]*; Jaime M. Guidry Auvil*[13]*; Daniela S. Gerhard*[13]*; Paul Meltzer*[13]
[1]The Jackson Laboratory for Genomic Medicine; [2]Connecticut Children's Medical Center; [3]Texas Children's Hospital/Baylor College of Medicin; [4]Boston Children's Hospital/Harvard Medical School; [5]Children's Oncology Group; [6]M.D. Anderson Cancer Center; [7]Children's Hospital Los Angeles/University of Southern California; [8]Chiba University; [9]National Cancer Center of Japan; [10]Saitama University; [11]Princess Margaret Hospital/University of Toronto; [12]Universidade Federal de Sao Paulo; [13]National Cancer Institute

10:45 am - 11:00 am — Discussant: ***Katie Janeway***

Thursday, 14 November, 2019

Paper #02 — 3251212
11:00 am - 11:12 am

GRACEFUL PROJECT: A GLOBAL COLLABORATION ON CIC-DUX4, BCOR-CCNB3, HIGH GRADE UNDIFFERENTIATED ROUND CELL SARCOMA (URCS)

Emanuela Palmerini[1]*; Marco Gambarotti*[1]*; Ravin Ratan*[7]*; Steven DuBois*[8]*; Michael J. Nathenson*[8]*; Antoine Italiano*[9]*; Enrique de Alava*[12]*; Robin Jones*[13]*; Salvatore Provenzano*[2]*; Giovanni Grignani*[3]*; Virginia Ferraresi*[4]*; Rossella Bertulli*[2]*; Giacomo G. Baldi*[11]*; Antonella Brunello*[6]*; Elisa Carretta*[1]*; Elisabetta Setola*[1]*; Angelo Paolo Dei Tos*[5]*; Alessandra Longhi*[1]*; Anna Paioli*[1]*; Marilena Cesari*[1]*; Michela Pierini*[1]*; Uta Dirksen*[14]*; Christian Rothermundt*[14]*; Javier Martin-Broto*[12]*; Bruno Vincenzi*[10]

[1]*Istituto Ortopedico Rizzoli, Bologna, BO, Italy;* [2]*Istituto Nazionale dei Tumori, Milano, MI, Italy;* [3]*Istituto di Candiolo, Candiolo, TO, Italy;* [4]*Istituto Nazionale Tumori "Regina Elena", Roma, RM, Italy;* [5]*Azienda ULSS2, Treviso, TV, Italy;* [6]*Istituto Oncologico Veneto, Padova, PD, Italy;* [7]*MD Anderson Cancer Center, Houston, TX, USA;* [8]*Dana-Faber Cancer Institute, Boston, MA, USA;* [9]*Institut Bergonié, Bordeaux, France;* [10]*Policlinico Universitario Campus Biomedico, Roma, RM, Italy;* [11]*AUSL4 Toscana, Prato, PO, Italy;* [12]*IBIS Instituto de Biomedicina de Sevilla, Sevilla, Spain;* [13]*The Royal Marsden, London, United Kingdom;* [14]*Kantonsspital St.Gallen, St. Gallen, Switzerland*

Paper #03 — 3244146
11:12 am - 11:24 am

TRANSCRIPTOMIC LANDSCAPE OF 79 HOMOGENOUSLY TREATED OSTEOSARCOMA TUMORS AT DIAGNOSIS REVEALS TUMOR CLONES AND MICROENVIRONMENT INTERPLAY ASSOCIATED WITH OSTEOSARCOMA PROGNOSIS

Antonin Marchais, PhD[1]*; Maria Eugenia Marques da Costa*[1]*; Bastien Job*[3]*; Robin Droit*[1]*; Rachid Abbas*[2]*; Anne G. Brouchet*[4]*; Françoise Redini*[5]*; Olivia Fromigué*[1]*; Cyril Lervat*[6]*; Hélène Pacquement*[7]*; Catherine Devoldere*[4]*; Claudine Schmitt*[4]*; Damien Bodet*[4]*; Sophie Piperno-Neumann*[7]*; Natacha Entz-Werle*[4]*; Perrine Marec-Berard*[8]*; Martha Jimenez*[9]*; Gilles Vassal*[1]*; Birgit Geoerger*[1]*; Laurence Brugieres*[1]*; Nathalie Gaspar*[1]

[1]*Pediatry, Gustave Roussy Cancer Campus, Villejuif, France;* [2]*SBE, Gustave Roussy, Villejuif, France;* [3]*INSERM, Villejuif, France;* [4]*CHU, Toulouse, France;* [5]*University, Nantes, France;* [6]*Centre Oscar Lambret, Lille, France;* [7]*Institut Curie, Paris, France;* [8]*IHOP, Lyon, France;* [9]*UNICANCER, Paris, France*

Paper #04 — 3255224
11:24 am - 11:36 am

IMPACT OF NEXT GENERATION SEQUENCING (NGS) ON DIAGNOSTIC AND THERAPEUTIC OPTIONS IN SOFT-TISSUE AND BONE SARCOMA (STSB)

Mrinal M. Gounder[1]*; Sally Trabucco*[2]*; Dexter X. Jin*[2]*; Narasimham Agaram*[1]*; Sandra P. D'Angelo*[1]*; Mark Dickson*[1]*; Mary Louise Keohan*[1]*; Ciara Kelly*[1]*; William D. Tap*[1]*; Siraj Ali*[2]

[1]*Memorial Sloan Kettering Cancer Center, New York, NY, USA;*
[2]*Foundation Medicine, Boston, MA, USA*

Paper #05 — 3255373
11:36 am - 11:48 am

TRACING SARCOMA EVOLUTION REVEALS CLONAL ORIGIN OF ADVANCED METASTASIS

Yuning Tang*; Jianguo Huang; Hongyuan Zhang; Hidetoshi Tsushima; David Kirsch; Benjamin Alman*
Duke University, Durham, NC, USA

11:48 am - 12:00 pm — Discussant: ***Juneko Grilley-Olson***

12:00 pm - 1:00 pm — Lunch — *Second Floor*

12:00 pm - 1:00 pm — Board of Directors Meeting — *Ran Room, 3rd Floor*

1:00 pm - 3:00 pm — – SESSION 3 – — *Kiku Ballroom*

Clinical Trials + Precision Medicine

Chairs: **Andrew Wagner** and **Christine Simmons**

Paper #06
1:00 pm - 1:12 pm

3255423

MULTI-INSTITUTIONAL EUROPEAN SINGLE-ARM PHASE II TRIAL OF PAZOPANIB IN ADVANCED TYPICAL SOLITARY FIBROUS TUMORS: A COLLABORATIVE SPANISH (GEIS), ITALIAN (ISG), AND FRENCH (FSG) SARCOMA GROUPS STUDY

*Josefina Cruz[2]; Nadia Hindi[1]; Sarah Dumont[3]; Nicolas Penel[4]; Pablo Luna[5]; Enrique de Alava[6]; Jean-Yves Blay[7]; Silvia Stacchiotti[8]; Paola Collini[8]; Andres Redondo[9]; Daniel Bernabeu[10]; Antonio López Pousa[11]; Giovanni Grignani[12]; David d. Moura[13]; Javier Martinez-Trufero[14]; Philippe Terrier[15]; Marie Karanian[7]; Axel Le Cesne[3]; Paolo Casali[8]; **Javier Martin-Broto**[1]*

[1]Medical Oncology, Hospital Universitario Virgen del Rocio/Instituto de Biomedicina de Sevilla (IBIS), Seville, Spain; [2]Medical Oncology, Hospital Universitario de Canarias, Tenerife, Spain; [3]Medical Oncology, Gustave Roussy Cancer Campus, Villejuif, France; [4]Oscar Lambret Cancer Center, Lille, France; [5]Medical Oncology, Hospital Universitario Son Espases, Palma de Mallorca, Spain; [6]Pathology, Hospital Universitario Virgen del Rocio, Seville, Spain; [7]Centre Léon Bérard, Lyon, France; [8]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [9]Medical Oncology, Hospital Universitario La Paz (IdiPAZ), Madrid, Spain; [10]Radiology, Hospital Universitario La Paz, Madrid, Spain; [11]Medical Oncology, Hospital Sant Pau, Barcelona, Spain; [12]Medical Oncology, Istituto di Candiolo-Fondazione del Piemonte per l'Oncologia IRCCS Candiolo, Turin, Italy; [13]Group of Advanced Therapies and Biomarkers in Oncology, Institute of Biomedicine of Seville, Ibis/Hospital Universitario Virgen Del Rocio/Csic/Universidad De Sevilla, Seville, Spain; [14]Medical Oncology, Hospital Universitario Miguel Servet, Zaragoza, Spain; [15]Pathology, Gustave Roussy Cancer Campus, Villejuif, France

Paper #07
1:12 pm - 1:24 pm

3253244

DEVELOPMENT AND VALIDATION OF A MOLECULAR SIGNATURE PREDICTIVE OF DURABLE CLINICAL BENEFIT FOLLOWING PAZOPANIB THERAPY IN ADVANCED SOFT TISSUE SARCOMA

Paul Huang[1]*; Alex Lee[1]; Chris Wilding[1]; Frank McCarthy[1]; Nafia Guljar[1]; Khin Thway[2]; Ben Fulton[3]; Sara Walker[3]; Alexandra Bell[4]; Fiona Graham[4]; Elaine MacDuff[5]; Wei Lin Goh[6]; Timothy Kwang Yong Tay[7]; Christina Messiou[2]; Richard Buus[1]; Cyril Fisher[8]; Mohamad Farid[6]; Jeff White[3]; Ian Judson[2]; Maggie Cheang[1]; Robin Jones[2]*

[1]Institute of Cancer Research, London, United Kingdom; [2]Royal Marsden Hospital, London, United Kingdom; [3]Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom; [4]NHS Greater Glasgow & Clyde Biorepository, Glasgow, United Kingdom; [5]Pathology, NHS Greater Glasgow & Clyde, Glasgow, United Kingdom; [6]National Cancer Centre Singapore, Singapore, Singapore; [7]Singapore General Hospital, Singapore, Singapore; [8]University Hospitals Birmingham, Birmingham, United Kingdom

Paper #08
1:24 pm - 1:36 pm

3255734

VALIDATION OF GEISTRA SCORE: A PREDICTIVE TOOL OF TRABECTEDIN (TB) BENEFIT IN ADVANCED SOFT TISSUE SARCOMAS (ASTS), BASED ON GROWTH MODULATION INDEX (GMI). A RETROSPECTIVE REGISTRY-BASED ANALYSIS FROM SPANISH GROUP OF SARCOMA RESEARCH (GEIS)

Javier Martinez-Trufero, PhD MD[1]*; Luis Miguel De Sande Gonzalez*[2]*; Pablo Luna*[19]*; Javier Martin-Broto*[3]*; Rosa Alvarez*[4]*; Antonio Casado*[5]*; Roberto Diaz Beveridge*[6]*; Andres Poveda*[7]*; Juana Maria Cano*[8]*; Josefina Cruz*[9]*; Antonio López Pousa*[10]*; Maria Angeles Vaz Salgado*[11]*; Claudia M. Valverde Morales*[12]*; Isabel Sevilla*[13]*; Jeronimo Martinez*[14]*; Jordi Rubio Casadevall*[15]*; Ana De Juan*[16]*; Juan Antonio Carrasco*[17]*; Antonio Gutierrez*[18]

[1]*Medical Oncology , Hospital Universitario Miguel Servet, Zaragoza, Zaragoza, Spain;* [2]*Medical Oncology, Complejo Asistencial Universitario de Leon, Leon, Leon, Spain;* [3]*Medical Oncology, Hospital Virgen del Rocio, Sevilla, Sevilla, Spain;* [4]*Medical Oncology, Hospital Gregorio Marañon, Madrid, Madrid, Spain;* [5]*Medical Oncology, Hospital Clinico San Carlos, Madrid, Madrid, Spain;* [6]*Medical Oncology, Hospital La Fe, Valencia, Spain;* [7]*Instituto Valenciano de Oncologia, Valencia, Spain;* [8]*Medical oncology, Hospital General de Ciudad Real, Ciudad Real, Spain;* [9]*Hospital Universitario Canarias, Santa Cruz de Tenerife, Spain;* [10]*Hospital Sant Pau, Barcelona, Spain;* [11]*Hospital Ramon y Cajal, Madrid, Spain;* [12]*Medical Oncology, Hospital Vall D'Hebron, Barcelona, Spain;* [13]*Hospital Virgen de la Victoria, Malaga, Spain;* [14]*Hospital Virgen de la Arrixaca, Murcia, Spain;* [15]*Instituto Catalan Oncologia, Girona, Spain;* [16]*Hospital Marques de Valdecilla, Santander, Spain;* [17]*Hospital Alvaro Cunqueiro, Vigo, Spain;* [18]*Hospital Son Espases, Palma de Mallorca, Spain;* [19]*Hospital son Espases, Palma de Mallorca, Spain*

Paper #09
1:36 pm - 1:48 pm

3255286

NANOTECHNOLOGIES FOR CAPTURE AND RELEASE OF EWING SARCOMA-DERIVED CIRCULATING TUMOR CELLS

Jiantong Dong[2]*; Yazhen Zhu*[2]*; Noah C. Federman*[4]*; Hsian-Rong Tseng*[2]*; Paul S. Weiss*[1]*;* ***Steven J. Jonas, MD, PhD***[3]

[1]*Chemistry & Biochemistry, Materials Science & Engineering, Bioengineering, and the California NanoSystems Institute, University of California, Los Angeles, Los Angeles, CA, USA;* [2]*Molecular and Medical Pharmacology & the California NanoSystems Institute, University of California, Los Angeles, Los Angeles, CA, USA;* [3]*Pediatrics, Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research at UCLA, University of California, Los Angeles, Los Angeles, CA, USA;* [4]*Pediatrics, University of California, Los Angeles, Los Angeles, CA, USA*

1:48 pm - 2:00 pm

Discussant: ***Anastasia Constantinidou***

Paper #10
2:00 pm - 2:12 pm

3254588

LAROTRECTINIB EFFICACY AND SAFETY IN PATIENTS WITH TRK FUSION SARCOMAS

George D. Demetri[1]*; Catherine M. Albert*[2]*; Daniel S. Tan*[3]*; Stefan Bielack*[4]*; Daniel Orbach*[5]*; Steven DuBois*[6]*; Noah C. Federman*[7]*; Birgit Geoerger*[8]*; Shivaani Kummar*[9]*; Theodore W. Laetsch*[10]*; Ramamoorthy Nagasubramanian*[11]*; Alexander Drilon*[12]*; David S. Hong*[13]*; David M. Hyman*[12]*; Ulrik Lassen*[14]*; Ray McDermott*[15]*; Alberto Pappo*[16]*; Neerav Shukla*[12]*; Shivani Nanda*[17]*; Barrett H. Childs*[17]*; Leo Mascarenhas*[18]*; Cornelis M. van Tilburg*[19]

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Paper #11
2:12 pm - 2:24 pm

3255999

ENTRECTINIB IN *NTRK* FUSION-POSITIVE SARCOMA: INTEGRATED ANALYSIS OF PATIENTS ENROLLED IN STARTRK-2, STARTRK-1 AND ALKA-372-001

Stephen V. Liu[1]*; Luis Paz-Ares*[2]*; James Hu*[3]*; Jürgen Wolf*[4]*; Byung Chul Cho*[5]*; Maciej Krzakowski*[6]*; Christine H. Chung*[7]*; Manish Patel*[8]*; Matthew Taylor*[9]*; Harald Zeuner*[10]*; Amine Aziez*[10]*; Xinhui Huang*[11]*; Stuart Osborne*[10]*; Anna Farago*[12]

[1]Georgetown University, Washington, , USA; [2]Hospital Universitario 12 de Octubre, Madrid, Spain; [3]University of Southern California/Norris Cancer Center, Los Angeles, CA, USA; [4]Center for Integrated Oncology, University Hospital of Cologne, Cologne, Germany; [5]Yonsei Cancer Center, Seoul, Korea (the Republic of); [6]Maria Sklodowska-Curie Institute of Oncology, Warsaw, Poland; [7]Moffitt Cancer Center, Tampa, FL, USA; [8]University of Minnesota, Department of Medicine, Minneapolis, MN, USA; [9]Oregon Health & Science University, Portland, OR, USA; [10]F. Hoffmann-La Roche, Basel, Switzerland; [11]Genentech, San Francisco, CA, USA; [12]Massachusetts General Hospital, Boston, MD, USA

Paper #12
2:24 pm - 2:36 pm

3206452

WEEKLY *NAB*-SIROLIMUS IN PATIENTS WITH ADVANCED MALIGNANT PERIVASCULAR EPITHELIOID CELL TUMORS (PECOMA): RESULTS FROM AMPECT, AN OPEN-LABEL PHASE 2 REGISTRATION TRIAL WITH INDEPENDENT RADIOLOGY REVIEW

Mark Dickson[1]*; Vinod Ravi*[11]*; Richard F. Riedel*[2]*; Kristen Ganjoo*[3]*; Brian A. Van Tine*[4]*; Rashmi Chugh*[5]*; Lee Cranmer*[6]*; Erlinda Gordon*[7]*; Jason Hornick*[8]*; David Kwiatkowski*[8]*; Heng Du*[8]*; Berta Grigorian*[9]*; Anita N. Schmid*[9]*; Shihe Hou*[9]*; Katherine Harris*[9]*; Neil Desai*[9]*; Andrew Wagner*[10]

[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]Duke Cancer Institute, Durham, NC, USA; [3]Stanford University, Stanford, CA, USA; [4]Washington University in Saint Louis, St. Louis, MO, USA; [5]University of Michigan, Ann Arbor, MI, USA; [6]Univ Washington/Fred Hutchinson Cancer Res Ctr, Seattle, WA, USA; [7]Sarcoma Oncology Center, Santa Monica, CA, USA; [8]Brigham and Women's Hospital, Boston, MA, USA; [9]Aadi Bioscience, Pacific Palisades, CA, USA; [10]Dana-Farber Cancer Institute, Boston, MA, USA; [11]MD Anderson Cancer Center, Houston, TX, USA

Paper #13
2:36 pm - 2:48 pm

3250355

A PHASE 1 DOSE ESCALATION STUDY OF INTRAVENOUS TK216 IN PATIENTS WITH RELAPSED OR REFRACTORY EWING SARCOMA

Paul Meyers, MD[1]*; Joseph A. Ludwig*[2]*; Noah C. Federman*[3]*; Najat C. Daw*[4]*; Margaret E. Macy*[5]*; Richard F. Riedel*[6]*; Jodi A. Muscal*[7]*; Xen Ianopoulos*[9]*; James Breitmeyer*[9]*; Jeffrey Toretsky*[8]

[1]Memorial Sloan-Kettering Cancer Center, New York, NY, USA; [2]Internal Medicine, MD Anderson Cancer Center, Houston, TX, USA; [3]Pediatrics, UCLA Medical Center, Los Angeles, CA, USA; [4]Pediatrics, MD Anderson Cancer Center, Houston, TX, USA; [5]Pediatrics, Children's Hospital of Colorado, Aurora, CO, USA; [6]Internal Medicine, Duke University Medical Center, Durham, NC, USA; [7]Pediatrics, Texas Children's Hospital, Houston, TX, USA; [8]Pediatrics, George Washington University Medical Center, Washington, DC, USA; [9]Oncternal Therapeutics, San Diego, CA, USA

2:48 pm - 3:00 pm — Discussant: ***Bob Maki***

3:00 pm - 3:30 pm — Afternoon Break & Poster Viewing — *3rd Floor*

3:30 pm - 5:30 pm — – SESSION 4 – — *Kiku Ballroom*

Bone Sarcomas

Chairs: **Taka Ueda** and **Roberta Sanfillipo**

Paper #14
3:30 pm - 3:42 pm

3229546

TRAINED AND TESTED DECISION TREE OF RADIOGRAPHIC PARAMETERS RELIABLY PREDICTS ASEPTIC FAILURE OF COMPRESSIVE OSSEOINTEGRATION ENDOPROSTHESES

Lindsay Parlee[1]*; Yee-Cheen Doung*[1]*; James Hayden*[1]*; Ryland Kagan*[1]*;*
Kenneth R. Gundle, MD[2]

[1]Orthopaedics & Rehabilitation, Oregon Health & Science University, Portland, OR, USA; [2]Operative Care Division, Portland VA Medical Center, Portland, OR, USA

Paper #15
3:42 pm - 3:54 pm

3256557

NAVIGATED EXTREMITY SARCOMA RESECTION: ACCURACY AND REPRODUCIBILITY USING A NOVEL FLUOROSCOPY-BASED REGISTRATION TECHNIQUE FOR JOINT-SPARING BONE CUTS

Ibrahim S. Alshaygy*; Jean-Camille Mattei; Georges Basile; Anthony Griffin; Xun Lin; Peter Ferguson; Jay Wunder*
Orthopaedic Department, Mount Sinai Hospital, Toronto, ON, Canada

Thursday, 14 November, 2019

Paper #16
3:54 pm - 4:06 pm

3235120

ROLE OF EMT TRANSCRIPTION FACTORS IN THE METASTATIC POTENTIAL OF OSTEOSARCOMA

Sana Mohiuddin, MBBS[1]*; Salah-Eddine Lamhamedi Cherradi*[2]*; Dhruva K. Mishra*[4]*; Kristi Pence*[4]*; Standhya Krishnan*[2]*; Brian A. Menegaz*[2]*; David McCall*[1]*; Alejandra R. Velasco*[2]*; Danh D. Truong*[2]*; Branko Cuglievan*[1]*; Amelia Vetter*[2]*; Eric R. Molina*[3]*; Min P. Kim*[4]*; Joseph A. Ludwig*[2]

[1]Pediatrics, MD Anderson Cancer Center, Houston, TX, USA; [2]Sarcoma Medical Oncology, MD Anderson Cancer Center, Houston, TX, USA; [3]Rice University, Houston, TX, USA; [4]Houston Methodist, Houston, TX, USA

Paper #17
4:06 pm - 4:18 pm

3249338

VACCINATION TO ENHANCE THE ANTI-TUMOR ACTIVITY OF GD2 CHIMERIC ANTIGEN RECEPTOR EXPRESSING VZV-SPECIFIC T CELLS IN RELAPSED OSTEOSARCOMA

Sarah Whittle, MD[1]*; Natalia N. Lapteva*[2]*; Margaret Gilbert*[2]*; Mina Al-Sabbagh*[2]*; Bambi Grilley*[2]*; Carlos A. Ramos*[2]*; Bilal Omer*[2]*; Tao Wang*[2]*; Hao Liu*[2]*; Stephen Gottschalk*[3]*; Helen Heslop*[2]*; Cliona Rooney*[2]*; Lisa L. Wang*[1]

[1]Pediatrics, Baylor College of Medicine, Houston, TX, USA; [2]Cell and Gene Therapy, Baylor College of Medicine, Houston, TX, USA; [3]St. Jude Children's Research Hospital, Memphis, TN, USA

4:18 pm - 4:30 pm

Discussant: ***Steve Thorpe***

Paper #18
4:30 pm - 4:42 pm

3256545

SOLITARY BONE METASTASES FROM SARCOMAS: IS THERE ANY PLACE FOR CURATIVE SURGERY?

Jean-Camille Mattei, MD, PhD*; Ibrahim S. Alshaygy; Georges Basile; Anthony Griffin; Peter Ferguson; Jay Wunder*

AP-HM, Aix-Marseille University, Marseille, France

Paper #19
4:42 pm - 4:54 pm

3255440

COMPARISON OF MAP VERSUS MAPIE (POOR HISTOLOGIC RESPONSE) OR MAP PLUS PEGYLATED INTERFERON-α (GOOD HISTOLOGIC RESPONSE) IN NEWLY-DIAGNOSED RESECTABLE OSTEOSARCOMA: RESULTS FROM THE EURAMOS-1 TRIAL WITH LONG-TERM FOLLOW-UP

Katherine A. Janeway, MD[1]*; Fiona C. Ingleby*[2]*; Sigbjorn Smeland*[3]*; Jeremy Whelan*[4]*; Neyssa Marina*[5]*; Mark Bernstein*[6]*; Trude Butterfass-Bahloul*[7]*; Gabriele Calaminus*[8]*; Lor Randall*[9]*; Karen Sanders*[2]*; Babasola Popoola*[2]*; Mark Krailo*[10]*; Matthew R. Sydes*[2]*; Stefan Bielack*[11]

[1]Dana Farber Cancer Institute, Boston, MA, USA; [2]University College London, London, United Kingdom; [3]Lund University, Lund, Sweden; [4]University College London Hospitals, London, United Kingdom; [5]Five Prime Therapeutics, Inc, San Francisco, CA, USA; [6]University of Toronto, Toronto West Hospital, Toronto, ON, Canada; [7]Centre for Clinical Trials, University Hospital Muenster, Muenster, Germany; [8]UKB University of Bonn, Bonn, Germany; [9]UC Davis Health, Sacramento, CA, USA; [10]Keck School of Medicine, University of Southern California, Los Angeles, CA, USA; [11]Stuttgart Cancer Center, Olgahospital, Stuttgart, Germany

Thursday, 14 November, 2019

Paper #20
4:54 pm - 5:06 pm

3228794

APATINIB PLUS CAMRELIZUMAB (SHR-1210) FOR UNRESECTABLE HIGH-GRADE OSTEOSARCOMA (APFAO) PROGRESSING AFTER CHEMOTHERAPY: A SINGLE ARM, OPEN-LABEL, PHASE 2 TRIAL

Lu Xie, MD[1]*; Jie Xu*[1]*; Wei Guo*[1]*; Jin Gu*[2]*; Xin Sun*[1]*; Kuisheng Liu*[1]*; Xiaodong Tang*[1]*; Kunkun Sun*[3]*; Danhua Shen*[3]*; Yuan Li*[4]

[1]*Musculoskeletal Tumor Center, Peking University People's Hospital, Beijing, China;* [2]*Surgical Oncology, Peking University Shougang Hospital, Beijing, China;* [3]*Pathology Department, Peking University People's Hospital, Beijing, China;* [4]*Radiology Department & Nuclear Medicine Department, Peking University People's Hospital, Beijing, China*

Paper #21
5:06 pm - 5:18 pm

3255674

DEVELOPMENT AND VALIDATION OF A NOVEL SODIUM FLUORIDE-PET RESPONSE CRITERIA FOR SOLID TUMORS (NAFCIST) IN A PHASE 1 CLINICAL TRIAL OF ALPHA PARTICLE RADIUM 223 IN OSTEOSARCOMA

Vivek Subbiah, MD[1]*; Pete Anderson*[2]*; Eric Rohren*[3]*; Gregory Ravizzini*[4]*; Homer Macapinlac*[4]*; Kalevi Kairemo*[4]

[1]*Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX, USA;* [2]*Cleveland Clinic, Cleveland, OH, USA;* [3]*Baylor, Houston, TX, USA;* [4]*Nuclear Medicine, MD Anderson Cancer, Houston, TX, USA*

5:18 pm - 5:30 pm

Discussant: ***Silvia Stacchiotti***

5:30 pm - 6:30 pm

Poster Viewing Reception *3rd Floor*

Friday, 15 November, 2019

6:00 am - 5:30 pm	Registration	*Kiku Lobby, 4th Floor*
6:15 am - 7:30 am	Sunrise in Tokyo	*Kiku Ballroom*
6:15 am - 6:20 am	Case Introduction: Metastatic Ewing Sarcoma *Herbert Loong*	
6:20 am - 6:35 am	Pathology and Overview of Small Blue Round Cell Tumours *Judith Bovee*	
6:35 am - 6:50 am	Surgical Approaches to Localized Ewing Sarcoma *Kenneth Rankin*	
6:50 am - 7:05 am	Role of Systemic Therapy in Ewing Sarcoma *Jeremy Lewin*	
7:05 am - 7:20 am	Metastatic Ewing – When Is There a Role for RT *Angela Hong*	
7:20 am - 7:30 am	Wrap-up and What's New in Ewing Sarcoma @ CTOS 2019? *Damon Reed*	
7:00 am - 8:00 am	Executive Committee Meeting	*Ran Room, 3rd Floor*

8:00 am - 8:30 am — – SESSION 5 – — *Kiku Ballroom*

Sarcoma of the Year: DSRCT

Chairs: **Makoto Endo** and **Jon Trent**

Paper #22
8:00 am - 8:12 am

3251509

WHOLE ABDOMINOPELVIC RADIOTHERAPY AND RADIOIMMUNOTHERAPY AFTER COMPLETE RESECTION OF DESMOPLASTIC SMALL ROUND CELL TUMOR (DSRCT): MAJOR IMPACT ON SURVIVAL

Shakeel Modak, MD[1]; *James Saltsman*[1]; *Neeta Pandit-Taskar*[2]; *Emily Slotkin*[1]; *Todd Heaton*[1]; *Justin T. Gerstle*[1]; *Suzanne Wolden*[3]; *Michael P. LaQuaglia*[1]
[1]*Pediatrics, Memorial Sloan Kettering Cancer Center, New York, NY, USA;* [2]*Radiology, Memorial Sloan Kettering Cancer Center, New York, NY, USA;* [3]*Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA*

Paper #23
8:12 am - 8:24 am

3254390

SINGLE-CELL RNA-SEQUENCING IDENTIFIES DISTINCT TUMOR CELL SUBPOPULATIONS AND IMMUNE INFILTRATE IN DESMOPLASTIC SMALL ROUND CELL TUMORS (DSRCT)

Julien Vibert[1]; ***Clémence Hénon***[2]; *Nadège Gruel*[1]; *Léo Colmet-Daage*[2]; *Asuka Kawai-Kawashi*[2]; *Thomas Eychenne*[2]; *Joshua Waterfall*[1]; *Julien Adam*[3]; *Axel Le Cesne*[4]; *Olivier Mir*[5]; *Charles Honoré*[6]; *Olivier Delattre*[1]; *Sarah Watson*[1]; *Sophie Postel-Vinay*[2]
[1]*INSERM, UMR830, Cancer, Hétérogénéité, Instabilité et Plasticité, Institut Curie, Paris, France;* [2]*INSERM, UMR981, ATIP-Avenir Group, Gustave Roussy Cancer Campus, Villejuif, France;* [3]*Department of Pathology, Gustave Roussy Cancer Campus, Villejuif, France;* [4]*Department of Cancer Medicine, Gustave Roussy Cancer Campus, Villejuif, France;* [5]*Department of Ambulatory Care, Gustave Roussy Cancer Campus, Villejuif, France;* [6]*Department of Cancer Surgery, Gustave Roussy Cancer Campus, Villejuif, France*

8:24 am - 8:30 am — Discussant: ***Bill Tap***

8:30 am - 9:30 am | – SESSION 6 – | Kiku Ballroom

Multi-Disciplinary Care

Chairs: **Melissa Burgess** and **Norio Yamamoto**

Paper #24
8:30 am - 8:42 am

3253497

A PHASE III RANDOMISED CONTROLLED TRIAL COMPARING HISTOTYPE-TAILORED NEOADJUVANT CHEMOTHERAPY AND STANDARD CHEMOTHERAPY IN PATIENTS WITH HIGH-RISK SOFT TISSUE SARCOMAS (ISG-1001): A SARCULATOR-BASED PROGNOSTIC RISK STRATIFICATION ANALYSIS

Sandro Pasquali[1]; *Emanuela Palmerini*[2]; *Vittorio Quagliuolo*[3]; *Javier Martin-Broto*[4]; *Antonio López Pousa*[5]; *Giovanni Grignani*[6]; *Antonella Brunello*[7]; *Jean-Yves Blay*[8]; *Oscar Tendero*[9]; *Roberto D. Beveridge*[10]; *Virginia Ferraresi*[11]; *Iwona Lugowska*[12]; *Domenico Merlo*[13]; *Valeria Fontana*[13]; *Emanuela Marchesi*[14]; *Davide M. Donati*[2]; *Elena Palassini*[1]; *Silvia Stacchiotti*[1]; *Silvia Baguè*[15]; *Jean M. Coindre*[16]; *Angelo Paolo Dei Tos*[17]; *Piero Picci*[14]; *Paolo Bruzzi*[13]; *Paolo Casali*[1]; *Alessandro Gronchi*[1]
[1]*Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy;* [2]*Istituto Ortopedico Rizzoli, Bologna, Italy;* [3]*Humanitas Cancer Centre, Rozzano, Italy;* [4]*Virgen del Rocío University Hospital, Valencia, Spain;* [5]*Hospital Sant Pau, Barcellona, Spain;* [6]*Candiolo Cancer Institute - FPO, IRCCS, Candiolo, Italy;* [7]*Veneto Institute of Oncology, Padova, Italy;* [8]*Centre Léon Bérard, Lyon, France;* [9]*Hospital Universitario Son Espases, Palma de Mallorca, Spain;* [10]*Hospital Universitario y Politécnico La Fe, Valencia, Spain;* [11]*Istituto Nazionale Tumori Regina Elena, Rome, Italy;* [12]*Instytut im. Marii Sklodowskiej-Curie, Warsaw, Poland;* [13]*IST Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy;* [14]*Italian Sarcoma Group, Bologna, Italy;* [15]*Hospital de la Santa Creu i Sant Pau, Barcelona, Spain;* [16]*Institut Bergonie, Bordeaux, France;* [17]*University of Padova, Padova, Italy*

Paper #25
8:42 am - 8:54 am

3253041

THERAPEUTIC RELEVANCE OF MOLECULAR SCREENING PROGRAM FOR PATIENTS WITH SARCOMA? ANALYSIS FROM THE PROFILER TRIAL

Armelle Dufresne; *Patrick Arnaud-Coffin; Mehdi Brahmi; Olivier Tredan; Pierre Meeus; Daniel Pissaloux; Valery Attignon; David Perol; Jean-Yves Blay*
Centre Leon Berard, Lyon, France

Paper #26
8:54 am - 9:06 am

3253370

PERSONALISED MEDICINE FOR HIGH-RISK PAEDIATRIC AND AYA SARCOMA PATIENTS

Emmy D. Fleuren, PhD[1]; *Jinhan Xie*[1]; *Paulette Barahona*[1]; *Alexandra Sherstryuk*[1]; *Daniel Batey*[1]; *Jin Yi Lim*[1]; *Loretta Lau*[1]; *Dong Anh Khuong Quang*[1]; *Tim Failes*[1]; *Shu-Oi Chow*[1]; *Chelsea Mayoh*[1]; *Marie Wong*[1]; *Amit Kumar*[1]; *ZERO Omics Team*[1]; *ZERO Preclinical Drug Testing Team*[1]; *ZERO Senior Management Team*[1]; *David Thomas*[2]; *Toby Trahair*[1]; *Michelle Haber*[1]; *Emily Mould*[1]; *Richard Lock*[1]; *David Ziegler*[1]; *Vanessa Tyrrell*[1]; *Mark Cowley*[1]; *Paul Ekert*[1]
[1]*Children's Cancer Institute, Sydney, New South Wales, Australia;* [2]*Garvan Institute of Medical Research, Sydney, New South Wales, Australia*

Paper #27
9:06 am - 9:18 am

3256280

RE-IRRADIATION FOR RECURRENT CHORDOMAS OF THE SPINE AND SACRUM WITH HIGH DOSE STEREOTACTIC BODY RADIATION THERAPY

Chinzi J. Jin[1]; *Anne Reiner*[2]; *Adam Schmitt*[1]; *Daniel Higginson*[1]; *Ilya Laufer*[3]; *Eric Lis*[5]; *Ori Barzilai*[3]; *Patrick Boland*[4]; *Mark H. Bilsky*[3]; ***Yoshiya Yamada, MD, FRCPC***[1]
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9:18 am - 9:30 am — Discussant: ***Will Tseng***

9:30 am - 10:00 am — Morning Break — *3rd Floor*

10:00 am - 11:00 am — – SESSION 7 – — *Kiku Ballroom*

Radiation Oncology

Chairs: **David Kirsch** and **Sarah Dumont**

Paper #28
10:00 am - 10:12 am

3242507

SPATIALLY-FRACTIONATED STEREOTACTIC BODY RADIOTHERAPY FOR LOCALIZED UNRESECTABLE, OLIGO-METASTATIC OR WIDELY-METASTATIC CONVENTIONAL TYPE CHONDROSARCOMA: A PROSPECTIVE PHASE I TRIAL

Sai Duriseti, MD, PhD[1]*; James Kavanaugh*[1]*; Sreekrishna Goddu*[1]*; Tammy Senter*[1]*; Jennifer Harris*[1]*; Michael Watts*[1]*; Clifford Robinson*[1]*; Angela Hirbe*[2]*; Brian A. Van Tine*[2]*; Matthew Spraker*[1]

[1]*Radiation Oncology, Washington University in St. Louis, St. Louis, MO, USA;* [2]*Medical Oncology, Washington University in St. Louis, St. Louis, MO, USA*

Paper #29
10:12 am - 10:24 am

3250148

THE RADIO-ENHANCER HAFNIUM OXIDE NANOPARTICLE, NBTXR3 ACTIVATED BY RADIATION THERAPY IN PATIENTS WITH LOCALLY ADVANCED SOFT TISSUE SARCOMA: A PHASE II/III TRIAL

Sylvie Bonvalot[1]*; Piotr Rutkowski*[2]*; Juliette Thariat*[3]*; Sébastien Carrère*[4]*; Anne Ducassou*[5]*; Marie-Pierre Sunyach*[6]*; Peter Agoston*[7]*; Angela Hong*[8]*; Augustin Mervoyer*[9]*; Marco Rastrelli*[10]*; Victor Moreno*[11]*; Rubi Li*[12]*; Béatrice Tiangco*[13]*; Vincent Servois*[1]*; Patricia Saïd*[14]*; Mikaela Dimitriu*[14]*; Eva Wardelmann*[15]*; Philippe Terrier*[16]*; Alexander Lazar*[17]*; Judith Bovee*[18]*; Cécile Le Péchoux*[16]*; Zsusanna Papai*[19]

[1]*Institut Curie, Paris, France;* [2]*Maria Sklodowska-Curie Institute -Oncology Center, Warsaw, Poland;* [3]*Centre François Baclesse, Caen, France;* [4]*Centre Regional De Lutte Contre Le Cancer Paul Lamarque, Montpellier, France;* [5]*Institut Universitaire du Cancer de Toulouse-Oncopole (IUCT-O), Toulouse, France;* [6]*Léon Bérard Cancer Center, Lyon, France;* [7]*Országos Onkologiai Intézet, Budapest, Hungary;* [8]*The University of Sydney, Camperdown, New South Wales, Australia;* [9]*Institut de Cancerologie de l'Ouest- Rene Gauducheau, Saint-Herblain, France;* [10]*Istituto Oncologico Veneto IRCCS, Padua, Italy;* [11]*Hospital Fundación Jimenez Diaz, Madrid, Spain;* [12]*St. Luke's Medical Center, Quezon City, Philippines;* [13]*The Medical City APS Cancer Institute, Pasig City, Philippines;* [14]*Nanobiotix, SA, Paris, France;* [15]*University Hospital Münster, Münster, Germany;* [16]*Institute Gustave Roussy, Villejuif, France;* [17]*MD Anderson Cancer Center, Houston, TX, USA;* [18]*Leiden University Medical Center, Leiden, Netherlands;* [19]*Hungarian Defence Forces, Budapest, Hungary*

Paper #30
10:24 am - 10:36 am

3255664

SPATIALLY FRACTIONATED GRID RADIOTHERAPY PRIOR TO NEOADJUVANT CONVENTIONALLY FRACTIONATED RADIOTHERAPY FOR VERY HIGH-RISK SOFT TISSUE AND OSTEO- SARCOMAS: PROMISING PATHOLOGIC RESPONSE WITH SAFE DOSE ESCALATION

James W. Snider, MD[1]*; Jason Molitoris*[1]*; Susan Shyu*[2]*; Stephanie Rice*[2]*; Emily Kowalski*[2]*; Cristina Decesaris*[2]*; Jill Remick*[2]*; Lori Campbell*[2]*; Nader Hanna*[1]*; Vincent Ng*[1]*; William Regine*[1]

[1]*Department of Radiation Oncology, University of Maryland School of Medicine, Baltimore, MD, USA;* [2]*Department of Radiation Oncology, University of Maryland Medical Center, Baltimore, MD, USA*

Paper #31 3250473
10:36 am - 10:48 am

ANGIOSARCOMA OF THE SCALP AND FACE: COMPARING RADIATION DOSE DISTRIBUTIONS BETWEEN HIGH-DOSE-RATE SURFACE APPLICATOR (HDR-SA) BRACHYTHERAPY AND VOLUMETRIC MODULATED ARC THERAPY (VMAT)

Devarati Mitra, MD, PhD[2]*; Yaguang Pei*[1]*; Ivan Buzurovic*[1]*; Philip Devlin*[1]*; Elizabeth Baldini*[1]*; Miranda Lam*[1]
[1]*Radiation Oncology, Dana Farber Cancer Institute, Boston, MA, USA;*
[2]*Radiation Oncology, MD Anderson Cancer Center, Houston, TX, USA*

10:48 am - 11:00 am Discussant: ***Shane Zaidi***

11:00 am - 12:00 pm – SESSION 8 – *Kiku Ballroom*

East Meets West in Sarcoma Care

Chairs: **Bruno Vincenzi** and **Ashish Gulia**

Paper #32 3247634
11:00 am - 11:12 am

PREVALENCE AND PROGNOSTIC IMPACT OF COMORBIDITIES IN SARCOMAS: A POPULATION-BASED STUDY OF 3746 PATIENTS IN HONG KONG

Herbert H. Loong, MBBS, MRCP, FHKCP, FHKAM[1]*; Carlos K. Wong*[2]*; Chu-wa Ho*[2]*; Teresa Tse*[3]*; SC Sampson Kwan*[4]*; Linda K. Leung*[3]*; Yat Ming Lau*[3]
[1]*Department of Clinical Oncology, The Chinese University of Hong Kong, Hong kong, Hong Kong;* [2]*Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, Hong Kong;* [3]*Department of Clinical Oncology, Prince of Wales Hospital, Hong Kong, Hong Kong;* [4]*Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, Hong Kong*

Paper #33 3255511
11:12 am - 11:24 am

CLINICAL OUTCOME OF CLEAR CELL CHONDROSARCOMA: A MULTICENTER STUDY FROM JAPANESE MUSCULOSKELETAL ONCOLOGY GROUP

Robert Nakayama, MD, PhD[1]*; Keiko Hayakawa*[2]*; Makoto Endo*[4]*; Eisuke Kobayashi*[3]*; Shunsuke Hamada*[5]*; Tsukasa Yonemoto*[6]*; Hiroyuki Kawashima*[7]*; Kenichiro Hamada*[8]*; Itsuo Watanabe*[9]*; Hiroyuki Futani*[10]*; Takahiro Goto*[11]*; Toshifumi Ozaki*[12]
[1]*Department of Orthopaedic Surgery, Keio University, Shinjuku, Tokyo, Japan;* [2]*Department of Orthopaedic Surgery, Cancer Institute Hospital for JFCR, Tokyo, Japan;* [3]*Department of Musculoskeletal Oncology and Rehabilitation, National Cancer Center Hospital, Tokyo, Japan;* [4]*Department of Orthopaedic Surgery, Kyushu University, Hakata, Japan;* [5]*Department of Orthopaedic Surgery, Nagoya University, Nagoya, Japan;* [6]*Department of Orthopaedic Surgery, Chiba Cancer Center, Chiba, Japan;* [7]*Department of Orthopaedic Surgery, Niigata University, Niigata, Japan;* [8]*Department of Orthopaedic Surgery, Osaka University, Osaka, Japan;* [9]*Department of Orthopaedic Surgery, Tokyo Dental College Ichikawa General Hospital, Ichikawa, Japan;* [10]*Department of Orthopaedic Surgery, Hyogo College of Medicine, Kobe, Japan;* [11]*Department of Orthopaedic Surgery, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan;* [12]*Department of Orthopaedic Surgery, Okayama University Graduate School of Medicine, Okayama, Japan*

Paper #34 3255902
11:24 am - 11:36 am

CHEMOTHERAPY UTILIZATION AND TIMING IN PRIMARY, LOCALIZED, HIGH-GRADE SOFT TISSUE SARCOMA: PATTERNS OF CARE IN THE NATIONAL CANCER DATABASE

Danielle S. Graham, MD, MBA[1]; *Mykola Onyshchenko*[2]; *Mark A. Eckardt*[3]; *Benjamin DiPardo*[1]; *Srirnam Venigalla*[4]; *Scott Nelson*[5]; *Bartosz Chmielowski*[6]; *Arun Singh*[6]; *Jacob Shabason*[4]; *Fritz C. Eilber*[7]; *Anusha Kalbasi*[8]
[1]*Surgery, University of California, Los Angeles, Los Angeles, CA, USA;* [2]*Hematology & Oncology, Harbor-UCLA, Los Angeles, CA, USA;* [3]*Surgery, Yale School of Medicine, Los Angeles, CA, USA;* [4]*Radiation Oncology, University of Pennsylvania Health System, Philadelphia, PA, USA;* [5]*Pathology, University of California, Los Angeles, Los Angeles, CA, USA;* [6]*Hematology & Oncology, University of California, Los Angeles, Los Angeles, CA, USA;* [7]*Surgical Oncology, University of California, Los Angeles, Los Angeles, CA, USA;* [8]*Radiation Oncology, University of California, Los Angeles, Los Angeles, CA, USA*

Paper #35 3217091
11:36 am - 11:48 am

CLINICIANS' ADHERENCE TO PRACTICE GUIDELINES FOR SOFT TISSUE SARCOMA ANALYZED WITH QUALITY INDICATOR

Shintaro Iwata[1]; *Tomone Watanabe*[2]; *Yoko Kato*[3]; *Fumihiko Nakatani*[1]; *Eisuke Kobayashi*[1] *Naoyo Takakura*[3]; *Naohiro Higashi*[2]; *Akira Kawai*[1]
[1]*Dept. Musculoskeletal Oncology and Rehabilitation, National Cancer Canter Hospital, Tokyo, Japan;* [2]*Center for Cancer Control and Information Services, National Cancer Center, Tokyo, Japan;* [3]*Rare Cancer Center, National Cancer Center Hospital, Tokyo, Japan*

11:48 am - 12:00 pm Discussant: ***Tom Chen***

12:00 pm - 1:00 pm Lunch *Second Floor*

12:00 pm - 1:00 pm Board of Directors Meeting *Ran Room, 3rd Floor*

1:00 pm - 2:00 pm – SESSION 9 – *Kiku Ballroom*

GIST

Chairs: **Vicki Keedy** and **Yu Oyama**

Paper #36 3254072
1:00 pm - 1:12 pm

INVICTUS: A PHASE 3, INTERVENTIONAL, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO ASSESS THE SAFETY AND EFFICACY OF RIPRETINIB (DCC-2618) IN PATIENTS WITH ADVANCED GASTROINTESTINAL STROMAL TUMORS (GIST) WHO HAVE RECEIVED TREATMENT WITH PRIOR ANTICANCER THERAPIES (NCT03353753)

Jean-Yves Blay[12]; *Steven Attia*[1]; *Sebastian Bauer*[13]; *Ping Chi*[2]; *Gina D'Amato*[3]; *Suzanne George*[4]; *Hans Gelderblom*[14]; *Michael Heinrich*[5]; *Robin L. Jones*[6]; *Peter Reichardt*[15]; *Patrick Schöffski*[7]; *César Serrano*[8]; *John Zalcberg*[9]; *Julie Meade*[10]; *Kelvin Shi*[10]; *Rodrigo Ruiz Soto*[10]; ***Margaret von Mehren***[11]
[1]*Mayo Clinic, Jacksonville, FL, USA;* [2]*Memorial Sloan Kettering, Manhattan, NY, USA;* [3]*University of Miami Health System, Miami, FL, USA;* [4]*Dana-Farber Cancer Institute, Boston, MA, USA;* [5]*Portland VA Health Care System and Knight Cancer Institute, Portland, OR, USA;* [6]*Royal Marsden and Institue of Cancer Research, London, United Kingdom;* [7]*Leuven Cancer Institute, Leuven, Belgium;* [8]*Vall D'Hebron Institute of Oncology, Barcelona, Spain;* [9]*Medical Oncology, Monash University and Alfred Health, Melbourne, Victoria, Australia;* [10]*Deciphera Pharmaceuticals, LLC, Waltham, MA, USA;* [11]*Fox Chase Cancer Center, Philadelphia, PA, USA;* [12]*Centre Léon Bérad, Lyon, France;* [13]*Sarcoma Center, West German Cancer Center, University Hospital Essen, Essen, Germany;* [14]*Leiden University Medical Center, Leiden, Netherlands;* [15]*Department of Oncology and Palliative Care, Helios Klinikum Berlin-Buch, Berlin, Germany*

Paper #37
1:12 pm - 1:24 pm

3258046

CLINICAL RESPONSE TO AVAPRITINIB BY RECIST AND CHOI CRITERIA IN ≥4TH LINE (4L+) AND PDGFRA EXON 18 GASTROINTESTINAL STROMAL TUMORS (GIST)

Michael Heinrich, MD[1]; *Robin L. Jones*[2]; *Margaret von Mehren*[3]; *Sebastian Bauer*[4]; *Yoon-Koo Kang*[5]; *Patrick Schöffski*[6]; *Ferry Eskens*[7]; *Olivier Mir*[8]; *Philippe Cassier*[9]; *César Serrano*[10]; *William D. Tap*[11]; *Jonathan C. Trent*[12]; *Piotr Rutkowski*[13]; *Shreyaskumar Patel*[14]; *Sant Chawla*[15]; *Eyal Meiri*[16]; *Teresa Zhou*[17]; *Maria Roche*[17]; *Suzanne George*[18]

[1]*OHSU Knight Cancer Institute, Portland, OR, USA;* [2]*Royal Marsden Hospital and Institute of Cancer Research, London, United Kingdom;* [3]*Fox Chase Cancer Center, Philadelphia, PA, USA;* [4]*University of Duisburg-Essen, Essen, Germany;* [5]*Asan Medical Centre, Seoul, Korea (the Democratic People's Republic of);* [6]*University Hospitals Leuven Leuven Cancer Institute, Leuven, Belgium;* [7]*Erasmus MC Cancer Institute, Rotterdam, Netherlands;* [8]*Institut Gustave Roussy, Villejuif, France;* [9]*Centre Léon Bérard, Lyon, France;* [10]*Vall d' Hebron Institute of Oncology, Barcelona, Spain;* [11]*Memorial Sloan Kettering Cancer Center, New York, NY, USA;* [12]*Sylvester Comprehensive Cancer Center University of Miami, Miami, FL, USA;* [13]*Maria Sklodowska-Curie Institute–Oncology Center, Warsaw, Poland;* [14]*MD Anderson Cancer Center, Houston, TX, USA;* [15]*Sarcoma Oncology Center, Santa Monica, CA, USA;* [16]*Cancer Treatment Center of America, Atlanta, GA, USA;* [17]*Blueprint Medicines Corporation, Cambridge, MA, USA;* [18]*Dana Farber Cancer Institute, Boston, MA, USA*

Paper #38
1:24 pm - 1:36 pm

3214982

GENOTYPE-SPECIFIC ACTIVITY AND SAFETY OF CABOZANTINIB IN PATIENTS WITH GASTROINTESTINAL STROMAL TUMOR AFTER FAILURE OF IMATINIB AND SUNITINIB. EARLY MOLECULAR DATA FROM EORTC PHASE 2 TRIAL 1317 "CABOGIST"

Patrick Schöffski[1]; *Olivier Mir*[5]; *Bernd Kasper*[9]; *Zsuzsanna Papai*[10]; *Jean-Yves Blay*[11]; *Antoine Italiano*[12]; *Charlotte Benson*[3]; *Katerina Kopeckova*[6]; *Nasim Ali*[4]; *Palma Dileo*[7]; *Axel Le Cesne*[5]; *Franka Menge*[9]; *Sophie Cousin*[12]; *Céline Charon-Barra*[13]; *Agnieszka Wozniak*[1]; *Sandrine Marreaud*[8]; *Saskia Litiere*[8]; *Axelle Nzokirantevye*[8]; *Hans Gelderblom*[2]

[1]*General Medical Oncology, University Hospitals Leuven, Leuven, Belgium;* [2]*Department of Medical Oncology, Leiden University Medical Center, Leiden, Netherlands;* [3]*Sarcoma Unit, Royal Marsden Hospital, London, United Kingdom;* [4]*Clatterbridge Cancer Centre, Wirral, United Kingdom;* [5]*Department of Medical Oncology, Institut Gustave Roussy, Villejuif, France;* [6]*Department of Oncology of the 2nd Faculty of Medicine, Charles University and University Hospital in Motol, Praha, Czechia;* [7]*University College London, London, United Kingdom;* [8]*European Organization for Research and Treatment of Cancer, Brussels, Belgium;* [9]*Sarcoma Unit - Interdisciplinary Tumor Center, Mannheim University Medical Center, Mannheim, Germany;* [10]*State Medical Centre Budapest, Budapest, Hungary;* [11]*Centre Léon Bérard, Lyon, France;* [12]*Sarcoma Unit, Institut Bergonié, Bordeaux, France;* [13]*Centre Georges François Leclerc, Dijon, France*

Paper #39
1:36 pm - 1:48 pm

3247216

GASTROINTESTINAL STROMAL TUMOR LOCATION WITHIN THE STOMACH CORRELATES WITH TUMOR MUTATION PROFILE

Jason K. Sicklick[1]; ***Jorge R. de la Torre Medina***[1]; *Sudeep Banerjee*[1]; *Vi Nguyen*[4]; *Maha Alkhuziem*[3]; *Santiago Horgan*[3]; *Chih-Min Tang*[1]; *Mayra Yebra*[1]; *Hyunho Yoon*[1]; *Robert Mallory*[1]; *Hitendra Patel*[2]; *Shumei Kato*[2]; *Wilson Kwong*[5]; *Micheal Chang*[5]; *Syed Fehmi*[5]; *Thomas Savides*[5]; *Adam Burgoyne*[2]; *Paul Fanta*[2]

[1]*Department of Surgery, Division of Surgical Oncology, University of California, San Diego, La Jolla, CA, USA;* [2]*Medical Oncology, UC San Diego, San Diego, CA, USA;* [3]*Department of Surgery, UC San Diego, San Diego, CA, USA;* [4]*Medical School, UC San Diego, San Diego, CA, USA;* [5]*Department of Gastroenterology, UC San Diego, San Diego, CA, USA*

1:48 pm - 2:00 pm

Discussant: ***Axel Le Cesne***

Friday, 15 November, 2019

2:00 pm - 3:00 pm — – HERMAN SUIT LECTURE – — *Kiku Ballroom*

Precision Sarcoma Care

Jay Wunder

(Mount Sinai Hospital, Toronto, Ontario, Canada)

Chair and Moderator: **Irene Andrulis**

3:00 pm - 3:30 pm — Afternoon Break — *3rd Floor*

3:30 pm - 5:30 pm — – SESSION 10 – — *Kiku Ballroom*

Retroperitoneal / Pelvic Sarcomas

Chairs: **Andrew Bishop** and **Dirk Strauss**

Paper #40
3:30 pm - 3:42 pm

3253011

PATTERNS OF RECURRENCE AND SURVIVAL PROBABILITY FOLLOWING SECOND RELAPSE OF RETROPERITONEAL SARCOMA: A STUDY FROM TARPSWG

Winan van Houdt[1]; Marco Fiore[2]; Francesco Barretta[2]; Piotr Rutkowski[3]; Jean-Yves Blay[4]; Guy Lahat[5]; Dirk Strauss[6]; Ricardo J. 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 P. Bagaria[16]; Robert Canter[17]; John Mullen[18]; Dario Callegaro[2]; Mark Fairweather[19]; Rosalba Miceli[2]; Chan Raut[19]; Alessandro Gronchi[2]; ***Rebecca Gladdy, MD, PhD****[15]*

[1]Netherlands Cancer Institute, Amsterdam, Netherlands; [2]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [3]Maria Sklodowska-Curie Memorial Cancer Center, Warsaw, Poland; [4]Centre Leon Berard, Lyon, France; [5]Tel Aviv Sourasky Medical Center, Tel Aviv, Israel; [6]Royal Marsden Hospital, London, United Kingdom; [7]Moffitt Cancer Center, Tampa, FL, USA; [8]Yale School of Medicine, New Haven, CT, USA; [9]Candiolo Cancer Institute – FPO, IRCCS, Torino, Italy; [10]Istituto Clinico Humanitas IRCCS, Milan, Italy; [11]Institut Bergonie, 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, ON, Canada; [15]Mount Sinai Hospital, Princess Margaret Hospital, University of Toronto, Toronto, ON, Canada; [16]Mayo Clinic Jacksonville, Jacksonville, FL, USA; [17]University of California-Davis School of Medicine, Davis, CA, USA; [18]Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; [19]Brigham and Women's Hospital, Dana-Farber Institute, Harvard Medical School, Boston, MA, USA

Paper #41
3:42 pm - 3:54 pm

3254877

POST-OPERATIVE MORBIDITY AFTER RESECTION OF RECURRENT RETROPERITONEAL SARCOMA: A REPORT FROM THE TRANS-ATLANTIC AUSTRALASIAN RPS WORKING GROUP (TARPSWG)

Carolyn Nessim, MD, MSc[1]; *Chan Raut*[20]; *Dario Callegaro*[19]; *Francesco Barretta*[2]; *Piotr Rutkowski*[3]; *Jean-Yves Blay*[4]; *Dirk Strauss*[5]; *Ricardo J. Gonzalez*[6]; *Nita Ahuja*[7]; *Giovanni Grignani*[8]; *Vittorio Quagliuolo*[9]; *Eberhard Stoeckle*[10]; *Antonino De Paoli*[11]; *Venu Pillarisetty*[12]; *Carol J. Swallow*[13]; *Sanjay P. Bagaria*[22]; *Robert Canter*[14]; *John Mullen*[15]; *Elisabetta Pennacchioli*[16]; *Frits van Coevorden*[17]; *Kenneth Cardona*[18]; *Marco Fiore*[19]; *Mark Fairweather*[20]; *Alessandro Gronchi*[19]; *Guy Lahat*[21]

[1]*Surgery, The Ottawa Hospital, Ottawa, ON, Canada;* [2]*Surgery, Istituto di tumori di Milan, Milan, Italy;* [3]*Surgery, Maria Sklodowska-Curie Institute - Oncology Center, Warsaw, Poland;* [4]*Surgery, Lyon Cancer Center, Lyon, France;* [5]*Surgery, Royal Marsden, London, United Kingdom;* [6]*Surgery, Moffitt Cancer Center, Tampa, FL, USA;* [7]*Surgery, Yale University, New Haven, CT, USA;* [8]*Surgery, Istituto di Candiolo, Torino, Italy;* [9]*Surgery, Istituto Clinico Humanitas IRCCS, Milan, Italy;* [10]*Institut Bergonie, Bordeaux, France;* [11]*Surgery, Centro di Riferimento Oncologico di Aviano, Aviano, Italy;* [12]*Surgery, Seattle Cancer Center Alliance, Seattle, WA, USA;* [13]*Surgery, University of Toronto, Toronto, ON, Canada;* [14]*Surgery, UC Davis Health, Davis, CA, USA;* [15]*Surgery, Massachusetts General Hospital, Boston, MA, USA;* [16]*Surgery, European Institute of Oncology, Milan, Italy;* [17]*Surgery, Netherlands Cancer Institute, Amsterdam, Netherlands;* [18]*Surgery, Winship Cancer Institute, Emory, Atlanta, GA, USA;* [19]*Surgery, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy;* [20]*Surgery, Brigham and Women's Hospital/Harvard Medical School, Boston, MA, USA;* [21]*Surgery, Cancer Biology Research Center Tel Aviv University, Tel Aviv, Israel;* [22]*Mayo Clinic, Jacksonville, FL, USA*

Paper #42
3:54 pm - 4:06 pm

3247745

COMPARISON OF TOTAL (IPSILATERAL) RETROPERITONEAL LIPECTOMY VERSUS STANDARD COMPLETE RESECTION IN PATIENTS WITH RETROPERITONEAL LIPOSARCOMA: A RETROSPECTIVE FIVE-INSTITUTION STUDY

Shahbaz Hanif[1]; *Cheng Li Miao*[2]; *Fa Bo Qiu*[3]; *Wei Qi Lu*[4]; *Dai You Guo*[5]; *Xiao Song Rao*[6]; *Gao Kui Zhang*[7]; *Jun Chen*[2]; *Wen Jie Li*[2]; *Wen Qing Liu*[2]; *Xiao Bing Chen*[2]; *Meng Meng Xiao*[2]; *Li Chao Cha*[3]; *Jiong Yuan Wang*[4]; *Yu Bo Ren*[6]; *Hao Yun Yang*[7]; *William W. Tseng*[8]; ***Cheng Hua Luo***[2]

[1]*Beijing Spanal Medical Scientific Co. Ltd., Beijing, China;* [2]*Dept. of Retroperitoneal Tumor Surgery, Peking University International Hospital, Beijing, China;* [3]*Dept. of Retroperitoneal Tumor Surgery, Affiliated Hospital of Qingdao University, Qingdao, China;* [4]*Dept. of General Surgery, Zhongshan Hospital of Fudan University, Shanghai, China;* [5]*Department of Abdominal Surgery, Yunnan Cancer Hospital, Kunming, China;* [6]*Department of Pathology, Peking University International Hospital, Beijing, China;* [7]*HBR Data Science Ltd., Beijing, China;* [8]*Department of Surgery, Section of Surgical Oncology, University of Southern California, Keck School of Medicine, Los Angeles, CA, USA*

Paper #43
4:06 pm - 4:18 pm

3256471

THE EFFECT OF PREOPERATIVE TREATMENT ON THE PERFORMANCE OF PREDICTIVE NOMOGRAMS IN PRIMARY RETROPERITONEAL SARCOMA (RPS)

Deanna Ng[1]; *David Cyr*[1]; *Dario Callegaro*[1]; *Alessandro Gronchi*[2]; *David Shultz*[3]; *Savtaj Brar*[1]; *Peter Chung*[3]; *Rebecca Gladdy*[1]; *Charles Catton*[3]; *Carol J. Swallow*[1]

[1]*Department of Surgery, Mount Sinai Hospital and University of Toronto, Toronto, ON, Canada;* [2]*Surgical Oncology, Fondazione IRCCS Istituto Nazionale Tumori Milano, Milan, Italy;* [3]*Radiation Oncology, Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada*

4:18 pm - 4:30 pm

Discussant: ***Jason Sicklick***

Friday, 15 November, 2019

Paper #44
4:30 pm - 4:42 pm

3253843

PREOPERATIVE LEIOMYOSARCOMA RISK-SCORE FOR DISCRIMINATION OF LEIOMYOSARCOMA VS. LEIOMYOMA OF THE UTERUS

*Günther Köhler[2]; Marcus Vollmer[4]; Neetika Nath[4]; Philipp-Andreas Hessler[5]; **Peter Hohenberger, MD, PhD**[1]; Matthias Evert[3]; Dominika Trojnarska[2]; Katja Evert[3]; Katarina Dennis[5]; Marek Zygmunt[2]; Lars Kaderali[4]*
[1]Dept. of Surgery, Div. of Surgical Oncology and Thoracic Surgery, Mannheim, Germany; [2]Department of Obstetrics and Gynecology, University Medicine Greifswald, Greifswald, Germany; [3]Institute of Pathology, University of Regensburg, Regensburg, Germany; [4]Institute of Bioinformatics, University Medicine Greifswald, Greifswald, Germany; [5]Hospital Sachsenhausen, Department of Gynecologic Surgery, Frankfurt/Main, Germany

Paper #45
4:42 pm - 4:54 pm

3253748

OUTCOMES ANALYSIS OF THE MULTIMODALITY TREATMENT OF PATIENTS WITH CAVAL LEIOMYOSARCOMA

Malcolm H. Squires, MD, MS[1]*; Stephen Politano[1]; Raphael Pollock[1]; James L. Chen[2]; Valerie Grignol[1]*
[1]Division of Surgical Oncology, The Ohio State University, Columbus, OH, USA; [2]Division of Medical Oncology, Department of Internal Medicine, The Ohio State University, Columbus, OH, USA

Paper #46
4:54 pm - 5:06 pm

3256534

FUNCTIONAL DURABILITY OF ACETABULAR RECONSTRUCTION FOLLOWING RESECTION OF PELVIC SARCOMAS

Tomohiro Fujiwara*; Koichi Ogura; Alexander Christ; Mohamed Yakoub; Yusuke Tsuda; John H. Healey; Nicola Fabbri*
Memorial Sloan Kettering Cancer Center, New York, NY, USA

Paper #47
5:06 pm - 5:18 pm

3256805

CARBON ION RADIOTHERAPY FOR SACRAL SARCOMAS

Reiko Imai*; Hiroshi Tsuji; Tadashi Kamada*
QST NIRS Hospital, National Institutes for Quantum and Radiological Science and Technology, Chiba, Japan

5:18 pm - 5:30 pm

Discussant: ***Alex Gronchi***

6:30 pm – 10:30 pm

GALA - Reception and Dinner at Happo En *Happo En*
Cocktail Attire
Buses will depart at 6:00 pm from the Hilton Tokyo Hotel. *(Badges are required)*

Saturday, 16 November, 2019

6:00 am - 6:00 pm	Registration	*Kiku Lobby, 4th Floor*
6:15 am - 7:30 am	Sunrise in Tokyo	*Kiku Ballroom*
6:15 am - 6:20 am	Case Introduction: GIST *Herbert Loong*	
6:20 am - 6:35 am	Pathology and Overview of GISTs *Elizabeth Demicco*	
6:35 am - 6:50 am	Surgery and Systemic Therapy in GISTs *Toshirou Nishida*	
6:50 am - 7:05 am	Localized Treatment in Patients with Advanced GISTs *Jason Chan*	
7:05 am - 7:20 am	Wrap Up and What's New in GIST @ CTOS 2019? *Albiruni Razak*	
7:20 am - 7:30 am	Looking Forward – Sunrise in Florida *Herbert Loong*	

8:00 am - 10:00 am — – SESSION 11 – — *Kiku Ballroom*

Paediatric Sarcomas

Chairs: **Theirry Alcindor** and **Elizabeth Stewart**

Paper #48
8:00 am - 8:12 am

3253869

FIRST RESULTS OF THE EURO EWING 2012 TRIAL COMPARING TWO CHEMOTHERAPY REGIMENS IN NEWLY DIAGNOSED EWING SARCOMA

Keith Wheatley, DPhil[1]*; Veronica Moroz*[1]*; Perrine Marec-Berard*[2]*; Javier Martin-Broto*[9]*; Hans Gelderblom*[3]*; Sandra J. Strauss*[4]*; Nathalie Gaspar*[5]*; Jennifer Anderton*[1]*; Jean-Pierre Mahieu*[1]*; Ana Sastre*[6]*; Valerie Laurence*[7]*; Jeremy Whelan*[4]*; Bernadette Brennan*[8]

[1]CRCTU, University of Birmingham, Birmingham, United Kingdom; [2]Centre Léon Bérard, Lyon, France; [3]European Organisation for Research and Treatment of Cancer, Brussels, Belgium; [4]University College London Hospitals NHS, London, United Kingdom; [5]Gustave Roussy cancer campus, Paris, France; [6]La Paz Hospital, Madrid, Spain; [7]Institute Curie, Paris, France; [8]Royal Manchester Children's Hospital, Manchester, United Kingdom; [9]Universitary Hospital Virgen del Rocio, Sevilla, Spain

Paper #49
8:12 am - 8:24 am

3222400

RANDOMIZED PHASE 3 TRIAL OF GANITUMAB ADDED TO INTERVAL COMPRESSED CHEMOTHERAPY FOR PATIENTS WITH NEWLY DIAGNOSED METASTATIC EWING SARCOMA: A REPORT FROM THE CHILDREN'S ONCOLOGY GROUP (COG)

Steven DuBois[1]*; Julia Glade Bender*[2]*; Allen Buxton*[3]*; Nadia Laack*[4]*; Lor Randall*[5]*; Helen Chen*[17]*; Nita Seibel*[17]*; Stephanie Terezakis*[6]*; Christine Hill-Kayser*[7]*; Andrea Hayes-Jordan*[8]*; Joel Reid*[4]*; Lisa Teot*[9]*; Dinesh Rakheja*[10]*; Richard Womer*[7]*; Carola Arndt*[4]*; Stephen Lessnick*[11]*; Brian Crompton*[1]*; Edward Kolb*[12]*; Heike Daldrup-Link*[13]*; Eric Eutsler*[14]*; Damon Reed*[15]*; Katherine A. Janeway*[1]*; Mark Krailo*[3]*; Richard Gorlick*[16]
[1]*Dana-Farber Cancer Institute, Boston, MA, USA;* [2]*Memorial Sloan-Kettering Cancer Center, New York, NY, USA;* [3]*Children's Oncology Group, Monrovia, CA, USA;* [4]*Mayo Clinic, Rochester, MN, USA;* [5]*UC Davis, Sacramento, CA, USA;* [6]*University of Minnesota, Minneapolis, MN, USA;* [7]*Children's Hospital of Philadelphia, Philadelphia, PA, USA;* [8]*University of North Carolina, Chapel Hill, NC, USA;* [9]*Boston Children's Hospital, Boston, MA, USA;* [10]*UT Southwestern, Dallas, TX, USA;* [11]*Nationwide Children's Hospital, Columbus, OH, USA;* [12]*Nemours Children's Hospital, Wilmington, DE, USA;* [13]*Stanford Universtiy, Palo Alto, CA, USA;* [14]*Washington University, St. Louis, MO, USA;* [15]*Moffitt Cancer Center, Tampa, FL, USA;* [16]*MD Anderson Cancer Center, Houston, TX, USA;* [17]*National Cancer Institute, Bethesda, MD, USA*

Paper #50
8:24 am - 8:36 am

3279595

A PHASE III RANDOMIZED TRIAL OF ADDING VINCRISTINE-TOPOTECAN-CYCLOPHOSPHAMIDE (VTC) TO STANDARD CHEMOTHERAPY IN INITIAL TREATMENT OF NON-METASTATIC EWING SARCOMA – A REPORT FROM THE CHILDREN'S ONCOLOGY GROUP

Patrick Leavey[1]*; Mark Krailo*[2]*; Steven DuBois*[3]*; Holcombe E. Grier*[3]*; Douglas S. Hawkins*[4]*; Bruce Pawel*[5]*; Helen Nadel*[6]*; Richard Womer*[7]*; Del Stringham*[8]*; Kenneth Brown*[9]*; Damon Reed*[10]*; Mark Bernstein*[11]*; Katherine A. Janeway*[3]*; Neyssa Marina*[12]*; Nadia Laack*[13]*; Lor Randall*[14]*; Richard Gorlick*[15]*; Leo Mascarenhas*[5]
[1]*Pediatrics, UT Southwestern Medical Center, Dallas, TX, USA;* [2]*Children's Oncology Group, Monrovia, CA, USA;* [3]*Dana-Farber/Harvard Cancer Center, Boston, MA, USA;* [4]*Seattle Children's Hospital, Seattle, WA, USA;* [5]*Children's Hospital of Los Angeles, Los Angeles, CA, USA;* [6]*Lucile Packard Children's Hospital Stanford University, Stanford, CA, USA;* [7]*Children's Hospital of Philadelphia and University of Philadelphia, Philadelphia, PA, USA;* [8]*Children's Hospital of Orange county, Orange, CA, USA;* [9]*University of British Columbia, Vancouver, BC, Canada;* [10]*John's Hopkins All Children's Hospital, St. Petersburgh, FL, USA;* [11]*IWK Health Centre, Port Williams, NS, Canada;* [12]*Five Prime Therapeutics, San Francisco, CA, USA;* [13]*Mayo Clinic, Rochester, MN, USA;* [14]*University of California Davis Comprehensive Cancer Center, Sacramento, CA, USA;* [15]*MD Anderson, Houston, TX, USA*

Paper #51
8:36 am - 8:48 am

3223938

OUTCOME OF PATIENTS WITH RELAPSED OR PROGRESSIVE EWING SARCOMA ENROLLED ON PHASE 2 CLINICAL TRIALS: A REPORT FROM THE CHILDREN'S ONCOLOGY GROUP (COG)

Anderson B. Collier, MD[1]*; Mark Krailo*[2]*; Ha Dang*[2]*; Steven DuBois*[3]*; Douglas S. Hawkins*[4]*; Mark Bernstein*[5]*; Lisa Bomgaars*[6]*; Damon Reed*[7]*; Richard Gorlick*[8]*; Katherine A. Janeway*[3]
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8:48 am - 9:00 am

Discussant: ***Martin McAbe***

Paper #52
9:00 am - 9:12 am

3253193

DO CHILDREN AND ADOLESCENTS WITH COMPLETELY RESECTED ALVEOLAR RHABDOMYOSARCOMA (RMS) REQUIRE RADIATION? A REPORT FROM THE CHILDREN'S ONCOLOGY GROUP (COG)

Jamie Aye, MD[1]; *Yueh-Yun Chi*[2]; *Jing Tian*[2]; *Suzanne Wolden*[3]; *Douglas S. Hawkins*[4]; *Abha Gupta*[5]
[1]*Pediatric Hematology Oncology, Children's of Alabama, University of Alabama at Birmingham, Birmingham, AL, USA;* [2]*Biostatistics, University of Florida, Gainesville, FL, USA;* [3]*Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA;* [4]*Pediatric Hematology Oncology, Seattle Children's Hospital, Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, USA;* [5]*Pediatric Hematology Oncology, Hospital for Sick Children, University of Toronto, Toronto, ON, Canada*

Paper #53
9:12 am - 9:24 am

3253900

ASSESSING THE PROGNOSTIC VALUE OF EARLY ANATOMIC RESPONSE TO INDUCTION CHEMOTHERAPY IN PEDIATRIC RHABDOMYOSARCOMA: A SYSTEMATIC REVIEW

Bas Vaarwerk[1]; ***Roelof van Ewijk, Fellow in Pediatric Oncology, MD***[1]; *Willemijn B. Breunis*[2]; *Rick R. van Rijn*[3]; *Johanna H. van der Lee*[4]; *Hans Merks*[1]
[1]*Princess Máxima Center for Pediatric Oncology, Utrecht, Netherlands;* [2]*Oncology and Children's Research Center, University Children's Hospital, Zurich, Switzerland;* [3]*Department of Radiology and Nuclear Medicine, Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands;* [4]*Paediatric Clinical Research Office, Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands*

Paper #54
9:24 am - 9:36 am

3256271

EUROPEAN PEDIATRIC SOFT TISSUE SARCOMA STUDY GROUP MTS2008 STUDY: RESULTS OF A PROTOCOL FOR METASTATIC RHABDOMYOSOSARCOMA

Hans Merks, MD, PhD[1]; *Gianni Bisogno*[2]; *Gian Luca de Salvo*[3]; *Ilaria Zanetti*[2]; *Daniel Orbach*[4]; *Veronique Minard-Colin*[5]; *Anna Kelsey*[6]; *Helene Martelli*[7]; *Kieran McHugh*[8]; *Alison Cameron*[9]; *Heidi Glosli*[10]; *Andrea Ferrari*[11]; *Christophe Bergeron*[12]; *Meriel Jenney*[13]; *Julia Chisholm*[14]
[1]*Princess Maxima Center for Pediatric Oncology, Utrecht, Netherlands;* [2]*Division of Haematology-Oncology- Department of Woman's and Child's Health, Padova University Hospital, Padova, Italy;* [3]*Clinical Trial and Biostatistics Unit, Istituto Oncologico Veneto, Padova, Italy;* [4]*SIREDO Oncology Center Care- Innovation and Research for Children-Adolescents and Young Adults with Cancer, Institut Curie- PSL University, Paris, France;* [5]*Department of Child and Adolescent Cancer, Institute Gustave Roussy, Paris, France;* [6]*Department of Diagnostic Paediatric Histopathology, Central Manchester University Hospitals NHS Foundation Trust, Manchester, United Kingdom;* [7]*Department of Pediatric Surgery, Hôpital Universitaire Bicêtre, Paris, France;* [8]*Department of Pediatric Radiology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom;* [9]*Department of Clinical Oncology, University Hospitals Bristol, Bristol, United Kingdom;* [10]*Department of Pediatric Oncology, Rikshospitalet, Oslo, Norway;* [11]*Department of Pediatric Oncology, Istituto Tumori Milano, Milan, Italy;* [12]*Institut d'Hématologie et d'Oncologie Pédiatrique, Centre Léon Bérard, Lyon, France;* [13]*Department of Pediatric Oncology, Children's Hospital for Wales, Cardiff, United Kingdom;* [14]*Children and Young Peoples Unit, The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom*

Paper #55 3251949
9:36 am - 9:48 am

SAFETY AND FEASIBILITY OF MAGNETIC RESONANCE-GUIDED HIGH INTENSITY FOCUSED ULTRASOUND (MR-HIFU) FOR THE ABLATION OF RELAPSED OR REFRACTORY PEDIATRIC SOLID TUMORS INCLUDING DESMOID TUMORS

AeRang Kim, MD, PhD[1]*; Karun V. Sharma*[2]*; Pavel Yarmolenko*[3]*; James I. Geller*[4]*; Joseph G. Pressey*[4]*; John M. Racadio*[5]*; Haydar Celik*[3]*; Avinash Eranki*[3]*; Matthew Lanier*[6]*; Caitlin Tydings*[1]*; Ari Partanen*[7]*; Peter C. Kim*[8]

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9:48 am - 10:00 am Discussant: ***Aaron Weiss***

10:00 am - 10:30 am Morning Break *3rd Floor*

10:30 am - 11:30 am – NINA AXELRAD LECTURE – *Kiku Ballroom*

Osteosarcoma: On the Verge of Improving Outcome
Richard Gorlick
(MD Anderson Cancer Center, Houston, Texas, USA)

Chair and Moderator: **Damon Reed**

11:30 am - 12:00 pm – SESSION 12 – *Kiku Ballroom*

Young Investigator Awards

Chair and Moderator: **Kurt Weiss**

Paper #56 3256173
11:30 am - 11:45 am

LONGITUDINAL PROGNOSTICATION IN PATIENTS WITH PRIMARY RETROPERITONEAL SARCOMA TREATED WITH SURGERY: DEVELOPMENT AND EXTERNAL VALIDATION OF A DYNAMIC PROGNOSTIC NOMOGRAM

Dario Callegaro, MD[1]*; Francesco Barretta*[2]*; Carol J. Swallow*[3]*; Dirk Strauss*[4]*; Sylvie Bonvalot*[5]*; Charles Honoré*[6]*; Eberhard Stoeckle*[7]*; Frits van Coevorden*[8]*; Rick Haas*[9]*; Piotr Rutkowski*[10]*; Yvonne Schrage*[11]*; Mark Fairweather*[12]*; Lorenzo Conti*[1]*; Nikolaos Vassos*[4]*; Rebecca Gladdy*[3]*; Deanna Ng*[3]*; Winan van Houdt*[8]*; Rosalba Miceli*[2]*; Chan Raut*[12]*; Alessandro Gronchi*[1]

[1]Surgical Oncology, Fondazione IRCCS Istituto Nazionale Tumori Milano, Milan, Italy; [2]Clinical Epidemiology, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy; [3]Surgery, University of Toronto, Toronto, ON, Canada; [4]Surgery, Royal Marsden Hospital, London, United Kingdom; [5]Surgery, Institut Curie, Paris, France; [6]Surgery, Institut Gustave Roussy, Villejuif, France; [7]Surgery, Institut Bergonie, Bordeaux, France; [8]Surgery, The Netherlands Cancer Institute, Amsterdam, Netherlands; [9]Radiation Oncology, The Netherlands Cancer Institute, Amsterdam, Netherlands; [10]Surgery, Maria Sklodowska-Curie Institute-Oncology Center, Warsaw, Poland; [11]Surgery, Leiden University Medical Center, Leiden, Netherlands; [12]Surgery, Brigham and Women's Hospital, Boston, MA, USA

Paper #57 3254081
11:45 am - 12:00 pm
DISSECTING THE ROLE OF FUS-DDIT3 IN MYXOID LIPOSARCOMA RESPONSE TO RADIATION THERAPY
Mark Chen[1]*; Nathan Leisenring*[1]*; Andrea R. Daniel*[1]*; Joseph Foster*[2]*; Eric Xu*[1]*; Andrea Ventura*[3]*; Ian J. Davis*[2]*; David Kirsch*[1]
[1]Duke University, Durham, NC, USA; [2]University of North Carolina - Chapel Hill, Chapel Hill, NC, USA; [3]Memorial Sloan Kettering Cancer Center, New York, NY, USA

12:00 pm - 1:00 pm Lunch *Second Floor*

1:00 pm - 1:30 pm *Kiku Ballroom*

LSERA Award
Dr. Sam Behjati, MA, BMBCh, PhD, MRCPCH

1:30 pm - 3:30 pm – SESSION 13 – *Kiku Ballroom*

Soft Tissue Sarcomas: Biology

Chairs: **Paul Huang** and **Winan van Houdt**

Paper #58 3255107
1:30 pm - 1:42 pm
COMPREHENSIVE GENOMIC ANALYSIS OF EWSR1-NFATC2 FUSION SARCOMAS IDENTIFY DISTINCTIVE GENOMIC ALTERATIONS AND UPREGULATION OF THE MTOR PATHWAY
Nathan D. Seligson, PharmD[1]*; Richard Maradiaga*[2]*; John Hays*[2]*; Sherri Millis*[3]*; James L. Chen*[2]
[1]University of Florida, Jacksonville, FL, USA; [2]Ohio State University, Columbus, OH, USA; [3]Foundation Medicine, Phoenix, AZ, USA

Paper #59 3256379
1:42 pm - 1:54 pm
EXPRESSION OF CIC-DUX4 IN HEK293FT CELLS INCREASES THE LEVELS OF THE ONCOMETABOLITES L-2-HYDROXYGLUTARATE AND D-2-HYDROXYGLUTARATE
Kelsi R. Willis[1]*; Richard L. Boriack*[2]*;* ***Dinesh Rakheja, MD***[1]
[1]Pathology, University of Texas Southwestern Medical Center, Dallas, TX, USA; [2]Pathology and Laboratory Medicine, Children's Health, Dallas, TX, USA

Paper #60 3254542
1:54 pm - 2:06 pm
GENE EXPRESSION CHANGES ASSOCIATED WITH DEDIFFERENTIATION IN LIPOSARCOMA PREDICT OVERALL SURVIVAL
Nicholas Shannon*; Xuan Qiu; Joey W. Tan; Josephine Hendrikson; Deanna Ng; Chin-Ann J. Ong; Grace Hwei Ching Tan; Claramae Shulyn Chia; Melissa Ching Ching Teo http://www.nccs.com.sg/, Singapore, Singapore*

Paper #61 3255278
2:06 pm - 2:18 pm
EXPLORING THE TP53 AXIS AS A THERAPEUTIC VULNERABILITY IN SYNOVIAL SARCOMA
Mushtaq Muhammad[1]*; Jennifer Wilson*[1]*; Jamie Yu*[2]*; Ian Lock*[3]*; Toshihiko Nishisho*[2,4]*; Torsten O. Nielsen*[2]*; Kevin B. Jones*[5]*;* ***Bertha Brodin, PhD***[1]
[1]Department of Microbiology, Tumor and Cell Biology, Karolinska Institutet; [2]Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, BC, Canada; [3]Huntsman Cancer Institute, Salt Lake City, Utah; [4]Department of Orthopedics, Tokushima University Graduate School, Tokushima, Japan; [3]Department of Oncology and Pathology, Karolinska Institutet, Stockholm, Sweden; [5]Department of Orthopedics, University of Utah School of Medicine, Salt Lake City, Utah, USA

2:18 pm - 2:30 pm Discussant: ***Torsten Nielsen***

Saturday, 16 November, 2019

Paper #62 — 3256131
2:30 pm - 2:42 pm

ARGININE STARVATION AND DOCETAXEL INDUCE C-MYC DRIVEN HENT1 SURFACE EXPRESSION TO OVERCOME GEMCITABILE TRASPORTER LEVEL RESISTANCE IN ASS1 NEGATIVE SARCOMAS

Bethany C. Prudner; Richa Rathore; Angela Hirbe; ***Brian A. Van Tine***
Washington University in St. Louis, Saint Louis, MO, USA

Paper #63 — 3253588
2:42 pm - 2:54 pm

ALTERATIONS IN DNA DAMAGE RESPONSE PATHWAY GENES ACROSS SARCOMA SUBTYPES

Evan J. Rosenbaum, MD[1]*; Philip Jonsson*[2]*; Viswatej Avutu*[1]*; Ping Chi*[1]*; Mark Dickson*[1]*; Ciara Kelly*[1]*; Mary Louise Keohan*[1]*; Mrinal M. Gounder*[1]*; Benjamin A. Nacev*[1]*; Jason E. Chan*[1]*; Sandra P. D'angelo*[1]*; Martee L. Hensley*[1]*; Diana Mandelker*[3]*; Mark Donoghue*[2]*; Zsofia K. Stadler*[3]*; Marc Ladanyi*[3]*; Cristina Antonescu*[4]*; Sam Singer*[5]*; William D. Tap*[1]*; Sujana Movva*[1]
[1]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]Center for Molecular Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [3]Department of Molecular Genetics, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [4]Clinical Genetics, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [5]Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Paper #64 — 3253095
2:54 pm - 3:06 pm

SLFN11 IS NECESSARY - BUT NOT SUFFICIENT - TO SENSITIZE PEDIATRIC SARCOMAS TO DNA DAMAGING AGENTS

Jessica Gartrell, MD*; Marcia Mellado-Largarde; Michael Clay; Jia Xie; Nathaniel Twarog; Nancy Martinez; Michele Connelly; Koon-Kiu Yan; Jiyang Yu; Shaina Porter; Shondra Miller; Lauren Hoffman; Hyekyung Plumley; April Sykes; Natasha Sahr; Kaley Blankenship; Armita Bahrami; Christopher Tinkle; Sara Federico; Elizabeth Stewart; Anang Shelat*
Oncology, St. Jude Children's Research Hospital, Southaven, MS, USA

Paper #65 — 3255481
3:06 pm - 3:18 pm

SURVEY OF ACTIONABLE GENOMIC ALTERATIONS IN A COHORT OF SOFT TISSUE AND BONE SARCOMAS

Maya Kansara[1]*; Subotheni Thavaneswaran*[1]*; John Grady*[1]*; Mandy Ballinger*[1]*; Lucille Sebastian*[2]*; Audrey Silvestri*[1]*; Christine Napier*[1]*; Katrin Sjoquist*[2]*; Wendy Hague*[2]*; Anthony Joshua*[1]*; John Simes*[2]*; David Thomas*[1]
[1]Garvan Institute, Sydney, New South Wales, Australia; [2]Sydney Medical School, NHMRC Clinical Trials Centre, Sydney, New South Wales, Australia

3:18 pm - 3:30 pm — Discussant: ***Kevin Jones***

3:30 pm - 4:00 pm — Afternoon Break — *3rd Floor*

4:00 pm - 5:00 pm | – SESSION 14 – | Kiku Ballroom

Sarcomas: Novel Therapy

Chairs: **Nicholas Bernthal** and **Marie Ahlstrom**

Paper #66
4:00 pm - 4:12 pm

3254636

EFFECTIVE TREATMENT OF ALVEOLAR SOFT PART SARCOMA WITH SINGLE AGENT ATEZOLIZUMAB

Geraldine O'Sullivan Coyne[1]; Nancy Moore[1]; Elad Sharon[2]; Naoko Takebe[1]; Lamin Juwara[3]; William Read[14]; Richard F. Riedel[15]; James Hu[4]; Melissa Burgess[5]; Brian A. Van Tine[6]; Priscilla Merriam[13]; Elizabeth Davis[7]; Anthony Conley[16]; John Glod[11]; Brian Ladle[9]; Scott Okuno[12]; Scott Christensen[17]; Larry R. Rubinstein[10]; James Doroshow[8]; ***Alice Chen***[1]

[1]Developmental Therapeutics Clinic, Division of Cancer Research and Diagnosis, National Cancer Institute, Bethesda, MD, USA; [2]Cancer Therapy Evaluation Program, National Cancer Institute, Shady Grove, MD, USA; [3]Clinical Research Directorate/Clinical Monitoring Research Program, Frederick National Laboratory for Cancer Research, National Cancer Institute, Bethesda, MD, USA; [4]Medical Oncology, University of Southern California, Los Angeles, CA, USA; [5]Hematology/Oncology, UPMC Hillman Cancer Center, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA; [6]Division of Oncology, Siteman Cancer Center, Washington University in St. Louis, St. Louis, MO, USA; [7]Medicine, Vanderbilt University Medical Center, Nashville, TN, USA; [8]Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, MD, USA; [9]Pediatric Oncology, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins Hospital, Baltimore, MD, USA; [10]Biometrics Research Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Shady Grove, MD, USA; [11]Pediatric Oncology Branch, National Cancer Institute, Bethesda, MD, USA; [12]Medical Oncology, Mayo Clinic, Rochester, MN, USA; [13]Dana-Farber Cancer Institute, Boston, MA, USA; [14]Winship Cancer Institute, Emory University, Atlanta, GA, USA; [15]Duke Cancer Institute, Duke University Health System, Durham, NC, USA; [16]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [17]UC Davis Comprehensive Cancer Center, Sacramento, CA, USA

Paper #67
4:12 pm - 4:24 pm

3212975

THE SYNOVIAL SARCOMA SUBSET ANALYSIS OF THE MULTI-HISTOLOGY PHASE I TRIAL OF ADP-A2M4 (MAGE-A4)

Brian A. Van Tine[1]*; David S. Hong[2]; Dejka Araujo[2]; Melissa Johnson[3]; Jeffrey Clarke[4]; David Liebner[5]; Kunle Odunsi[6]; Anthony Olszanski[7]; Samik Basu[8]; Francine Brophy[8]; Tom Holdich[8]; Malini Iyengar[8]; Rafael Amado[8]; Marcus Butler[9]*

[1]Medical Oncology, Washington University in St. Louis, St. Louis, MO, USA; [2]MD Anderson Cancer Center, Houston, TX, USA; [3]Sarah Cannon, Nashville, TN, USA; [4]Duke University, Durham, NC, USA; [5]Ohio State University Medical Center, Columbus, OH, USA; [6]Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA; [7]Fox Chase Cancer Center, Philadelphia, PA, USA; [8]Adaptimmune, Philadelphia, PA, USA; [9]Princess Margaret Cancer Centre, Toronto, ON, Canada

Paper #68
4:24 pm - 4:36 pm

3255157

IMMUNOSARC: A COLLABORATIVE SPANISH (GEIS) AND ITALIAN (ISG) SARCOMA GROUPS PHASE I/II TRIAL OF SUNITINIB PLUS NIVOLUMAB IN ADVANCED SOFT TISSUE AND BONE SARCOMAS: RESULTS OF THE PHASE II SOFT TISSUE SARCOMA COHORT

*Javier Martin-Broto[1]; **Nadia Hindi**[1]; Giovanni Grignani[2]; Javier Martinez-Trufero[3]; Andres Redondo[4]; Claudia Valverde[5]; Antonio López Pousa[6]; Silvia Stacchiotti[7]; Emanuela Palmerini[8]; Enrique de Alava[9]; David d. Moura[10]; Herminia Perez-Vega[11]; Paola Collini[7]; Irene Otero[12]; Patricio Ledesma[13]; Emanuela Marchesi[14]; Lorenzo D'Ambrosio[2]; Jose A Lopez-Martin[12]*

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Paper #69
4:36 pm - 4:48 pm

3255439

MOLECULAR ANALYSIS OF ARCHIVAL INFLAMMATORY MYOFIBROBLASTIC TUMOR TISSUE SAMPLES FROM EORTC 90101 "CREATE" AND CORRELATION WITH RESPONSE TO CRIZOTINIB

***Che-Jui Lee**[1]; Patrick Schöffski[2]; Elodie Modave[3]; Bram Boeckx[3]; Diether Lambrechts[3]; Jozef Sufliarsky[4]; Hans Gelderblom[5]; Jean-Yves Blay[6]; Agnieszka Wozniak[1]*

[1]Department of Oncology, KU Leuven, Leuven, Belgium; [2]Department of General Medical Oncology and Department of Oncology, UZ Leuven and KU Leuven, Leuven, Belgium; [3]VIB Center for Cancer Biology and Department of Human Genetics, VIB and KU Leuven, Leuven, Belgium; [4]National Cancer Institute, Bratislava, Slovakia; [5]Department of Medical Oncology, Leiden University Medical Center, Leiden, Netherlands; [6]Department of Medical Oncology, Centre Léon Bérard/Université Claude Bernard Lyon Institute, Lyon, France

4:48 pm - 5:00 pm

Discussant: ***Bernd Kasper***

5:00 pm - 6:00 pm

– SESSION 15 –

Kiku Ballroom

Challenges in MPNST and NF1

Chairs: **Kirsten Sundby Hall** and **Haydee Caro**

Paper #70
5:00 pm - 5:12 pm

3327498

CHALLENGES IN THE DIAGNOSIS OF NF1-MPNSTS: PATHOLOGY PERSPECTIVE

Alexander J. Lazar

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

Saturday, 16 November, 2019

Paper #71 — 3253627
5:12 pm - 5:24 pm

GENOMICS OF MPNST (GEM) CONSORTIUM: IN-DEPTH GENOMIC CHARACTERIZATION OF NF1-ASSOCIATED AND SPORADIC MPNSTS

Angela Hirbe, MD, PhD[1]; *Isidro Ciriano-Cortes*[2]; *Nischalan Pillay*[3]; *Matija Snuderl*[4]; *Alyaa Al-Ibraheemi*[5]; *Marilyn Bui*[6]; *Brendan Dickson*[7]; *James Gusella*[8]; *Jesse Hart*[9]; *Kevin B. Jones*[10]; *Justin Jordan*[8]; *Raymond Kim*[7]; *Daniel Lindsay*[3]; *Yoshihiro Nishida*[11]; *Katherine Piculell*[5]; *Diane Shao*[5]; *Nicole J. Ullrich*[5]; *Xia Wang*[6]; *Peter Park*[12]; *Adrienne Flanagan*[3]; *David T. Miller*[5]

[1]*Medical Oncology, Washington University in St. Louis, St. Louis, MO, USA;* [2]*European Bioinformatics Institute, Cambridge, United Kingdom;* [3]*Royal National Orthopaedic Hospital and University College London Cancer Institute, London, United Kingdom;* [4]*New York University, New York, NY, USA;* [5]*Boston Children's Hospital, Boston, MA, USA;* [6]*Moffitt Cancer Center, Tampa, FL, USA;* [7]*Mount Sinai Hospital, Toronto, ON, Canada;* [8]*Massachusetts General Hospital, Boston, MA, USA;* [9]*Lifespan, Providence, RI, USA;* [10]*Huntsman Cancer Institute, Salt Lake City, UT, USA;* [11]*Nagoya University, Nagoya, Japan;* [12]*Harvard Center for Biomedical Informatics, Boston, MA, USA*

Paper #72 — 3316611
5:24 pm - 5:36 pm

CLINICAL TRIALS FOR MPNST: LESSONS LEARNED

AeRang Kim, MD, PhD
Children's National Medical Center, Washington, DC, USA

Paper #73 — 3317570
5:36 pm - 5:48 pm

CURRENT STATUS OF MANAGEMENT FOR NF1-MPNST IN JAPAN

Yoshihiro Nishida[1,2]; *Kunihiro Ikuta*[2,3]; *Maki Morikawa*[3]; *Norio Ozaki*[1,4]; *Hiroshi Urawaka*[5]; *Akira Kawai*[6]; *Takafumi Ueda*[7]; *Hideyuki Saya*[8]; *Naoki Ishiguro*[2]

[1]*Department of Rehabilitation Medicine, Nagoya University Hospital;* [2]*Department of Orthopaedic Surgery, Nagoya University Graduate School and School of Medicine;* [3]*Medical Genomics Center, Nagoya University Hospital;* [4]*Department of Psychiatry, Nagoya University Graduate School and School of Medicine;* [5]*Department of Medical Oncology, Nagoya University Graduate School and School of Medicine;* [6]*Department of Musculoskeletal Oncology, National Cancer Center Hospital;* [7]*Department of Orthopaedic Surgery, Osaka National Hospital;* [8]*Division of Gene Regulation, Institute for Advanced Medical Research, Keio University School of Medicine*

5:48 pm - 6:00 pm — Discussant: ***Yoshihiro Nishida***

6:00 pm - 6:30 pm — Members Business Meeting — *Kiku Ballroom*

6:30 pm — ADJOURN

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10:30 am - 12:00 pm

– SESSION 2 –

Novel Therapeutic Targets

Paper #01 3329872

TARGET: OSTEOSARCOMA

THE GENOMIC LANDSCAPE OF OSTEOSARCOMA: A TARGET REPORT

Ching C. Lau[1,2,3]*; Aaron Taylor*[1,3]*; Monika J.Y. Sun*[3]*; Alex Yu*[3]*; Jianhe Shen*[3]*; Lisa Teot*[4]*; Don Barkauskus*[5]*; Mark Krailo*[5]*; Richard Gorlick*[6]*; Timothy Triche*[7]*; Shintaro Iwata*[8,9]*; Miki Ohira*[8,10]*; Jay Wunder*[11]*; Irene Andrulis*[11]*; Silvia Regina Caminada de Toledo*[12]*; Antonio Sergio Petrilli*[12]*; Lisa Mirabello*[13]*; Sharon Savage*[13]*; Robert L. Walker*[13]*; Marbin Pineda*[13]*; Yuan Jiang*[13]*; Sven Bilke*[13]*; Jack Zhu*[13]*; Yonghong Wang*[13]*; Joshua Waterfall*[13]*; Chris T.K. Man*[3]*; Sean Davis*[13]*; Jaime M. Guidry Auvil*[13]*; Daniela S. Gerhard*[13]*; Paul Meltzer*[13]

[1]*The Jackson Laboratory for Genomic Medicine;* [2]*Connecticut Children's Medical Center* [3]*Texas Children's Hospital/ Baylor College of Medicin;* [4]*Boston Children's Hospital/Harvard Medical School;* [5]*Children's Oncology Group;* [6]*M.D. Anderson Cancer Center;* [7]*Children's Hospital Los Angeles/University of Southern California;* [8]*Chiba University;* [9]*National Cancer Center of Japan;* [10]*Saitama University;* [11]*Princess Margaret Hospital/University of Toronto;* [12]*Universidade Federal de Sao Paulo;* [13]*National Cancer Institute*

Osteosarcoma is the most common primary tumor in bone. As a result of many clinical trials since the 1970's, the prognosis of patients with localized disease has been substantially improved by the use of optimal neoadjuvant chemotherapy but remains much worse in patients with metastatic disease at diagnosis or recurrence. Therefore, the search for novel therapies is urgent. We conducted a genomic analysis study in the TARGET (Therapeutically Applicable Research to Generate Effective Therapy) consortium to identify novel biomarkers and therapeutic targets. Using 89 pretreatment cases as the discovery set and an additional 196 cases as the validation set, we generated data using multiple platforms including microarrays (gene expression, copy number, DNA methylation), quantitative PCR (microRNA) and next generation sequencing (RNA, whole exome, targeted exome, whole gene, whole genome) and telomere repeat C-circle analysis. Integrative analyses of these 285 cases demonstrates that osteosarcoma genomes are highly rearranged with numerous DNA breakpoints leading to complex copy number aberrations. Nearly all (>97%) cases have mutations or gene amplifications leading directly to loss of cell cycle control with *TP53* the most frequent (>90%) followed by *RB1*, *CDKN2A*, loss of function mutations and *CCNE1*, *CDK4*, and *MDM2* amplifications. In addition, mutations of other tumor suppressor genes notably *ATRX* and *PTEN* are frequent. Structural variants causing gene interruption or deletion are the major mechanism of gene inactivation with a smaller proportion of single nucleotide or small deletions. Similarly, proto-oncogenes are amplified and overexpressed as a result of genome rearrangements, but are seldom activated by small mutations. These amplified genes include *MYC*, *CCNE1*, *IGF1R*, and *CDK4*, which are candidate prognostic markers and therapeutic targets. There are also single and multi-gene signatures that show statistically significant correlations with both overall and progression free survival. *MYC* amplification is by far the strongest single gene prognostic predictor of poor survival in both localized and metastatic cases. In this presentation, we will present results of our final analyses.

Paper #02 3251212

GRACEFUL PROJECT: A GLOBAL COLLABORATION ON CIC-DUX4, BCOR-CCNB3, HIGH GRADE UNDIFFERENTIATED ROUND CELL SARCOMA (URCS)

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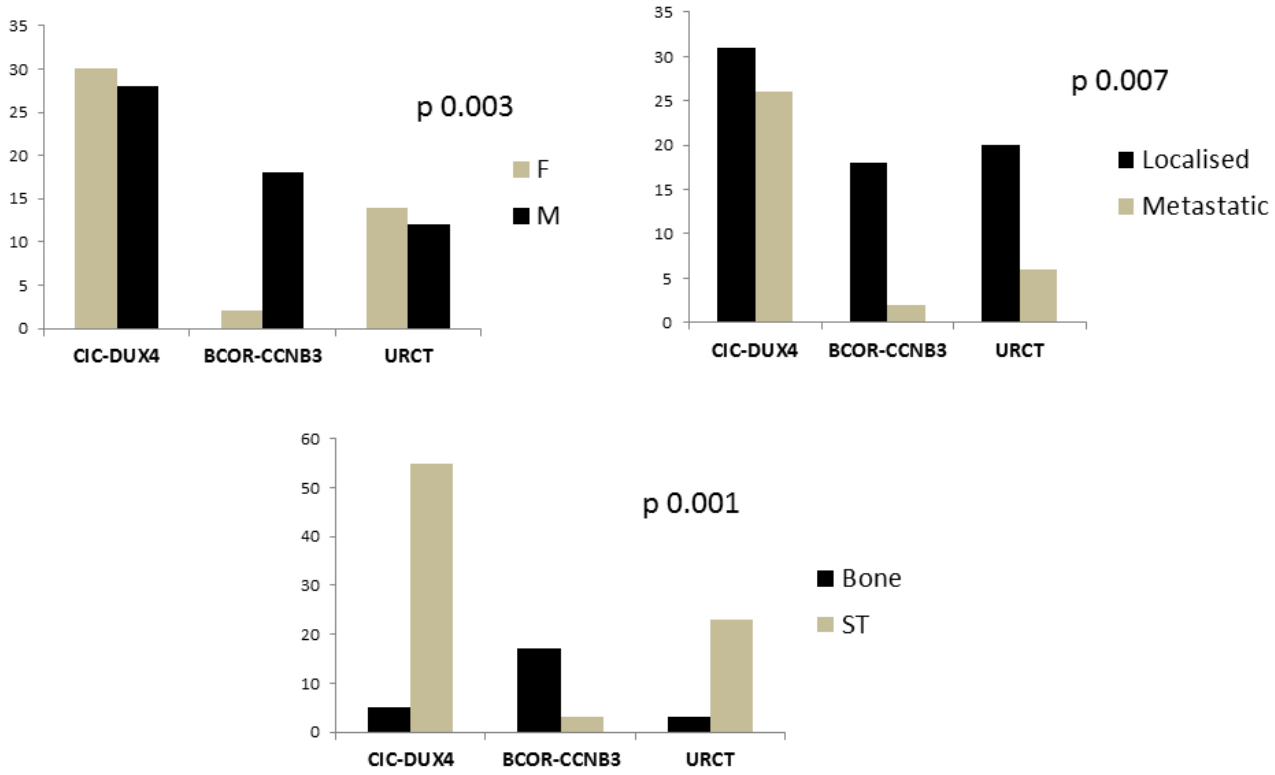
Objective: Undifferentiated round cell sarcomas (USRCSs) represent a diagnostic challenge. "Ewing-like" sarcomas, similar to Ewing sarcomas morphologically, carry different gene fusions, with *CIC-DUX4*, and *BCOR-CCNB3* being the most frequent (1.2 and 0.6% over 1500 cases; unpublished data). The optimal treatment for these ultra rare tumors is not known.

Methods: All cases with a diagnosis of URCS were reviewed for the purpose of the study, and *CIC-DUX4 / BCOR-CCNB3* translocations fusions were searched. Inclusion criteria for the present study were 1) a diagnosis of URCSs (negative for all Ewing translocations, *CIC-DUX4* and *BCOR-CCNB3*), a diagnosis of *CIC-DUX4* fusion-positive sarcoma, or a diagnosis of *BCOR-CCNB3* fusion-positive sarcoma; 2) clinical and outcome information available. Treatment, outcome and prognostic factors were examined.

Results: From 1983 to 2019 105 patients were treated in referral centers. Among them 59 (56%) patients had *CIC-DUX4* fusion (median age 30 years, 7-69 years), 20 (19%) *BCOR-CCNB3* (median age 16 years, 5-65 years), and 26 (25%) were URCSs (median age 42 years, 7-70 years). Seventy (67%) patients had localized disease and 35 (33%) had metastatic disease at the time of presentation: 30 (86%) to the lungs, (+ bone in 4; + lymph nodes in 2, + 3 visceral). 80 (76%) of the patients had soft tissue primary tumor (median size 8 cm, range 1-29 cm), while 25 (24%) had bone tumors. ECOG PS wa s 0 in 79 cases (83%), ≥1 in 16 (17%). Differences in presentation were observed amongst the specific entities, with higher prevalence for female gender, presence of metastases and soft tissue primary location in patients with *CIC-DUX4* tumors. In contrast, a male prevalence, bone presentation and a low rate of synchronous metastases were observed in patients with *BCOR-CCNB3* tumors (Figure 1). The local treatment was surgery in 55 (52%) patients, surgery + radiotherapy in 28 (27%) and radiotherapy in 13 (12%), whereas 7 patients did not undergo local treatment and in 2 it was not reported. No differences in local management were observed amongst the different entities. Chemotherapy was given to 89 patients: Ewing sarcoma regimen in 59 (66%), doxorubicin/ifosfamide (Doxo/IFO) in 17 (19%), osteosarcoma regimen in 5 (6%), not reported in 8. When chemotherapy was given preoperatively (62 cases), a good pathological response as defined by local pathologists was observed in 7/16 (44%) BCOR-CCN3 group (1/1 after Doxo/IFO, 5/7 after Ewing regimen, 1/4 after osteosarcoma regimen), and in 5/31 (16%) in the CIC-DUX4 group after Ewing regimen. In metastatic *CIX-DUX4* patients undergoing Ewing regimen the response rate (PR/CR) according to RECIST 1.1 was 8/18 (44%). With a median follow-up of 44 months (95%CI:35-54), the 3-year overall survival rate was 95% (95% CI 68- 99) in the *BCOR-CCNB3* group, 34% (95% CI 20-49) in *CIC-DUX4* (51% vs 15% in localized and metastatic cases), and 76% in URCS (95% CI 51-89; p=0.0001).

Conclusion: Patients with *BCOR-CCNB3* tumors usually respond to Ewing regimen and are of bone primary origin. In contrast, patients with *CIC-DUX4* tumors often present with metastatic soft-tissue tumors and have a poor pathologic response to chemotherapy. Molecular analysis is mandatory in all patients classified as URCS, with *CIC-DUX4* and *BCOR-CCNB3* presenting important differences in biological behaviour.

Figure 1. Clinical differences among CIC-DUX4, BCOR-CCNB3, URCT patients according to gender (F vs M), stage (localised vs metastatic) and primary tumor origin (bone vs soft tissues, ST)



Paper #03 3244146

TRANSCRIPTOMIC LANDSCAPE OF 79 HOMOGENOUSLY TREATED OSTEOSARCOMA TUMORS AT DIAGNOSIS REVEALS TUMOR CLONES AND MICROENVIRONMENT INTERPLAY ASSOCIATED WITH OSTEOSARCOMA PROGNOSIS

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Objective: Complex genetic aberrations and microenvironment (ME) in osteosarcoma (OTS) contributed to confuse observations at genetic level and have delayed introduction of new drugs, thus participated to the lack of survival improvement. To characterize at the transcriptomic level the genetic program modulation and the "tumor clones/microenvironment" interplay driving relapse and drug resistance across a homogeneously treated cohort of OTS.

Methods: ***Experiment.*** 79 OTS tumor samples at diagnosis issued from the first line OS2006 therapeutic trial are recapitulating the main clinical feature distribution of the whole cohort. ***Innovative bioinformatics approach.*** Bulk RNA-sequencing data from tumors represent total gene expression of tumor clones mixed up with numerous heterogeneous cells populating the ME. To study the transcriptomic landscape of tumor cells and their interaction with the ME, we decomposed RNA expression matrix by independent component analysis with ICASSO stabilization to extract 34 stable and independent gene components.

Results: ***Function of the independent components (IC).*** Functional analysis of genes populating the identified ICs revealed two kind of components, i) those recapitulating the genetic program/state of ME cell types and/or their interaction with tumor cells, ii) those specific to tumor clones with altered gene expression involving large chromosomic regions.

Identification of two OTS groups with different prognosis. Unsupervised analysis by hierarchical classification identified two distinct OTS groups at diagnosis with significant different overall survival (OS). With a median follow-up of 4.8 years, the 3y-OS was of 91.4% and 56.8% for G1 and G2 (p-val =0.00042), respectively. The G1 group identified tumors with favorable OS even after relapse. Multivariate analysis identified the G1/G2 stratification as the most contributing factor for OS.

G1/G2 stratification is associated with specific immune ME. Functional analysis by GSEA, differential expression analysis and gene network inference of genes populating the ICs contributing the most to the G1/G2 stratification, showed global enrichment for genes involved in the innate immune response in G1 tumors. In contrast, G2 was associated with angiogenesis, osteoclastic and adipogenic activity, often described as correlated with poor prognosis. Moreover, we observed specific tumor clones with altered gene expression involving large chromosomic regions. Integrating our results with CNV profiling (CGH array) we characterized specific CNVs significantly associated with each group.

Prognostic gene signature derived from G1/G2 stratification confirmed in an independent OTS cohort. Using a machine learning approach (glmnet), we defined a gene expression signature to predict G1/G2 tumors. To confirm the predictive power of our signature, we tested it on an independent cohort of 82 OTS tumors (https://ocg.cancer.gov/programs/target/projects/osteosarcoma), and compared their respective OS. As observed in the OS2006 cohort, G2 tumors from this cohort were significantly (p-val: 0.00039) associated with a worse prognosis than G1 tumors and therefore support the predictive power of the gene signature.

Conclusion: Taking advantage of machine learning algorithms, we defined several gene components describing tumor clones and OTS ME. Gene components stratify the cohort in good and poor prognostic tumors. Functional characterization of the components associates good prognostic tumors to innate immunity; poor prognostic tumors to angiogenic, osteoclastic, and adipogenic activities; and specific distinct CNVs to each group. Finally, we confirmed the predictive power of a minimal prognostic signature of 15 genes within independent cohort of 82 OTS tumors. This work might lead in near future to development of prognostic test and drive the setup of personalized therapy in OTS.

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Paper #04 3255224

IMPACT OF NEXT GENERATION SEQUENCING (NGS) ON DIAGNOSTIC AND THERAPEUTIC OPTIONS IN SOFT-TISSUE AND BONE SARCOMA (STSB)

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Objective: The utility of NGS in the clinical management of sarcoma pts was previously reported and we provide an update.

Methods: We retrospectively analyzed the NGS profile of patients who were sequenced using a panel of 405 cancer-related genes in DNA and 265 genes rearranged in RNA. Diagnostic and therapeutic implications of mutations (mut) were evaluated through published literature (OncoKb.org, Pubmed). Following IRB approval, we evaluated the clinical outcomes of pts who underwent NGS at MSKCC.

Results: From 2013–2018, we tested 7564 pts and had a median age of 52 yrs (<1-88), 52% females with 43 histologies, with sarcoma NOS (n = 1430) as the most frequent. Translocation-associated and genomically complex tumors were 23.2% and 76.8%, respectively. Pediatric and young adults (<30 yrs, P-AYA) were 21.9% of the cohort. Tumors with a mean purity of 56% were sequenced to a mean coverage of 704X with a mean allelic fraction of 0.41; 3829 rearrangements and 28,705 driver variants were found. Based on NGS, 11.7% had diagnostic errors and were most common in extra-skeletal chondrosarcoma, Ewing and synovial sarcoma. Tumor mutational burden (TMB) was 2.4/Mb (0–427) and cutoffs ≥15, ≥10 and ≥5 mut/Mb, was found in 2.8%, 3.8% and 12.9%, respectively. Angiosarcoma, UPS and MPNST harbored the highest frequency of TMB-H (≥15). TMB in P-AYA was significantly lower (1.6 vs. 2.4, $p < 0.0001$). Comparative genomics of osteosarcoma and UPS in P-AYA and older adults is ongoing. 36.6% of all patients had actionable alterations known to respond to an FDA approved or investigational drug. Novel genes in STSB include *AKT*, *ESR1*, *BRCA*, *NTRK*, *PTCH1*, *SMARCB1 and others.* Novel, actionable kinase fusions were noted in ALK, FGFR, NTRK1/2/3 and BRAF. Of the 107 MSKCC pts with clinical data, 60/107 (57%) had at least one TLA, of which 31 (30%) enrolled on a matched trial and 26 pts were ineligible or lacked access. Responses were seen with inhibitors to NTRK, IDH1, BRAF, TSC2, MDM2, SMARCB1, checkpoint and others.

Conclusion: Our data suggests that NGS has a significant impact in aiding diagnosis and selecting matched therapies in sarcoma.

Paper #05 3255373

TRACING SARCOMA EVOLUTION REVEALS CLONAL ORIGIN OF ADVANCED METASTASIS

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Duke University, Durham, NC, USA

Objective: Cellular heterogeneity is frequently observed in cancer, but the biological significance of the heterogeneous tumor clones is not well defined. The objective of this study is to investigate the dynamic interactions and functional consequences of different tumor clones during each stage of sarcomagenesis, from tumor progression, local recurrence to distant metastasis.

Methods: To prospectively trace tumor clones over the course of disease progression, we generated two complimentary lineage tracing mouse models of undifferentiated pleomorphic sarcoma (UPS). In the first model, we crossed the homozygous R26R-Confetti system with a Cre-inducible oncogenic *Kras*$^{LSL\text{-}G12D}$ allele and homozygous *p53*$^{f/f}$ alleles (*KPCC*). Following injection of Cre-expressing adenovirus into the gastrocnemius muscle, primary sarcomas permanently labeled with up to 8 distinct fluorescent reporters are formed at the injection site. To improve the clonal resolution, we utilized another lineage tracing method by leveraging genetic scars induced by CRISPR-Cas9. In this model, the Cre-inducible *Kras*^{G12D} allele is retained, and the Rosa26 locus expresses Cas9 endonuclease. Sarcomas are initiated by injecting adenovirus expressing Cre and sgRNA targeting *p53* (K-sgP53-Cas9). The genetic edits generated by CRISPR-Cas9 at the targeted region of *p53* can serve as barcodes marking independent tumor clones.

Results: Using complimentary multicolor reporter and CRISPR-Cas9 barcoding models, we traced clonal dynamics in an autochthonous mouse model of sarcoma. We show that primary tumor growth is associated with significant reduction in clonal heterogeneity over time. Local recurrence of the tumors following surgery or radiation therapy are driven by multiple clones. However, advanced distant metastasis from the primary tumors to the lungs is driven by clonal selection of a single metastatic clone (MC). Using RNA-seq and *in vivo* assays, we identified several candidate suppressors of metastasis, namely, *Rasd1*, *Reck*, and *Aldh1a2*. These genes are downregulated in the metastatic clones of the primary tumors prior to the formation of metastases. Over-expression of these putative suppressors of metastasis significantly impaired the ability of sarcoma cells to colonize the lungs.

Conclusion: Overall, by modeling clonal competition and selection, we describe in detail the clonal dynamics during each step of sarcoma progression, from tumor initiation, local recurrence after therapy, and to advanced metastasis. Advanced metastases are initiated from a single clone in the primary tumor, which offers the possibility of targeting specific clonal populations in a heterogeneous tumor to impede disease progression.

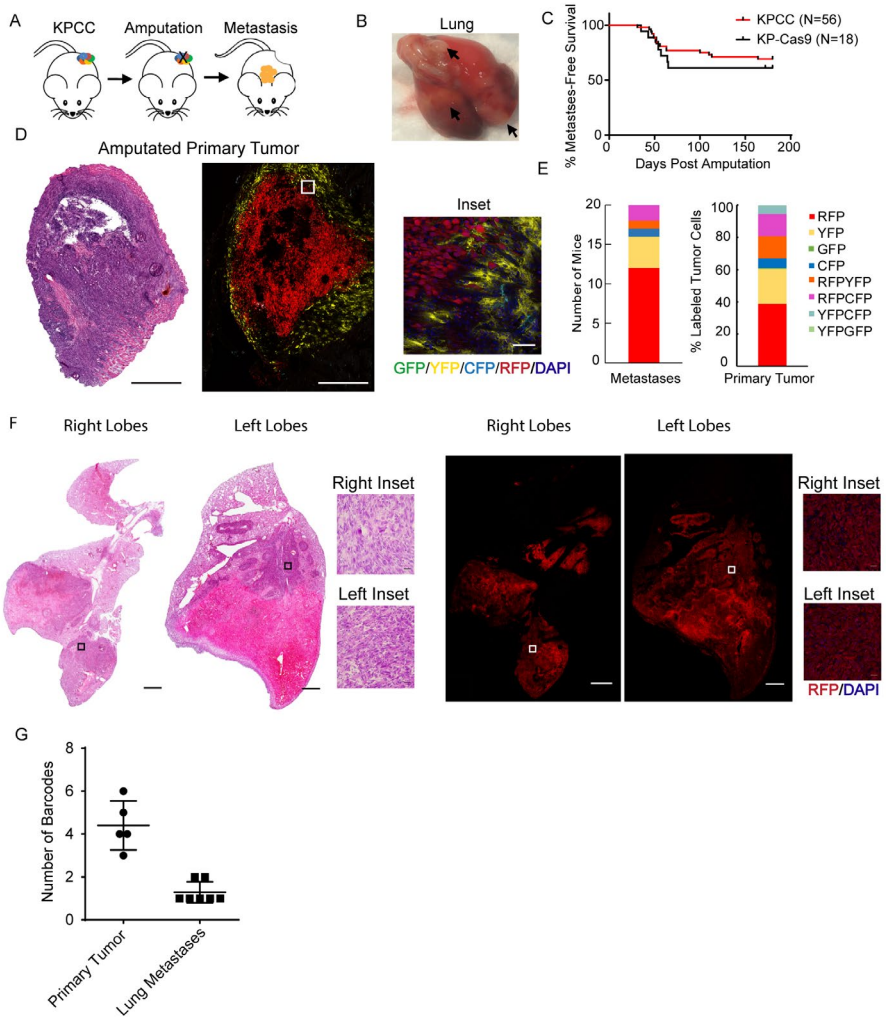

Figure 3

1:00 pm - 3:00 pm

– SESSION 3 –

Clinical Trials + Precision Medicine

Paper #06 3255423

MULTI-INSTITUTIONAL EUROPEAN SINGLE-ARM PHASE II TRIAL OF PAZOPANIB IN ADVANCED TYPICAL SOLITARY FIBROUS TUMORS: A COLLABORATIVE SPANISH (GEIS), ITALIAN (ISG), AND FRENCH (FSG) SARCOMA GROUPS STUDY

Josefina Cruz[2]; Nadia Hindi[1]; Sarah Dumont[3]; Nicolas Penel[4]; Pablo Luna[5]; Enrique de Alava[6]; Jean-Yves Blay[7]; Silvia Stacchiotti[8]; Paola Collini[8]; Andres Redondo[9]; Daniel Bernabeu[10]; Antonio López Pousa[11]; Giovanni Grignani[12]; David d. Moura[13]; Javier Martinez-Trufero[14]; Philippe Terrier[15]; Marie Karanian[7]; Axel Le Cesne[3]; Paolo Casali[8]; ***Javier Martin-Broto***[1]

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Objective: Solitary fibrous tumor (SFT) is a ubiquitous uncommon soft tissue tumor with a pronounced hemangiopericytoma-like vascular pattern, exhibiting rich VEGF (tumor and endothelial cells) and VEGFR1/2 (endothelial cells) expression. Pathologists distinguish typical SFT (T-SFT) and malignant SFT (M-SFT) based on mitosis (≤4 vs > 4), pleomorphism and/or necrosis. Yet, not clear boundaries are always seen between subtypes. We have recently published a European, multicentric, investigator-initiated, single-arm phase II trial exploring the activity of pazopanib (P) in M-SFT (Lancet Oncol Dec 2018). Here, we present the outcome of the T-SFT cohort of the same trial.

Methods: Most relevant inclusion criteria were: unresectable or metastatic, T-SFT (tumor tissue from diagnostic time) confirmed by central pathology review before accrual, with evidence of STAT6 overexpression by IHC, and/or rearrangement by FISH and/or NGS, ≥18 years, ECOG 0-2, progressive, measurable disease and no previous antiangiogenic agents. Main endpoint was response rate according to Choi criteria. Central radiological assessment was mandatory. P was administered at 800 mg/d continuously till progression or toxicity.

Results: From June 2014 to December 2018, 34 patients were enrolled in this cohort. The median age was 64 y (31-81). At baseline, ECOG 0/1/2 was distributed as 16/15/3; whereas, locally advanced/metastatic distribution was 11 (32%) and 23 (68%) respectively. At the time of the present analysis, 24 patients were deemed eligible and evaluable for response. Response rates according to local and central assessment were PR 6 (25%), SD 15 (62%), PD 3 (12%) and PR 12 (50%), SD 11 (46%), PD 1 (4%) respectively. With a median follow-up of 21 months, the median PFS following local and central assessment were 18.4 (6.6-30.1) and 9.8 (7.5-12.2) months respectively, both superior to that previously published in M-SFT cohort (5.57 m). The median of OS was 49.8 months. High tumor burden at baseline (> 116 mm), ECOG 1-2 vs 0, and PD by local or central response assessment showed significantly worse OS. Metastatic vs locally advanced patients had a similar outcome regarding OS.

Conclusion: Within this phase 2 study, pazopanib was confirmed to be active in T-SFT, with a longer progression-free survival (9.8 months) than observed in the M-SFT cohort (5.57 months). T-SFT showed a more indolent course, even in the metastatic/advanced setting, than M-SFT. Pazopanib seemed to improve the historical outcome obtained with chemotherapy in advanced SFT.

Paper #07 3253244

DEVELOPMENT AND VALIDATION OF A MOLECULAR SIGNATURE PREDICTIVE OF DURABLE CLINICAL BENEFIT FOLLOWING PAZOPANIB THERAPY IN ADVANCED SOFT TISSUE SARCOMA

Paul Huang[1]*; Alex Lee*[1]*; Chris Wilding*[1]*; Frank McCarthy*[1]*; Nafia Guljar*[1]*; Khin Thway*[2]*; Ben Fulton*[3]*; Sara Walker*[3]*; Alexandra Bell*[4]*; Fiona Graham*[4]*; Elaine MacDuff*[5]*; Wei Lin Goh*[6]*; Timothy Kwang Yong Tay*[7]*; Christina Messiou*[2]*; Richard Buus*[1]*; Cyril Fisher*[8]*; Mohamad Farid*[6]*; Jeff White*[3]*; Ian Judson*[2]*; Maggie Cheang*[1]*; Robin Jones*[2]
[1]Institute of Cancer Research, London, United Kingdom; [2]Royal Marsden Hospital, London, United Kingdom; [3]Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom; [4]NHS Greater Glasgow & Clyde Biorepository, Glasgow, United Kingdom; [5]Pathology, NHS Greater Glasgow & Clyde, Glasgow, United Kingdom; [6]National Cancer Centre Singapore, Singapore, Singapore; [7]Singapore General Hospital, Singapore, Singapore; [8]University Hospitals Birmingham, Birmingham, United Kingdom

Objective: Pazopanib (PZP) is a kinase inhibitor approved for the treatment of advanced soft tissue sarcoma (STS). There are no robust predictive biomarkers for PZP. The objective of this study is to identify and validate a predictive signature for the stratification of patients who are likely to achieve durable clinical benefit from PZP therapy.

Methods: Pre-PZP-treated formalin-fixed paraffin-embedded tumours from PZP-treated STS patients (RMH-SARC, n=38) with mixed histological subtypes were assessed for: (i) levels of PZP targets FGFR1 and PDGFRA by immunohistochemistry (IHC), (ii) TP53 mutational status by Sanger sequencing and (iii) 770 cancer-associated gene profiles using Nanostring. Biological subgroups were identified using consensus clustering. Gene Set Analysis and Significance Analysis of Microarrays (SAM) were used to identify genes and gene signatures whose expression were significantly associated with the biological subgroups (with a False Discovery Rate <5%).

A minimised gene set with the lowest cross-validation error was derived to recapitulate the biological subgroups; and a single sample predictor, Pazopanib Activity and Response in SARComa (PARSARC), was developed based on classification and nearest shrunken centroid methods. The performance of PARSARC was tested in an independent multi-centre cohort of patients with mixed histological subtypes (Global-SARC, n=30). The predictive value of PARSARC for progression-free (PFS) and overall survival (OS) in RMH-SARC and Global-SARC were evaluated using multivariable Cox regression analyses, adjusted for standard clinicopathological variables.

Results: Within RMH-SARC, 7 tumours were classified as low FGFR1 (F) and high PDGFRA (P) expression, defined as F-Lo/P-Hi. Nine tumours had TP53 mutation (TP53mut). Among the 22 TP53wt tumours which were not F-Lo/P-Hi, 3 molecular subgroups were identified based on distinct gene-expression profiles (Subgroups A n = 7, B n = 7, C n = 8). Subgroup B was enriched for leiomyosarcoma (LMS). An optimal 225-genes expression-based signature was developed to recapitulate these 5 distinct molecular subtypes (Subgroups A, B, C, F-Lo/P-Hi and TP53mut). Within the discovery set (RMH-SARC), Subgroup A had statistically significant superior PFS and OS (median (m) PFS 13 months (ms); mOS 34ms) compared to the rest of the cohort (mPFS 2.8ms; mOS 7ms). Subgroup A was significantly associated with better outcome compared to the rest of the cohort with hazard ratios (HR) for PFS of 0.22 (95% CI 0.07-0.63) and OS of 0.12 (95% CI 0.028-0.55) (Table 1).

In the independent multi-centre validation set (Global-SARC), each tumour was classified into one of the 5 molecular subtypes by the PARSARC classifier (Subgroup A n=11, B n=5, C n=6, F-Lo/P-Hi n=4 and TP53mut n=4), without knowledge of clinical outcome. As with the discovery cohort, all cases classified as subgroup B were LMS. Consistent with RMH-SARC, patients who were classified as subgroup A had significantly better clinical outcome (mPFS 12ms; mOS 33 ms) compared to the rest of the cohort (mPFS 3.5ms; mOS 5.3ms). The clinical value of Subgroup A was validated with HR for PFS of 0.28 (95% CI 0.11-0.73) and OS of 0.20 (95% CI 0.07-0.62) (Table 1).

Gene Set Analysis identified components of the Notch signalling pathway as upregulated in patients in Subgroup A when compared to the rest of cohort in both RMH-SARC and Global-SARC.

Conclusion: We have developed a 225-gene expression signature that identifies STS patients most likely to achieve durable benefit from PZP (Subgroup A), which has been validated in an independent multi-centre dataset. The PARSARC classifier has been incorporated into a web portal and will be made freely available for use by the sarcoma community.

Table 1

	N	Progression-Free Survival (PFS)				Overall Survival (OS)			
		Univariate		Multivariate*		Univariate		Multivariate*	
RMH-SARC		HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Subgroup A	7	0.22 (0.07-0.63)	0.005	0.13 (0.03-0.52)	0.004	0.12 (0.028-0.55)	0.006	0.069 (0.012-0.38)	0.002
Rest of the cohort	31	1	-	1	-	1	-	1	-
Global-SARC									
Subgroup A	11	0.28 (0.11-0.73)	0.009	0.08 (0.017-0.042)	0.002	0.20 (0.065-0.62)	0.005	0.0026 (0.00008-0.084)	<0.001
Rest of the cohort	19	1	-	1	-	1	-	1	-

*Adjusted for standard clinicopathological variables (age, histological subtype, grade and performance status).

Paper #08 3255734

VALIDATION OF GEISTRA SCORE: A PREDICTIVE TOOL OF TRABECTEDIN (TB) BENEFIT IN ADVANCED SOFT TISSUE SARCOMAS (ASTS), BASED ON GROWTH MODULATION INDEX (GMI). A RETROSPECTIVE REGISTRY-BASED ANALYSIS FROM SPANISH GROUP OF SARCOMA RESEARCH (GEIS)

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Objective: GMI has been described as a good predictive tool to evaluate the efficacy of Tb in ASTS . In a previous report we defined GEISTRA score in ASTS treated with Tb with 3 prognostic factors independently associated to GMI≥1.33 (L-Sarcoma subtype, metastatic free interval from initial diagnosis ≥ 8.1 months and Karnosfsky >80), showing a strong correlation with TTP or OR after Trabectedin (Tb). (Martinez-Trufero J, et al. J Clin Oncol 2017 35:15_suppl, 11070-11070) .In the present work, we aim to validate GEISTRA score in an independent validation series of additional 175 patients from the GEIS registry.

Methods: We have retrospectively analyzed ASTS patients from GEIS multicenter registry and their prognostic factors . All patients had been diagnosed of ASTS and treated with Tb in 24h continuous infusion schedule, from Jan 2007 to Jun 2016. All had previously received antracycline-based chemotherapy. We calculated GMI of T, outcome from T and from the previous line (T -1), and analyzed clinical profile of patients according with GMI in univariate and multivariate analysis (MA). We have previously reported a serie where we defined GEISTRA score (discovery serie) , and we have added a new serie of additional patients to validate that score (validation serie).

Results: We collected data from 379 patients (196 p discovery serie, and 183p validation) . All patients had previously received antracycline-based CT, 227 patients (59%) still when localized disease, and 152 p (40.1%) as first line in metastatic disease. Median follow-up of alive patients:75.1 m(95% CI 8.4-286.1 m). Median OS from initial diagnosis : 44.7m (95% CI 39.1-50.2 m). Median OS from metastatic diagnosis: 28.8 m (95% CI 25.3-32.3 m). Median TTP of Tb treatment : 3.8 m (95% CI 3.2-4.4) . Median OS of Tb treatment 12.6 m (95% CI 10.4-14.8m).GMI distribution of Tb treatment : 0 to 0,99: 217 p (57%), 1 to 1,33: 41p (11%), more than 1,33: 121p (32%). We found statistical association between GMI > 1,33 and OS, TTP from Tb treatment , and Tb response (Table 1) . PFS and OS analysis of both series showed independent significant prognostic value of GEISTRA score (Figure 1 and 2)

Conclusion: We have defined and validated GEISTRA score as a useful tool to better select which patients with ASTS are the best candidates to be treated with Tb.

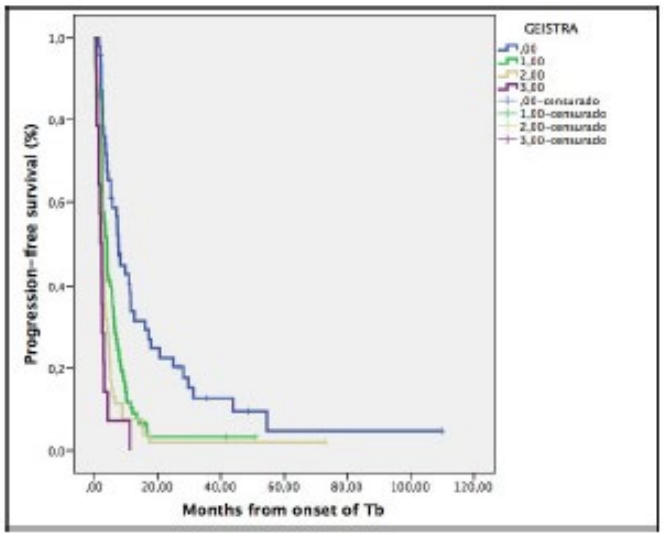
Relation Between GMI and Survival End-points

	Median OS from initial diagnosis (95%CI)	p	Median OS from Metastatic disease	p	Median TTP from Tb treatment	p
GMI						
- 0-1.33	38.1 (33.5-42.7)	<0.001	25 (21.6-28.5)	<0.001	2.5 (2.3-2.8)	<0.001
>1.33	70.8 (57.2-84.3)		46.7 (34.8-58.6)		9.8 (7.7-11.9)	

OS: overall survival; TTP: time to progression, Tb : Trabectedin, GMI: Growth Modulation Index

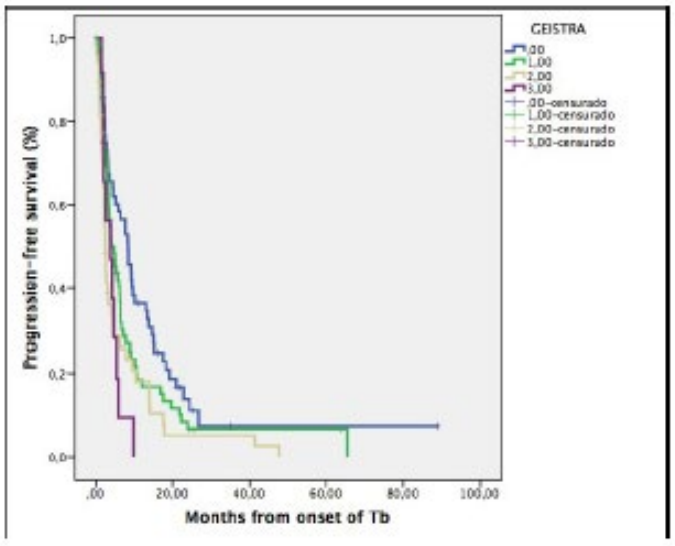
Figure 1. Time to progression curves according to GEISTRA score in Discovery serie (N: 196) and Validation serie (N: 183).

DISCOVERY SERIE



P<0.001

VALIDATION SERIE

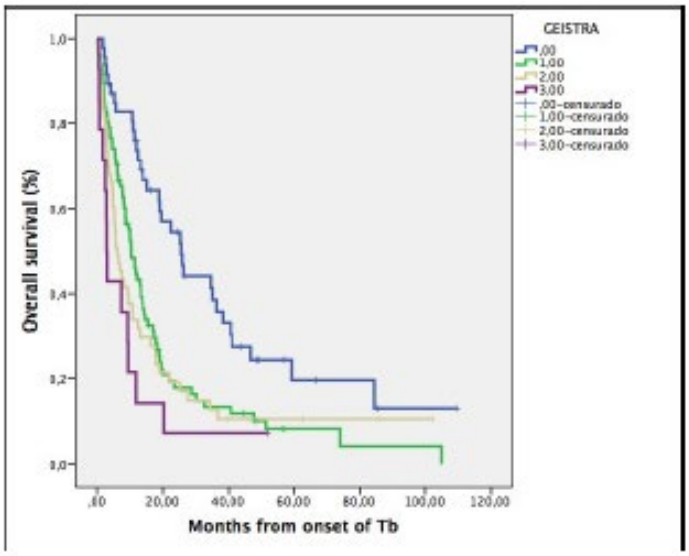


P= 0.004

Tb: Trabectedin.

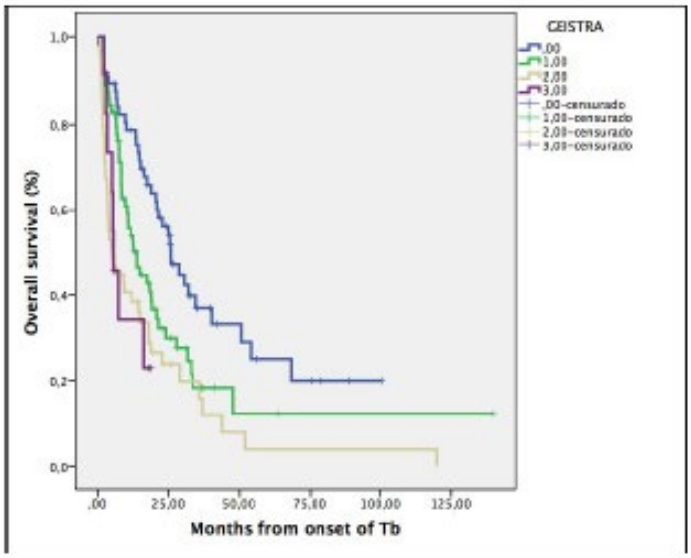
Figure 2. Overall survival curves according to GEISTRA score in Discovery serie (N: 196) and Validation serie (N: 183).

DISCOVERY SERIE



P<0.001

VALIDATION SERIE



P<0.001

Tb: Trabectedin.

Paper #09 3255286

NANOTECHNOLOGIES FOR CAPTURE AND RELEASE OF EWING SARCOMA-DERIVED CIRCULATING TUMOR CELLS

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Objective: Circulating tumor cells (CTCs) represent an ideal "liquid biopsy" source for well-preserved messenger RNA (mRNA) that can be used for molecular profiling of solid tumors. Existing CTC analysis platforms have been difficult to apply to sarcomas, in part, due to technical challenges in how to best target malignant cells for selective capture. Here, we describe initial tests and demonstrations of a system for CTC capture that leverages advances in nanomaterials and microfluidics to enable enumeration of CTCs derived from Ewing Sarcoma (EWS). We utilize CTC counts and copy numbers of EWSR1 gene rearrangements as metrics for device performance, which pave the way for translation of these nanotechnologies as non-invasive diagnostic solutions for guiding treatment intervention and monitoring disease progression in EWS patients.

Methods: Microfluidic devices with a serpentine channel configuration are fabricated *via* soft lithographic approaches. The channel roofs are lined with herringbone features that induce chaotic mixing behavior for directing cells into direct physical contact with the silicon (Si) nanostructures that line the channel bottoms, facilitating CTC capture. We employ biorthogonal click chemistries (*i.e.*,inverse-electron-demand Diels-Alder cycloadditionbetween tetrazine, Tz, and *trans*-cyclooctene, TCO) to mediate CTC capture and efficient enumeration within our microfluidic devices. These microfluidic "Click Chips" utilize Tz-moieties that are chemically tethered to Si nanowire substrates *via*silane chemistry. Prior to introduction into the microfluidic system, target cells are treated with a sarcoma-specific antibody targeting the LINGO1 surface protein conjugated to a TCO moiety.Interaction between the Tz-functionalized nanowires and TCO-grafted CTCs is facile and insensitive to biomolecules, water, and oxygen, leading to specific, rapid, and irreversible immobilization of the targeted cells. Introduction of a disulfide cleavage agent (*i.e.*,1,4–dithiothreitol, DTT) releases the CTCs from the silicon nanowires by cleaving the disulfide bond linking the Tz to the substrate. As background cells (*e.g.*, white blood cells) are captured nonspecifically, they are *not*released by freeing Tz-conjugates from the nanowires, reducing sample contamination.

Results: The expression of LINGO1 at the surface of EWS cell lines (A673) was confirmed *via*immunohistochemical analysis. We tested and verified the selective cell capture and release capabilities of the microfluidic Click Chips in simulated serum samples of human peripheral blood mononuclear cells spiked with LINGO1-expressing EWS cell lines. The samples are run through the Click Chip Devices with overall processing time for cell capture and release <25 min. Messenger RNA (mRNA) isolated from isolated CTCs was analyzed by digital droplet real time polymerase chain reaction (dd-RTPCR) analysis, confirming presence of EWSR gene fusions. In an initial pilot study, we demonstrate the capability to isolate extracellular vesicles (EVs) and CTCs from serum samples from an initial patient cohort (n=3) with metastatic EWS. We detect the presence EWS-FLI1 fusions in both captured EVs and CTCs *via* dd-RTPCR.

Conclusion: We demonstrated and are developing a nanotechnology-enabled solution for the selective capture of Ewing Sarcoma-derived CTCs. These technologies can be straightforwardly adapted for monitoring a wide range of other sarcomas and other pediatric malignancies. Ultimately, we will enable serial monitoring disease progression and response to treatment more rapidly and effectively to inform the management of pediatric cancer patients surpassing current diagnostic tools.

Paper #10 3254588

LAROTRECTINIB EFFICACY AND SAFETY IN PATIENTS WITH TRK FUSION SARCOMAS

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Objective: *NTRK* gene fusions are relatively rare oncogenic drivers in a diverse range of cancer types, including sarcomas, but are nearly pathognomonic in infantile fibrosarcoma. The highly selective FDA-approved TRK inhibitor larotrectinib has robust activity and is well tolerated in children and adults with TRK fusion cancer, irrespective of tumor type. We report updated efficacy and safety data for larotrectinib in patients with TRK fusion sarcomas.

Methods: Patients with TRK fusion sarcomas treated with larotrectinib were identified from three clinical trials (NCT02122913, NCT02576431, NCT02637687). Adult patients received larotrectinib 100 mg twice a day (BID; one patient in the phase I trial received 150 mg BID) and most pediatric patients received 100 mg/m^2 BID (maximum 100 mg BID). Disease status was investigator assessed every 8 weeks (RECIST v1.1).

Results: As of February 19, 2019, 69 patients with TRK fusion sarcomas had been treated: 6% (n=4) gastrointestinal stromal tumor, 42% (n=29) infantile fibrosarcoma, and 52% (n=36) other soft-tissue sarcomas (including spindle cell, inflammatory myofibroblastic tumor, malignant peripheral nerve sheath tumor, myopericytoma, epithelioid spindle, stromal tumor, synovial, lipofibromatosis, infantile myofibromatosis, adult fibrosarcoma, and not otherwise specified). Median age was 5.2 (range 0.1–61.0) years; 70% (n=48) of patients were pediatric (aged <18 years). Overall, 35% (n=24), 3% (n=2), and 61% (n=42) harbored *NTRK1*, *NTRK2*, and *NTRK3* gene fusions, respectively, with tumors from one patient unconfirmed. In total, 61% (n=42) of patients had previously received surgery, 72% (n=50) had prior systemic therapy, 19% (n=13) had received radiotherapy, and 13% (n=9) were treatment naive. The overall response rate in 68 patients evaluable for efficacy was 88% (n=60), with complete responses in 24% (n=16; two patients pending confirmation and three patients with pathologic complete response) and partial responses in 65% (n=44; seven patients pending confirmation). Best response of stable disease was reported in 7% (n=5) and progressive disease in 3% (two adults) of patients. In pediatric patients, the overall response rate was 94% (44/47) and in adult patients the response rate was 76% (16/21). At a median follow-up of 15.6 months, the overall median duration of response (range 1.6+ to 44.2+ months) had not been reached. Treatment duration ranged from 0.1 to 47.2+ months, with treatment ongoing in 68% (n=47) of patients at the time of data cut-off. Adverse events were mostly grade 1–2. Updated progression-free and overall survival results to be presented.

Conclusion: Larotrectinib treatment resulted in robust and durable responses with a favorable safety profile in adult and pediatric patients with TRK fusion sarcomas, regardless of histology. The biology accounting for the more favorable outcomes of pediatric patients warrants further investigation. These data strongly support the clinical importance of identifying *NTRK* gene fusions in patients with sarcomas.

Paper #11 3255999

ENTRECTINIB IN *NTRK* FUSION-POSITIVE SARCOMA: INTEGRATED ANALYSIS OF PATIENTS ENROLLED IN STARTRK-2, STARTRK-1 AND ALKA-372-001

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Objective: Neurotrophic receptor tyrosine kinase (*NTRK*) gene fusions in *NTRK1, NTRK2,* and *NTRK3* act as oncogenic drivers, and are potential therapeutic targets across a broad range of tumour types including sarcomas. Entrectinib is a CNS-active, potent inhibitor of TRKA/B/C and ROS1. Here we present integrated efficacy data from three trials of entrectinib in *NTRK* fusion-positive solid tumours focusing on patients with sarcomas, and safety data from the integrated safety population.

Methods: Patients with locally advanced/metastatic *NTRK*-fusion positive tumours (with or without baseline CNS disease) confirmed by nucleic acid-based methods were enrolled in three global phase 1/2 entrectinib trials at >150 sites in 15 countries (ALKA-372-001 [EudraCT 2012-000148-88], STARTRK-1 [NCT02097810], STARTRK-2 [NCT02568267]). The integrated efficacy evaluable population included TRK inhibitor-naïve adult patients with extracranial solid tumours harbouring a single, in frame *NTRK* fusion with measurable disease at baseline. Disease burden was assessed per blinded independent central review (BICR) using RECIST v1.1 after cycle 1 (4 weeks) then every 8 weeks thereafter. The primary endpoints were overall response rate (ORR) and duration of response (DOR) by BICR. Secondary endpoints included progression-free survival (PFS), overall survival (OS), and safety.

Results: The total efficacy-evaluable population comprised 54 adult patients with advanced/metastatic *NTRK*-fusion positive tumours; within this population there were 10 different tumour types and >19 histopathologies were identified. In the cohort of 13 patients with *NTRK*-fusion positive sarcomas, *NTRK1* and *NTRK3* gene fusions were detected (53.8% and 46.2%, respectively). Six subtypes of soft tissue sarcoma were identified: cervical adenosarcoma, dedifferentiated chondrosarcoma, endometrial stromal sarcoma, follicular dendritic cell sarcoma, gastrointestinal stromal tumour, and malignant peripheral nerve sheath tumour. Sarcoma 'not otherwise specified' was reported in 7 patients. The median age was 53 years (range 21-81 years), 46.2% of patients reported ≥2 prior systemic therapies, and all patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (61.5% and 38.5%, respectively). No patient had CNS metastases at baseline. ORR by BICR was 46.2% (95% CI 19.22-74.87), all were partial responses. Four patients (30.8%) had stable disease, 1 patient (7.7%) had disease progression, and 2 patients had missing/unevaluable data. Median (95% CI) DOR, PFS, and OS were: 10.3 (4.6-15.0), 11.0 (6.5-15.7), and 16.8 (10.6-20.9) months, respectively. Median treatment duration was 4.6 months. The safety population comprised 355 patients who received ≥1 dose of entrectinib, 60.5% of patients had grade 1 or 2 treatment-related adverse events (TRAEs), 27.6% had grade 3, 3.4% had grade 4, and there were no grade 5 TRAEs. The most frequently reported TRAEs were dysgeusia (41.4%), fatigue (27.9%), dizziness (25.4%) and constipation (23.7%). TRAEs led to dose reductions in 27.3%, interruptions in 25.4% and discontinuations in 3.9% of patients.

Conclusion: In this integrated analysis of global multicentre clinical trials, entrectinib was well tolerated and induced clinically meaningful, durable responses in patients with *NTRK*-fusion positive sarcomas.

Paper #12 3206452

WEEKLY *NAB*-SIROLIMUS IN PATIENTS WITH ADVANCED MALIGNANT PERIVASCULAR EPITHELIOID CELL TUMORS (PECOMA): RESULTS FROM AMPECT, AN OPEN-LABEL PHASE 2 REGISTRATION TRIAL WITH INDEPENDENT RADIOLOGY REVIEW

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Objective: Advanced malignant PEComa is a rare, aggressive sarcoma, with no approved treatment. Cytotoxic chemotherapies have limited benefit in this patient population. Case reports suggest that the PI3K/AKT/mTOR pathway is activated in PEComa and mTOR inhibition may be efficacious in this disease. ABI-009 is a novel albumin-bound intravenous mTOR inhibitor with increased tumor uptake, increased mTOR target suppression and distinct pharmacokinetic profile versus oral mTOR inhibitors. The AMPECT trial is the first prospective study in advanced malignant PEComa.

Methods: Patients with measurable disease and ECOG 0 or 1 received *nab*-sirolimus (100 mg/m^2 IV, weekly, 2/3 weeks) until progression or unacceptable toxicity. PEComa histology was confirmed centrally. Primary endpoint: overall response rate (ORR) by independent radiology review (IRR), assessed every 6 weeks (RECIST v1.1). Secondary endpoints: duration of response (DOR), progression-free-survival rate at 6 month (PFS6), median PFS and overall survival, and safety. Exploratory endpoints: investigator-assessed outcomes and mutational status. Sample size: based on an estimated ORR of 30% in 30 efficacy-evaluable patients, the lower bound of the 95% CI will exclude values less than 14.7%. The primary analysis was prospectively planned when all patients were treated ≥6 months.

Results: A total of 34 patients were treated. At the time of primary analysis (May 29, 2019), treatment was ongoing for 29% (10/34) patients. The most common primary site of tumors was the uterus (24%), pelvis (18%), retroperitoneum (18%), lung (12%), kidney (12%). 94% of patients had prior surgery and 21% had prior systemic therapy. Of the 34 enrolled pts, 29 (85%) had metastatic disease and 5 (15%) had locally advanced inoperable disease.

31 patients were evaluable for efficacy (ie, with centrally confirmed PEComa). The median time on treatment was 6.1 months (95% CI: 0.3, 28). The confirmed ORR by IRR was 39%, all partial responses (PR, 12/31, 95% CI: 21.8, 57.8), 52% stable disease (16/31, with 10/16 SD ≥12 weeks), and 10% progressive disease (PD 3/31); the disease control rate (CR + PR + SD ≥12 weeks) was 71% . One patient had an unconfirmed PR without subsequent scans and was assessed as SD ≥12 weeks. The majority of PRs (67%) were reached at the first post-baseline scan at week 6, with a median time to response of 1.4 months (95% CI: 1.3 to 2.8). The median DOR by independent review was not yet reached (range 4.2 to 27.7+ months), 75% (9/12) of PRs are ongoing, with 4 responders >1 year and 3 responders >2 year on therapy. Median PFS by IRR was 8.9 months (95% CI: 5.5; --) and PFS6 was 70%. Median OS was not reached, with 29 patients alive at the time of the primary analysis. One patient with locally advanced inoperable disease at study entry was able to undergo surgery after treatment for 6.9 months. Investigator-assessed confirmed responses were similar, with 42% ORR, 48% SD (10/15 SD ≥12 weeks), and 10% PD.

The most common (>30%) nonhematologic treatment-related AEs (TRAEs) of any grade were mucositis (79%), fatigue (59%), rash (56%), nausea (47%), diarrhea/weight loss (38% each), hyperglycemia (35%), and hypertriglyceridemia/hypercholesterolemia/decreased appetite (32% each). The most common (>30%) hematologic TRAEs were anemia (47%) and thrombocytopenia (32%). Pneumonitis (18%) was grade 1 or 2. The most common (>10%) grade 3 TRAEs were mucositis (18%), anemia (12%); No grade ≥4 TRAEs were observed. Mutational analysis was available for 25 patients and is reported separately.

Conclusion: The AMPECT study met its primary endpoint with an independently assessed ORR of 39%. This encouraging response rate along with durable responses, high rate of stable disease, and manageable toxicities suggested that *nab*-sirolimus is safe and effective in the treatment of advanced malignant PEComa and may represents an important new treatment option for these patients. NCT02494570

Paper #13 3250355

A PHASE 1 DOSE ESCALATION STUDY OF INTRAVENOUS TK216 IN PATIENTS WITH RELAPSED OR REFRACTORY EWING SARCOMA

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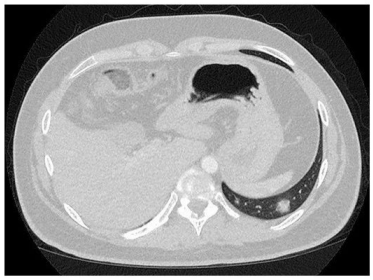
Objective: ES arises from a pathognomonic EWS-ets gene translocation and dysregulated mRNA splicing. These genetic defects result in the formation of fusion proteins, most commonly EWS-FLI1 and EWS-ERG, which have oncogenic transcription factor activity. Preclinical studies showed that tumor growth was inhibited after reduction of EWS-FLI1, yet pharmacologic targeting had been elusive. Toretsky et al. pursued an alternative approach by identifying a small molecule, YK-4-279, using surface plasmon resonance binding to full-length protein. YK-4-279 interferes with the requisite binding of EWS-FLI1 (or -ERG) to RNA-helicase A (RHA), thereby disrupting function and causing apoptosis. Our objective was to evaluate the impact of interference with RHA binding on advanced ES.

Methods: TK216, a more potent analog of (S)-YK-4-279, works by binding to EWS-FLI1 and blocking other proteins from interacting, including RHA. Enantiospecific inhibition of EWS-FLI1 with TK216 has been shown in transcription, growth, and splicing assays using ES cell lines and xenografts. We report preliminary results of a multi-institutional Phase 1 study of TK216 in patients with recurrent/refractory ES. The study enrolled patients >18 years in the first cohort, then >12 years, ≥10 years old in subsequent cohorts. The starting dose of TK216 was set at 1/10th of the STD10 value from preclinical studies, administered as a continuous intravenous infusion for seven days. We used a standard 3+3 enrollment scheme. The TK216 doses tested were 18, 36, 72, 144 and 288 mg/m^2/day for 7 days. After dose-limiting (DLT) hematopoietic toxicity was observed, TK216 was tested at 220 mg/m^2/day for 7 days (no DLT) and 10 days (DLT), followed by 200 mg/ m^2/day for 10 days. The only DLTs observed were hematopoietic. RECIST v1.1 was used to assess tumor response. There were no responses in the first 8 cohorts. At the time of this abstract submission, cohort 9 was actively enrolling at a TK216 dose of 200 mg/m^2/day for 14 days. Patients who received >144 mg/m^2/day achieved serum drug concentrations of TK216 that were greater than or equal to the concentrations observed to suppress tumor growth in preclinical models.

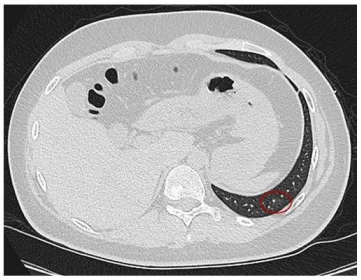
Results: A 19-year-old patient in cohort 9 had a partial response. The patient had multiple pulmonary metastases at initial diagnosis and was treated with conventional therapy: cycles of cyclophosphamide/doxorubicin/vincristine alternating with cycles of ifosfamide/etoposide, local control with surgery, postoperative radiation therapy (RT), and whole lung RT. Five months after completion of primary therapy, he developed recurrent pulmonary nodules and began irinotecan/temozolomide and achieved disease stabilization for 13 cycles; 3rd and 4th-line regimens included pazopanib and bevacizumab. Following radiographic progression of multiple pulmonary nodules over several months—documented by serial CT scans of the chest—the patient began treatment with TK216. After two cycles of TK216 at 200 mg/m^2/day with 14-day continuous infusion, restaging demonstrated almost complete resolution of the pulmonary nodules. Repeat imaging after 2 additional cycles showed sustained response. The patient experienced no treatment-related toxicity.

Conclusion: This outcome, in a first-in-human study of an agent targeting the EWS-ets fusion protein, demonstrates the feasibility of this strategy to reverse ES tumor growth. The trial is ongoing to study if the TK216 infusion can be safely extended beyond 14 days, to explore synergy between TK216 and vincristine, and to determine the response rate in an expansion cohort.

- LLL nodule 2/22/2019 13 mm target lesion



- LLL nodule 4/30/2019 resolved



3:30 pm - 5:30 pm

– SESSION 4 –

Bone Sarcomas

Paper #14 3229546

TRAINED AND TESTED DECISION TREE OF RADIOGRAPHIC PARAMETERS RELIABLY PREDICTS ASEPTIC FAILURE OF COMPRESSIVE OSSEOINTEGRATION ENDOPROSTHESES

Lindsay Parlee[1]; Yee-Cheen Doung[1]; James Hayden[1]; Ryland Kagan[1]; ***Kenneth R. Gundle, MD[2]***
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[2]Operative Care Division, Portland VA Medical Center, Portland, OR, USA

Objective: Compressive osseointegration fixation is an alternative to intramedullary fixation for endoprosthetic reconstruction. Short-segment fixation helps preserve bone stock for future revision and may decrease the rate of aseptic mechanical failure caused by stress shielding. A continuous force across the bone-implant interface induce bone implant integration and stable fixation. Due to this unique mode of fixation, aseptic mechanical failure inevitably presents different than stemmed implants radiographically. Thus, the radiographic parameters used to assess other forms of endoprosthetic reconstruction may be insufficient for identifying and predicting aseptic mechanical failure of compressive osseointegration fixation.

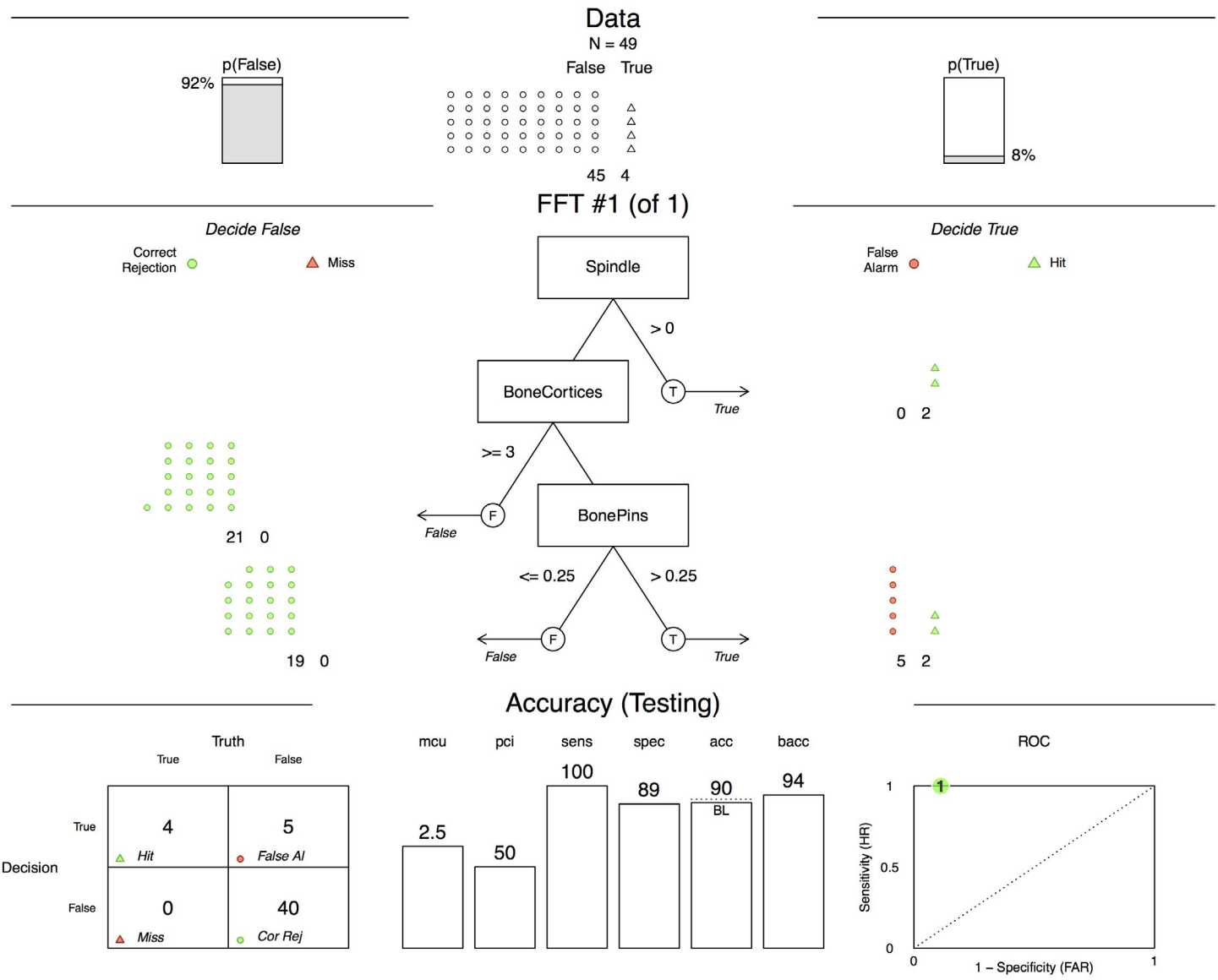
This study aimed to determine whether a reliable radiographic method could be developed to determine stable integration. Our first objective was to assess intra-rater and inter-rater reliability of radiographic measurements. Secondly, reliable measurements were used to train and then test a fast and frugal decision tree model based on separate radiographic cohorts.

Methods: In this two-phase study, separate cohorts of patient radiographs were evaluated to develop and validate (ie. train and test) a model to predict aseptic mechanical failure of the Compress (Biomet, Warsaw, IN, USA) in the lower extremity. On two occasions, separated by two months, 8 reviewers evaluated 11 radiographic parameters on 29 sets of radiographs obtained from the training cohort (n=132 implants in 109 patients). Sets consisting of anterior-posterior and lateral radiographs taken within 6 weeks postoperatively and at approximately 1-year follow up. A Fast and Frugal Tree (FFT) was constructed using radiographic parameters with substantial agreement: 1) SpindleDifference; 2) BoneCortices; and 3) BonePins.. The FFT model was tested using 49 sets of radiographs from the test cohort (n=87 implants in 82 patients). Three reviewers evaluated the sets a single time. The FFT predictions were compared to clinical outcomes and a confusion matrix generated (Fig. 1). In both phases of the study reviewers were blinded to the name, demographics, and outcomes of the implants for the patients.

Results: Six of 8 reviewers had non-significant intra-rater ICC for one or more parameters; all inter-rater ICC were highly reliable ($p<0.0001$). Parameters less reproducible by raters were not used as decision points in the FFT. The intra-rater and inter-rater reliability were highest for Spindle Difference (ICC=0.85; ICC=0.81) and Bone Cortices with Hypertrophy (ICC=0.79 ICC=0.68) thus they were used as decision points in the decision tree. The sensitivity and specificity of the training cohort were 100% and 87% respectively. When applied to the testing cohort, the FFT demonstrated 100% sensitivity and 89% specificity (Fig. 1). In the training cohort, it was also found that that when there was an observable change in spindle to anchor plug distance, this always indicated failure. Although the distance from the spindle to anchor plug signified failure, this measurement alone was not sensitive.

Conclusion: Radiographic parameters used alone do not reliably predict aseptic mechanical failure of compressive osseointegration endoprostheses. However, when radiographic parameters are assessed systematically with a fast and frugal decision tree, aseptic failure of compressive osseointegration endoprostheses can be predicted with high sensitivity and specificity.

Our model indicates that if the spindle is stable (has not changed height) and at least 3 cortices have bone hypertrophy, then stable osseointegration has occurred. However, failure is predicted in the absence of bone hypertrophy at the implant interface if the pin sites show hypertrophy. The modal trained and tested in our study can serve as a useful tool for clinicians as they follow patients with compressive osseointegration implants.


Data
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False True
45 4
p(False)
92%
p(True)
8%
FFT #1 (of 1)
Spindle
> 0
BoneCortices
T
True
>= 3
F
False
BonePins
<= 0.25
> 0.25
F
False
T
True
Decide False
Correct Rejection
Miss
21 0
19 0
Decide True
False Alarm
Hit
0 2
5 2
Accuracy (Testing)
Truth
True
False
True
False
Decision
4
Hit
5
False Al
0
Miss
40
Cor Rej
mcu
pci
sens
spec
acc
bacc
2.5
50
100
89
90
BL
94
ROC
Sensitivity (HR)
1 – Specificity (FAR)
0
0.5
1
1

Paper #15 3256557

NAVIGATED EXTREMITY SARCOMA RESECTION: ACCURACY AND REPRODUCIBILITY USING A NOVEL FLUOROSCOPY-BASED REGISTRATION TECHNIQUE FOR JOINT-SPARING BONE CUTS

Ibrahim S. Alshaygy; *Jean-Camille Mattei; Georges Basile; Anthony Griffin; Xun Lin; Peter Ferguson; Jay Wunder*
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Objective: We hypothesized that the accuracy of navigated bone cuts using 2D fluoroscopy image registration would be superior to un-navigated bone cuts in simulated Sawbones tumor models, and comparable to bone cuts made using a CT-guided navigation system.

Methods: Using a novel fluoscopy-based navigation system with a 3D planning tool, we made realistic extremity joint sparing bone cuts in custom Sawbones tumor models derived from cross-sectional imaging of real patient periarticular surface bone sarcomas. The navigation system includes commercially-available devices including a flat-panel mobile C-Arm (Philips), a real-time optical tool tracker (NDI Polaris), and in-house 3D visualization software. We developed a technique in which 2D fluoroscopy images taken at 0° and 90° with the mobile C-Arm were used to register the bone position to a pre-operative CT scan. Seven orthopedic oncologists performed 17 different navigated bone cuts (8 femur, 5 tibia, 4 humerus) in triplicate on three different Sawbones models identical to actual patient tumor scenarios using a navigated oscillating saw. In addition to tri-planar navigation, a 3D virtual view provided bone surface renderings, 3D representations of planar cutting tools, projection of cut planes on the inner table of the bone, and dynamic clipping planes. A post-resection CT scan was used to assess cut accuracy by measuring pitch, roll and entry point distance relative to each planned cut. These results were compared to a previous navigation study that assessed un-navigated and navigated bone cuts registered using intraoperative CT imaging rather than fluoroscopy as in this study.

Results: A total of 375 navigated bone cuts based on fluoroscopy-guided registration were analyzed. The mean distance error of the entry plane was 2.6 +/- 1.6 mm. The mean pitch and roll errors were 4.8°+/- 4.2° and 4.0°+/-3.1° respectively. A margin of 5mm between the target tumor volume and the planned cut resulted in a negative resection margin in more than 98% of osteotomies. 7 of 375 navigated cuts resulted in a positive margin resection.

Conclusion: The fluoroscopy-based navigation was superior to un-navigated cuts and comparable to navigated bone cuts using intra-operative CT registration. This could provide an accurate, reproducible and inexpensive method to improve upon intraoperative navigation using readily available fluoroscopy.

Paper #16 3235120

ROLE OF EMT TRANSCRIPTION FACTORS IN THE METASTATIC POTENTIAL OF OSTEOSARCOMA

Sana Mohiuddin, MBBS[1]*; Salah-Eddine Lamhamedi Cherradi*[2]*; Dhruva K. Mishra*[4]*; Kristi Pence*[4]*; Standhya Krishnan*[2]*; Brian A. Menegaz*[2]*; David McCall*[1]*; Alejandra R. Velasco*[2]*; Danh D. Truong*[2]*; Branko Cuglievan*[1]*; Amelia Vetter*[2]*; Eric R. Molina*[3]*; Min P. Kim*[4]*; Joseph A. Ludwig*[2]

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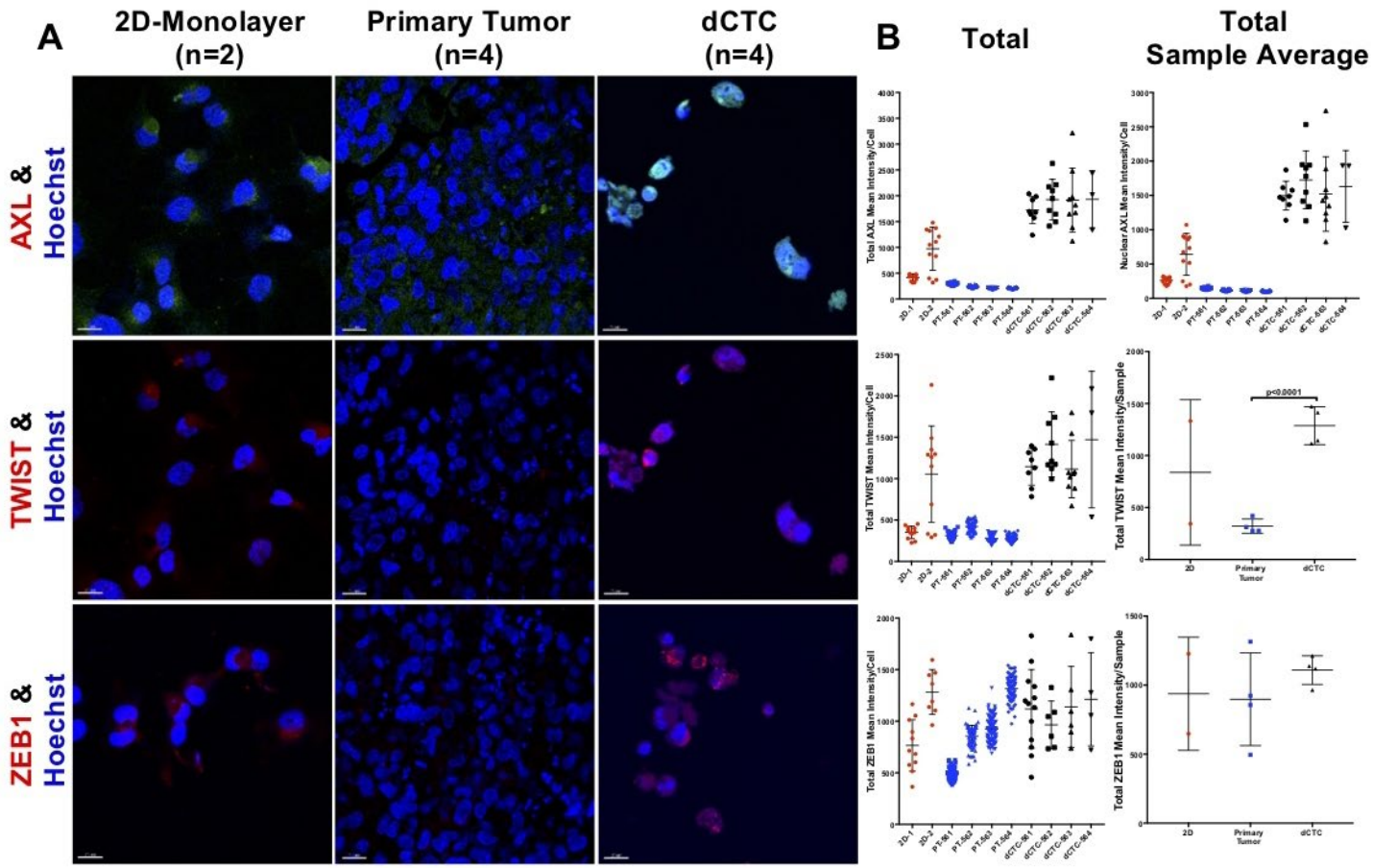
Objective: Osteosarcoma (OS) is a very aggressive bone tumor with high metastatic potential, and also the most common bone tumor to affect children and adolescents. The main culprit for mortality in OS is metastatic pulmonary disease, which originates from a highly selected group of tumor cells that acquire a heightened ability to migrate from the primary tumor, intravasate and survive in the bloodstream while circulating to remote sites. The early steps of this process are thought to be regulated by epithelial to mesenchymal translation (EMT)-related transcription factors (EMT-TFs) through an EMT like phenomenon which can surprisingly occur in non-epithelial malignancies such as glioma, leukemia, and sarcoma. To determine how EMT-TFs and other mediators of stemness contribute to the early steps of tumor metastasis, drug resistance and ultimately to the shedding of circulating tumor cells (CTC), we explored the presence and role of these EMT-TFs such as SNAIL, ZEB1, TWIST, and AXL in OS.

Methods: The acellularized rat lung (ACL) model used in our research provided a unique ability to isolate and characterize thousands of lab-derived circulating tumor cells (dCTCs) and compare them to the primary tumors formed in rat lung by injecting OS-D OS cell line. Expression of EMT-TFs (SNAIL, ZEB1, TWIST, AXL) in cells cultured in 2D monolayer, primary tumors (PT) formed in acellularized lung and the derived CTCs were evaluated by immune-fluorescence (IF) staining using confocal microscopy and quantified by IMARIS software. We also compared the level of expression of EMT-TFs in parental OS cell line MG63, and its derivative metastatic cell lines MG63.2 and MG63.3 by IF and western blotting. Circulating tumor cells were also isolated from OS patients for IF analysis of EMT-TFs and compared with their paired primary tumor.

Results: The dCTCs collected from ACL OS model showed substantially higher expression of SNAIL, TWIST and AXL, as well as considerably higher expression of ZEB1 compared with cells from 2D culture and PTs. Additionally, AXL showed significantly increased expression in metastatic cell lines MG63.2 and MG63.3 compared with the parental cell line MG63. ZEB1, TWIST or SNAIL did not replicate this difference in expression, most likely due to the phenotypic changes that cells undergo when grown on the 2D monolayer. Results from the ACL experiments were validated by comparing the expression of AXL, TWIST, and ZEB1 in CTCs collected from patients with a limited set of paired primary patient tumors.

Conclusion: An ACL model of the lung tumor microenvironment yielded an unparalleled opportunity to characterize lab-derived CTCs, using techniques that cannot readily be achieved from clinical specimens. Surprisingly, EMT-TFs were enriched in dCTCs, an important finding that suggests a small subset of OS cells—which are already high-grade—can become even more stem-like as they navigate the initial steps required of early metastasis. Though we have just begun to validate this result using paired tumor/CTC clinical samples, early evidence confirms our lab findings. The identification of EMT-TF in OS CTCs suggests that antagonists of AXL, ZEB, or TWIST might impede the earliest steps in the metastatic cascade.



Derived CTCs have heightened expression of EMT-TFs and markers of stemness. CTCs derived from the ACL model have significantly higher AXL, TWIST and ZEB1 as compared to respective primary tumor nodules and OS-D cells grown on 2D-monolayer. A. Immunofluorescence confocal microscopy staining. B. Scatter plots from quantification on IMARIS . PT = primary tumor; dCTC = derived CTC

Paper #17 3249338

VACCINATION TO ENHANCE THE ANTI-TUMOR ACTIVITY OF GD2 CHIMERIC ANTIGEN RECEPTOR EXPRESSING VZV-SPECIFIC T CELLS IN RELAPSED OSTEOSARCOMA

Sarah Whittle, MD[1]*; Natalia N. Lapteva*[2]*; Margaret Gilbert*[2]*; Mina Al-Sabbagh*[2]*; Bambi Grilley*[2]*; Carlos A. Ramos*[2]*; Bilal Omer*[2]*; Tao Wang*[2]*; Hao Liu*[2]*; Stephen Gottschalk*[3]*; Helen Heslop*[2]*; Cliona Rooney*[2]*; Lisa L. Wang*[1]
[1]Pediatrics, Baylor College of Medicine, Houston, TX, USA; [2]Cell and Gene Therapy, Baylor College of Medicine, Houston, TX, USA; [3]St. Jude Children's Research Hospital, Memphis, TN, USA

Objective: Chimeric antigen receptor (CAR) T cell therapy directed against solid tumors remains a clinical challenge due to multiple immune evasion mechanisms inhibiting the proliferation and persistence of adoptively transferred CAR-T cells. Most CARs are expressed on polyclonally activated T cells whose native antigen specificities are unknown. Our center has compared the use of Epstein-Barr virus (EBV)-specific T cells vs. CD3 and CD28 antibody-activated T-cells (ATCs), both modified with a CAR directed toward the GD2. EBV-specific GD2-CAR T cells circulated with higher frequency than GD2.CAR-ATCs but did not proliferate extensively. We hypothesized that the frequency and persistence of adoptively transferred *virus specific* T cells could be enhanced using a vaccine against the virus. We therefore generated varicella virus (VZV)-specific T cells to express a GD2 CAR, and these were administered in conjunction with the commercially available VZV vaccine (Zostavax) to patients with relapsed osteosarcoma, which is known to widely express GD2. The objective of this study was to determine the safety and efficacy of administering autologous VZV-specific T cells modified with a GD2. CAR (GD2.CAR.VZVSTs) in combination with VZV vaccine in patients with relapsed osteosarcoma.

Methods: We treated 8 patients with GD2.CAR.VZVSTs in escalating doses, from 1 x 10^6 to 1 x 10^8, in combination with varicella vaccination. We treated an additional 3 patients with lymphodepleting chemotherapy (fludarabine and cyclophosphamide), followed by GD2.CAR.VZVSTs in combination with varicella vaccination. We measured the frequency of VZV-specific T cells and transgene-positive cells in peripheral blood before and after infusion, using immunoassays and PCR. Clinical responses to therapy were assessed at 6 weeks after infusion.

Results: The therapy was found to be safe with no dose limiting toxicities observed. We observed increases in the frequency of VZVSTs and transgene positive cells after infusion and vaccination, correlating with increases in the frequency of T-cells specific for tumor antigens (epitope spreading). Two patients achieved stable disease after the 6-week observation period. Two patients received additional doses of GD2.CAR.VZVSTs, and one patient continues to receive cells with no additional therapy and remains with stable disease greater than 2 years after initial treatment.

Conclusion: The combination of GD2.CAR.VZVSTs and varicella vaccine is safe in patients with relapsed osteosarcoma. Further evaluation of this strategy in combination with lymphodepletion is ongoing, and combination with other immunomodulatory approaches to enhance expansion and persistence are warranted.

Paper #18 3256545

SOLITARY BONE METASTASES FROM SARCOMAS: IS THERE ANY PLACE FOR CURATIVE SURGERY?

Jean-Camille Mattei, MD, PhD; *Ibrahim S. Alshaygy; Georges Basile; Anthony Griffin; Peter Ferguson; Jay Wunder*
AP-HM, Aix-Marseille University, Marseille, France

Objective: 50% of high grade sarcomas will metastasize, mostly to the lungs. Resection of sarcoma lung oligo-metastases is mostly codified however there is no literature supporting curative surgical management of sarcomas bone metastases, which are rare. One study reported some success in locally-controlling bone metastases using radiofrequency ablation and literature is scarce about bone metastases history in sarcoma. Our goal was to describe bone metastases behaviour in sarcomas and to assess the impact of curative resection / intent-to treat management of solitary bone metastases from sarcomas on oncologic outcomes.

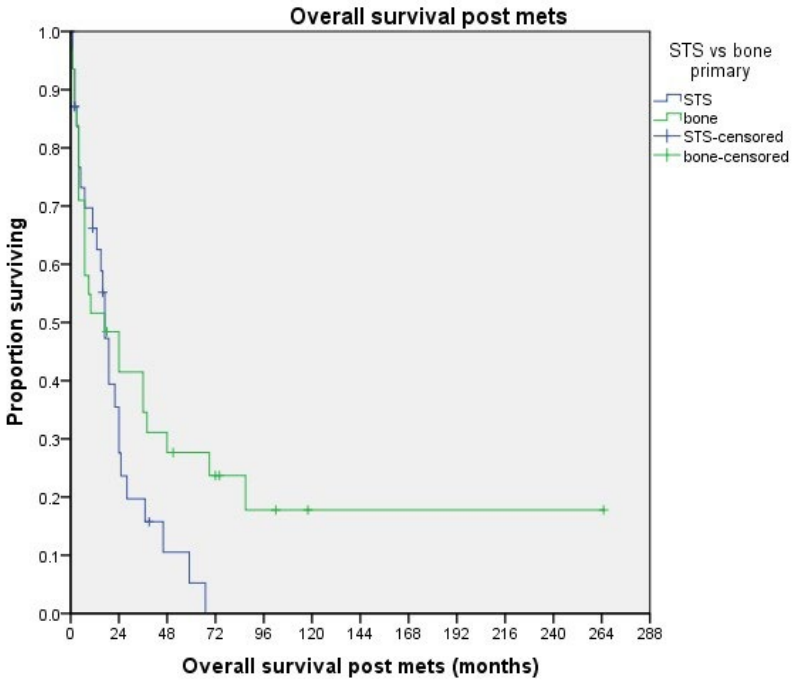
Methods: We examined our prospective database for all cases of solitary bone metastases from sarcoma treated with surgical wide resection between 1990 and 2016. Epidemiology, pathology, metastatic status upon diagnosis, type of first relapse, type of secondary relapses, their treatments, and oncological outcomes were assessed and compared between bone and soft tissue sarcomas, between operated patient and those who weren't and to literature.

Results: Over 1052 Primary bone sarcomas, 249 were metastatic patients, of which 85 patients presented bone metastases during their medical history (34% of metastatic patients). 37 had solitary bone metastasis as the first metastatic presentation (15%). There were more Osteosarcoma than Chondrosarcoma and Ewing histologies. Over 2713 Primary soft-tissue sarcomas, 707 were metastatic, of which 100 patients presented bone metastases during their medical history (14% of metastatic patients). 34 had solitary bone metastasis as the first metastatic presentation (5%). Undifferentiated Pleomorphic Sarcomas and Myxofibrosarcomas were the prevalent histological subtypes. Those 34 and 37 were retained for statistical analysis (71 patients total, STS and Bone sarcomas). Most of them occurred in Spine then Pelvis/Sacrum then femur. They were mostly Grade 3 (70%). 20% of patients were metastatic upon diagnosis (solitary metastasis) and 80% developed an isolated bone metastasis following resection of the primary tumour. 39 patients had surgery and 32 no surgery. Mean follow-up was 64 months. 88% underwent R0 resection of their primary bone metastasis, 6% were R1 and 6% R2 (intra-lesional curettage).

At the last follow-up,13% of patients were alive with no evidence of disease (ANED), 6% with evidence of disease (AWED) and 81% died of the disease (DOD). Median Overall survival was of 99 months [12-165] When primary tumour was a soft tissue sarcoma, DFS was of 25 months and MFS 43 months. In case of bone sarcoma, there were slightly better (31 and 50 months respectively), however with not significant in overall survival (Figure 1). **Patients who underwent wide excision of their solitary metastasis had a median survival of 36 months compared to 7 months in those who were non-operated. This difference was statistically significative (p<0,0001), Figure 2.**

Conclusion: OS was 19%, compared to 10 % usually reported in metastatic sarcomas for 10-year survival. Median DFS was better in solitary bone metastasis (28 vs 10 months in literature), so as median OS (99 months vs 15) compared with classically reported outcomes in metastatic sarcoma patients. 13% patients were alive with no evidence of the disease and an isolated bone metastasis from a bone sarcoma seems to have a better prognosis than from a STS. This result might be linked to a higher aggressiveness of sarcoma biology when a soft tissue tumour metastasizes in bone or to the role of chemotherapy sensitivity in bone sarcoma (though some of them were chondrosarcomas and non-responsive to chemotherapy).

As curative surgery for an isolated bone met from a sarcoma is associated with a low but definite possibility of long-term survival and as DFS, OS and median survival seemed to be improved by bone metastases wide excision and even if several recurrences occur, curative surgery with adjuvant therapies should be considered in selected patient.


Overall survival post mets
STS vs bone primary
STS
bone
STS-censored
bone-censored
Proportion surviving
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
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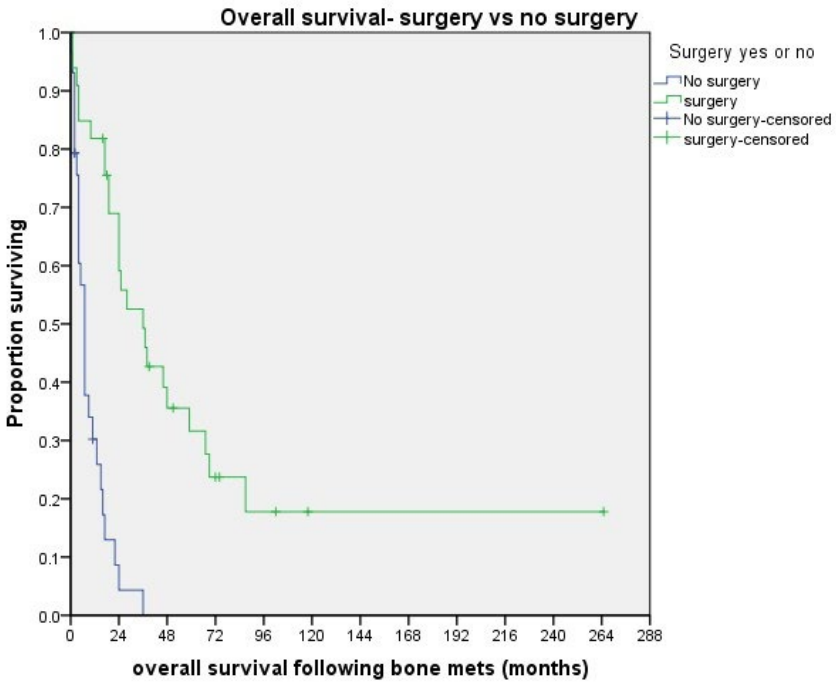
0
24
48
72
96
120
144
168
192
216
240
264
288
Overall survival post mets (months)


Overall survival- surgery vs no surgery
Surgery yes or no
No surgery
surgery
No surgery-censored
surgery-censored
Proportion surviving
1.0
0.9
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0.6
0.5
0.4
0.3
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168
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216
240
264
288
overall survival following bone mets (months)

Paper #19 3255440

COMPARISON OF MAP VERSUS MAPIE (POOR HISTOLOGIC RESPONSE) OR MAP PLUS PEGYLATED INTERFERON-α (GOOD HISTOLOGIC RESPONSE) IN NEWLY-DIAGNOSED RESECTABLE OSTEOSARCOMA: RESULTS FROM THE EURAMOS-1 TRIAL WITH LONG-TERM FOLLOW-UP

Katherine A. Janeway, MD[1]*; Fiona C. Ingleby*[2]*; Sigbjorn Smeland*[3]*; Jeremy Whelan*[4]*; Neyssa Marina*[5]*; Mark Bernstein*[6]*; Trude Butterfass-Bahloul*[7]*; Gabriele Calaminus*[8]*; Lor Randall*[9]*; Karen Sanders*[2]*; Babasola Popoola*[2]*; Mark Krailo*[10]*; Matthew R. Sydes*[2]*; Stefan Bielack*[11]

[1]Dana Farber Cancer Institute, Boston, MA, USA; [2]University College London, London, United Kingdom; [3]Lund University, Lund, Sweden; [4]University College London Hospitals, London, United Kingdom; [5]Five Prime Therapeutics, Inc, San Francisco, CA, USA; [6]University of Toronto, Toronto West Hospital, Toronto, ON, Canada; [7]Centre for Clinical Trials, University Hospital Muenster, Muenster, Germany; [8]UKB University of Bonn, Bonn, Germany; [9]UC Davis Health, Sacramento, CA, USA; [10]Keck School of Medicine, University of Southern California, Los Angeles, CA, USA; [11]Stuttgart Cancer Center, Olgahospital, Stuttgart, Germany

Objective: Three-drug chemotherapy with methotrexate, doxorubicin and cisplatin (MAP) has been an international standard for treatment of newly diagnosed osteosarcoma. EURAMOS-1 was a collaborative phase 3 randomized trial conducted by 4 cooperative groups to investigate risk-stratified, post-operative treatment for patients (pts) with newly-diagnosed resectable osteosarcoma, supplementing MAP with ifosfamide and etoposide (MAPIE) for pts with poor histologic response or followed by maintenance pegylated interferon-**α** (MAP-Ifn) for pts with good histologic response. We report long-term follow-up data from both randomisations.

Methods: EURAMOS-1 was a risk-stratified trial. Eligible consenting pts were randomised after surgery to continue standard MAP or to switch to the alternative approach. The trial primary objective was event-free survival (EFS). Good histologic response was defined as greater than 90% necrosis on pathologic evaluation of the resection specimen. Manuscripts reporting the primary objectives were previously published. This abstract reports on an analysis of outcomes after long-term follow-up planned for when ~147 deaths occurred in good responders. This threshold was met and data were frozen in Nov. 2018. Standard survival analysis methods were used.

Results: From 2006 to 2011, 2260 pts were registered when starting chemotherapy; 716 good response and 618 poor response pts were randomised. In the good response randomisation, median follow-up (FU) was 6.8 years (yr). With 215 EFS events and 141 deaths, there was no evidence of an improvement for MAP-Ifn in EFS (HR=0.85, 95%CI 0.64, 1.10; p=0.21) nor survival (HR=0.96, 95%CI 0.69, 1.33; p=0.80). In the poor response randomisation, median FU was 6.3 yr. With 328 EFS events and 215 deaths, there was no evidence of an improvement for MAPIE in EFS (HR=1.00, 95%CI 0.81, 1.24; p=0.99) nor survival (HR=1.06, 95%CI 0.81, 1.39; p=0.67). 12 good response and 20 poor response pts developed secondary malignancies (pending central review) with no difference for MAP-Ifn (HR=1.11, 95%CI 0.35, 3.50); however, the previously reported increase with MAPIE vs. MAP persists (HR=2.42, 95%CI 0.96, 6.34; p=0.061).

Conclusion: There was no evidence, with mature data from EURAMOS-1, that MAP-Ifn improves outcomes after osteosarcoma surgery for pts with a good response. Poor Ifn initiation rates after MAP (~25% never began Ifn therapy) may have resulted in the treatment effect being underestimated. There was also no evidence with mature data from EURAMOS-1 that MAPIE improves outcomes after osteosarcoma surgery for pts with a poor response to MAP. There is an increase in second malignancies following MAPIE which approaches statistical significance. Neither MAPIE nor MAP-Ifn was superior to MAP chemotherapy in the EURAMOS-1 trial in the initial planned analysis of EFS and in this planned analysis of EFS and OS with long-term follow-up data.

Paper #20 3228794

APATINIB PLUS CAMRELIZUMAB (SHR-1210) FOR UNRESECTABLE HIGH-GRADE OSTEOSARCOMA (APFAO) PROGRESSING AFTER CHEMOTHERAPY: A SINGLE ARM, OPEN-LABEL, PHASE 2 TRIAL

Lu Xie, MD[1]*; Jie Xu*[1]*; Wei Guo*[1]*; Jin Gu*[2]*; Xin Sun*[1]*; Kuisheng Liu*[1]*; Xiaodong Tang*[1]*; Kunkun Sun*[3]*; Danhua Shen*[3]*; Yuan Li*[4]
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Objective: Results of a previous study showed high objective response but short-term activity of apatinib in advanced osteosarcoma. We aimed to investigate the activity of apatinib in combination with camrelizumab in patients with inoperable high-grade osteosarcoma progressing after chemotherapy.

Methods: This open-label, phase 2 trial was conducted at Peking University People's Hospital. We enrolled patients (≥11 years old) with advanced osteosarcoma who progressed after chemotherapy. Patients received 500 mg apatinib orally once daily plus 200 mg camrelizumab by intravenous infusion every two weeks until disease progression or unacceptable toxicity. The primary end point was progression-free survival (PFS) at six months, which was based on RECIST, version 1.1. All analyses were performed on the intention-to-treatment population.

Results: We enrolled 43 patients between January 25th and September 4th 2018 of whom 41 patients were evaluable for efficacy. Eighteen (43.9%, 95%CI 28.5%, 60.3%) of 41 patients were progression free at six months and the 6-m PFS rate was 43.6% (95%CI 27.7%, 58.5%). Until final follow-up, the objective response rate was 22.0% (9/41). Additionally, the 4-m PFS rate was 62.5% (95%CI 45.7%, 75.5%), with a median PFS of 5.7 (95%CI 3.8, 6.9) months. The median OS has not yet been reached. There was no difference in PFS between different PD-L1 expression groups (p=0.491), with a PD-L1 positive rate of only 14.3% (4/28). Patients with pulmonary metastases tended to have a longer PFS in comparison to those with metastases in bones or other areas of the body (p=0.054). Toxic effects led to dose reductions, or short interruptions, or both in 24 (55.8%) of 43 patients and permanent discontinuation in four (9.3%) patients. There were no treatment-related deaths.

Conclusion: Although the combination of apatinib and camrelizumab seemed to prolong PFS in comparison to single agent apatinib in treating advanced osteosarcoma, it did not reach the prespecified target of 6-month PFS of 60% or greater. No significant survival benefit was observed in patients with tumors with higher PD-L1 expression. However, a longer follow-up period is required to determine the impact of this combination on overall survival.

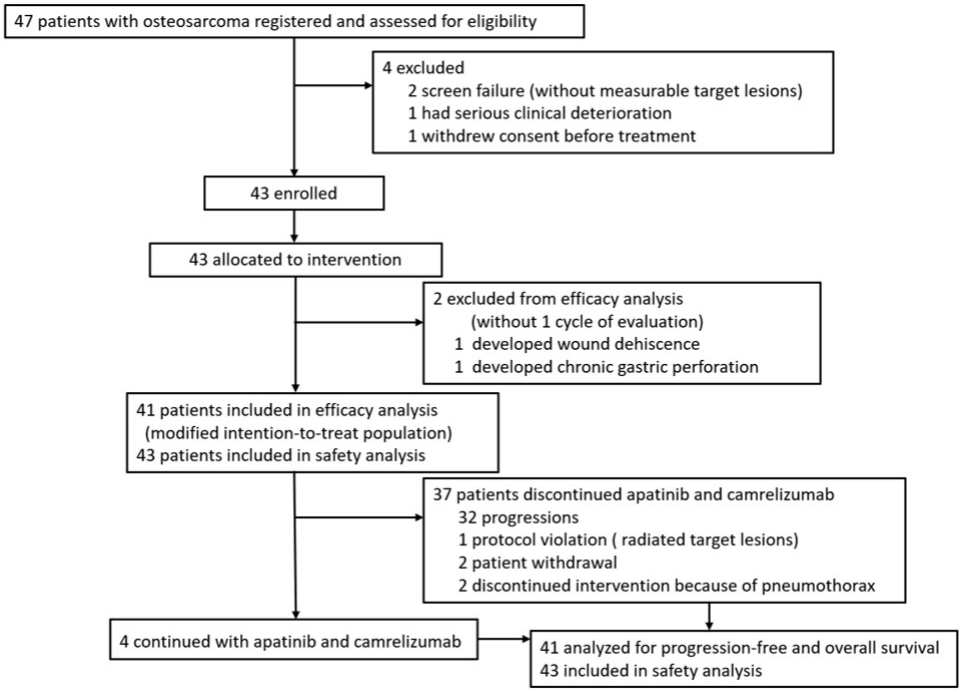


Table 1 Demographics

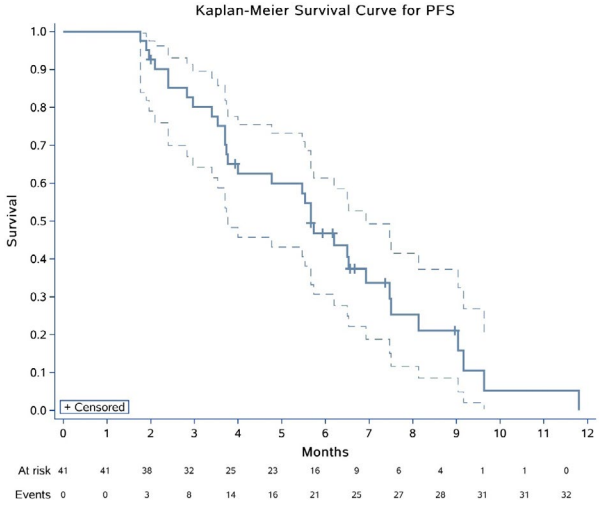
	For efficacy analysis (N=41)	p (Cox univariate analysis for PFS1)	Excluded from efficacy analysis (N=2)
Patients	41 (100.0%)		2 (100.0%)
Age2 (years) Median (Min, Max)	19 (11, 43)	0.82	(15, 62)
Gender		0.68	
Male	30 (73.2%)		1 (50.0%)
Female	11 (26.8%)		1 (50.0%)
ECOG performance status3 at enrollment		0.17	
0	34 (82.9%)		0 (0%)
1	7 (17.1%)		2 (100.0%)
Presence of metastasis		0.57	
No (locally advanced disease)	2 (4.9%)		0 (0%)
Yes	39 (95.1%)		2 (100.0%)
Sites of target and non-target lesions		0.004	
Lung only	18 (43.9%)		0 (0%)
Bone only	3 (7.3%)		0 (0%)
Lung and bone or viscera	20 (48.8%)		2 (100.0%)
Lines of previous chemotherapy including MAP/I5		0.76	
1	36 (87.8%)		1 (50.0%)
≥2	5 (12.2%)		1 (50.0%)
Primary tumor location		0.26	
Distal femur	13 (31.7%)		1 (50.0%)
Proximal tibia and fibula	12 (29.3%)		0 (0%)
Proximal humerus	8 (19.5%)		0 (0%)
Proximal femur	1 (2.4%)		0 (0%)
Axial skeleton	4 (9.8%)		1 (50.0%)
Others4	3 (7.3%)		0 (0%)
TSH9 elevated during treatment		0.01	
Yes	34 (82.9%)		N/A
No	7 (17.1%)		N/A
Baseline neutrophil lymphocyte ratio ≥3	41 (100.0%)	N/A	2 (100.0%)

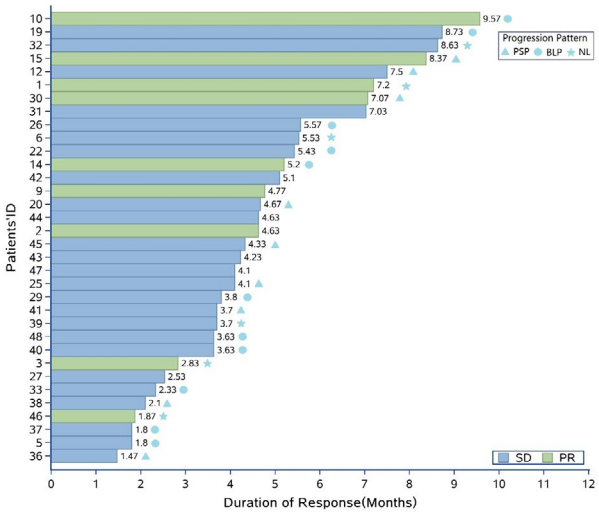
1PFS: progression-free survival; 2Groups defined according to Collins et al.: child (0-12 for males and 0-11 for females), adolescent (13-17 for males and 12-16 for females) and adult (≥18 for males and ≥17 for females); 3ECOG Abbreviation: Eastern Cooperative Oncology Group; 4Others including one polycentric osteosarcoma, one located at foot and one located at distal radius; 5MAP/I, including high-dose methotrexate, doxorubicin, cisplatin with or without ifosfamide. We defined these four agents as first-line chemotherapy; 6Alkaline phosphatase (ALP) cut-off value according to Bacci et al., (1993), defined as: cut-off: 2–10 y 350 IU/L; 10–13 y female 400 IU/L; 13–15 y male 500 IU/L; 20–50 y 100 IU/L; other childhood age 300 IU/L; 7NLR: neutrophil lymphocyte ratio; 8AE: Adverse Events; 9TSH: Thyroid Stimulating Hormone; 10N/A: data not available;

Table 2 Efficacy analysis

	Overall (n=43)
Confirmed objective response*	9 (20.9%)
Complete response	0
Partial response	9 (20.9%)
Stable disease ≥8 weeks	26 (60.5%)
Progressive disease	6 (14.0%)
ORR in evaluable patients	22.0% (9.3%, 34.6%)
DCR in evaluable patients	85.4% (70.8%, 94.4%)
CBR in evaluable patients	43.9% (28.5%, 60.3%)
Median time to response	1.8 (1.2~2.0)
Duration of response	
KM median (month)	5.2 (3.8~7.7)
Ongoing, n/N (%)	3/9 (33.3%)
Progression-free survival	
KM median	5.7 (3.8, 6.0)
4 months	62.5% (45,7%, 75.5%)
6 months	43.6% (27.7%, 58.5%)
Overall survival	
KM median (estimated)	13.7 (8.1, NR)
Patients' status at last follow-up	
AWD	27 (62.8%)
DOD	15 (34.9%)
Lost to follow-up	1 (2.3%)
Progression-free survival according to iRECIST	
KM median	7.9 (5.9, 10.0)
6 months	65.9% (51.4%, 80.4%)
Data are n (%); % (95% CI) or months (95% CI).	* Response was assessed in all enrolled patients.

ORR, overall response rate; DCR, disease control rate; CBR, clinical benefit rate; KM, Kaplan Meier; NR, not reached; AWD, alive with disease; DOD, died of disease; iRECIST, guidelines for response criteria for use in trials testing immune-therapeutics.





Paper #21 3255674

DEVELOPMENT AND VALIDATION OF A NOVEL SODIUM FLUORIDE-PET RESPONSE CRITERIA FOR SOLID TUMORS (NAFCIST) IN A PHASE 1 CLINICAL TRIAL OF ALPHA PARTICLE RADIUM 223 IN OSTEOSARCOMA

Vivek Subbiah, MD[1]*; Pete Anderson*[2]*; Eric Rohren*[3]*; Gregory Ravizzini*[4]*; Homer Macapinlac*[4]*; Kalevi Kairemo*[4]
[1]Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Cleveland Clinic, Cleveland, OH, USA; [3]Baylor, Houston, TX, USA; [4]Nuclear Medicine, MD Anderson Cancer, Houston, TX, USA

Objective: The development of osteosarcoma therapeutics has been challenging, in part because of the lack of appropriate criteria to evaluate responses. The current Response Evaluation Criteria in Solid Tumors (RECIST) are suboptimal for use in osteosarcoma because even responding tumors do not shrink. Response in osteosarcoma neoadjuvant therapy is instead evaluated by tumor necrosis from the resected specimens. Given the limitations of RECIST, criteria using PET/CT (PERCIST) were proposed using ^{18}F-FDG PET. However ^{18}F-FDG PET has limitations in bone response evaluation. 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: A 3+3 phase I, dose-escalation trial of $^{223}RaCl_2$ (50, 75, and 100 kBq/kg) was designed in patients with recurrent/metastatic osteosarcoma aged ≥15 years.Patients received 1-6 cycles of $^{223}RaCl_2$, 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.

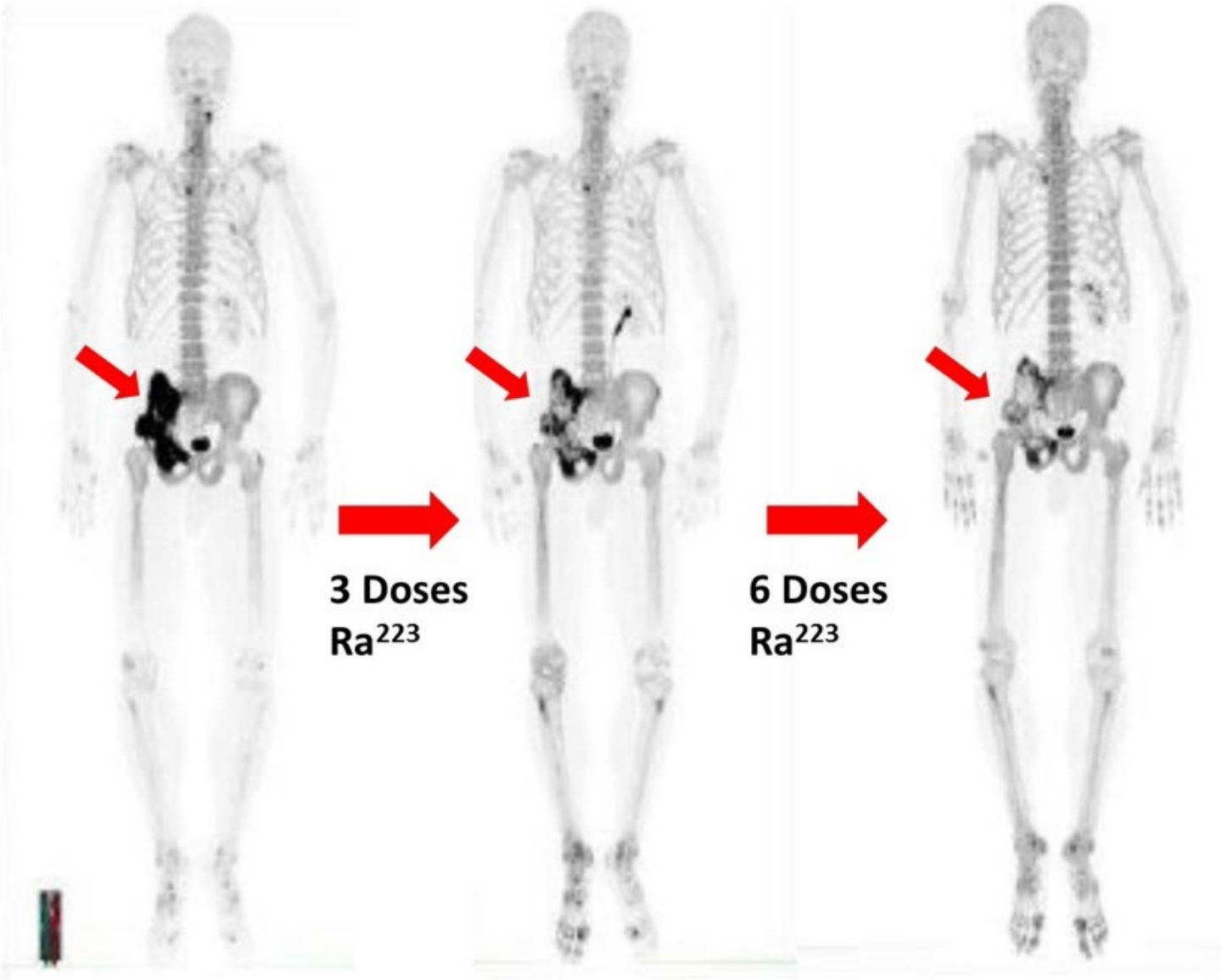
Results: Among 18 patients enrolled (including 15 males) aged 15-71 years, tumor locations included spine (*n* = 12, 67%), pelvis (*n* = 10, 56%), ribs (*n* = 9, 50%), extremity (*n* = 7, 39%), and skull (*n* = 2, 11%). Patients received 1-6 cycles of $^{223}RaCl_2$; cumulative doses were 6.84-57.81 MBq. NaF PET revealed more sites of metastases than did FDG PET. 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). Bronchopulmonary hemorrhage from Grade 3 thrombocytopenia (*N* = 1) was a DLT. The median overall survival time was 25 weeks.

Conclusion: Our results indicate that Na^{18}F-PET should be used in osteosarcoma staging. The first evaluation of the safety and efficacy of an alpha particle in high-risk osteosarcoma shows that the recommended phase II dose for $^{223}RaCl_2$ in osteosarcoma is 100 kBq/kg monthly (twice the dose approved for prostate cancer), with minimal hematologic toxicity, setting the stage for combination therapies. NAFCIST may be a promising criteria for high-risk osteosarcoma response evaluation, and correlates with survival. Further validation studies are needed.

Sodium fluoride-18 (Na18F) Positron Emission Tomography Response Criteria in Primary Bone Tumors (NAFCIST).

Response category	Criteria
Complete metabolic response	Normalization of all lesions (target and nontarget) to SUV less than mean skeletal SUV and equal to normal surrounding tissue SUV; verification with follow-up study in 1 month if anatomic criteria indicate disease progression
Partial metabolic response	>30% decrease in SUV peak ; verification with follow-up study if anatomic criteria indicate disease progression
Progressive metabolic disease	>30% increase in SUV peak; >75% increase in total Na18F burden of the five most active lesions; visible increase in extent of Na18F uptake; new lesions; verification with follow-up study if anatomic criteria indicate complete or partial response
Stable metabolic disease	Does not meet other criteria

aPrimary outcome determination is measured on the single most active lesion on each scan (not necessarily the same lesion). Secondary outcome determination is the summed activity of up to the five most intense lesions (no more than two lesions per organ). Abbreviations: SUV, standardized uptake value.


3 Doses
Ra223
6 Doses
Ra223

8:00 am - 8:30 am

– SESSION 5 –

Sarcoma of the Year: DSRCT

Paper #22 3251509

WHOLE ABDOMINOPELVIC RADIOTHERAPY AND RADIOIMMUNOTHERAPY AFTER COMPLETE RESECTION OF DESMOPLASTIC SMALL ROUND CELL TUMOR (DSRCT): MAJOR IMPACT ON SURVIVAL

Shakeel Modak, MD[1]*; James Saltsman*[1]*; Neeta Pandit-Taskar*[2]*; Emily Slotkin*[1]*; Todd Heaton*[1]*; Justin T. Gerstle*[1]*; Suzanne Wolden*[3]*; Michael P. LaQuaglia*[1]

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Objective: The prognosis for patients with DSRCT remains dismal despite aggressive multimodal therapy. Tumors are partially chemosensitive and complete resection (R1-resection) has been shown to improve outcome. However, most patients experience peritoneal relapse even after R1-resection. The role of post-resection treatment is unclear. We analyzed the effect of post-resection whole abdominopelvic radiotherapy (WAP-RT), intraperitoneal anti-B7H3 radioimmunotherapy with ^{131}I-omburtumab (IP-RIT) administered on a phase I study (NCT01099644), or both on survival in patients with DSRCT.

Methods: After approval from MSKCC Institutional Review Board we retrospectively analyzed records of patients with DSRCT undergoing surgery. R1-resection was defined as surgical removal of all radiologically evident disease within and outside the abdominopelvic cavity with ≤1cm^3 residual AND the absence of active liver disease. Progression-free (PFS) and overall survival (OS) from day of surgery were calculated using Kaplan Meier methods.

Results: Ninety-two patients treated at MSKCC between 2001-2018 underwent R-1 resection without prior progressive disease. Radiation records were available for review in 86/92 patients: these patients are the subjects of this report. Fifty-five patients received WAP-RT after R1-resection: 46 with IMRT and 5 with conventional radiotherapy. The type of WAP-RT was unknown in the remaining 4. Thirty-one patients did not receive radiotherapy due to patient/physician choice (n= 30) or very early relapse (n=1). All patients receiving radiotherapy were dosed at 3000cGy to the whole abdominopelvic region. Of the 55 patients receiving WAP-RT, 25 also received IP-RIT before WAP-RT. All (100%) patients who did not receive WAP-RT compared to 34/55 (62%) who received WAP-RT. PFS and OS for patients receiving WAP-RT was significantly better than those not receiving WAP-RT: median PFS was 11.5±2 vs 18.4±3 months (p <0.005) respectively; median OS was 34.2±7.5 and 54.1±9 months respectively (p=0.02). For patients treated after 2009 (when IP-RIT was first introduced), PFS and OS for those receiving IP-RIT+WAP-RT (n=25) was superior to those receiving WAP-RT alone (n=11) with a trend towards statistical significance (median PFS 18.8±7.5 vs 13.9±2.8 months respectively; median OS 36±7.3 vs 54.1±7 months respectively p=0.07 for PFS; p=0.09 for OS). Both therapies were well tolerated and administered on an outpatient basis.

Conclusion: WAP-RT after R1-resection significantly improved survival in patients with DSRCT. WAP-IMRT due to its improved toxicity profile should be considered standard-of-care in patients with DSRCT who can undergo R1-resection. IP-RIT with ^{131}I-omburtumab in addition to WAP-RIT appears to improve outcome further and the combination will be studied in a phase II trial anticipated to open in July 2019.

Paper #23 3254390

SINGLE-CELL RNA-SEQUENCING IDENTIFIES DISTINCT TUMOR CELL SUBPOPULATIONS AND IMMUNE INFILTRATE IN DESMOPLASTIC SMALL ROUND CELL TUMORS (DSRCT)

*Julien Vibert[1]; **Clémence Hénon**[2]; Nadège Gruel[1]; Léo Colmet-Daage[2]; Asuka Kawai-Kawashi[2]; Thomas Eychenne[2]; Joshua Waterfall[1]; Julien Adam[3]; Axel Le Cesne[4]; Olivier Mir[5]; Charles Honoré[6]; Olivier Delattre[1]; Sarah Watson[1]; Sophie Postel-Vinay[2]*

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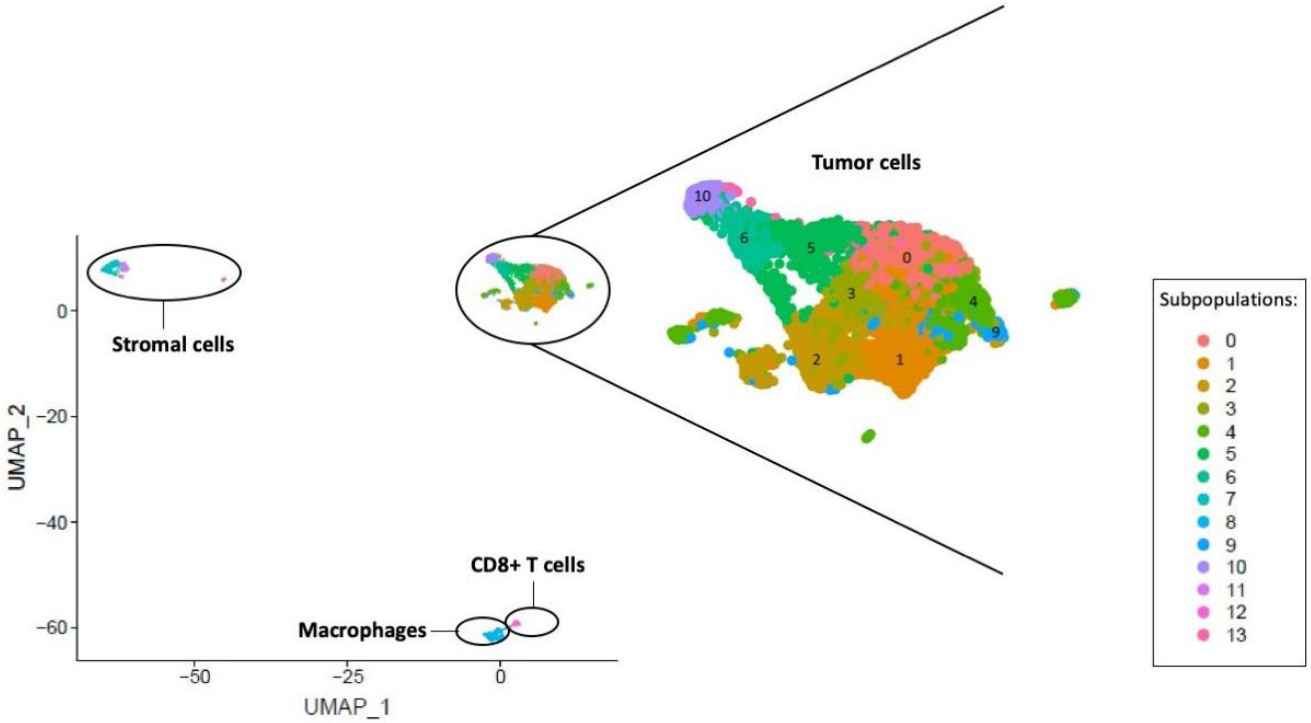
Objective: We aimed at evaluating transcriptional intra- and inter-tumor heterogeneity using single-cell RNA sequencing (scRNA-seq) in Desmoplastic Small Round Cell Tumors (DSRCT). DSRCT is characterized by a desmoplastic stromal reaction and homogeneous small round tumor cells with polyphenotypic differentiation. In order to investigate whether this immunophenotypic heterogeneity results from diverse transcriptional programs potentially driven by the chimeric transcription factor EWSR1-WT1, we performed scRNA-seq in multiple localizations of fresh DSRCT samples, aiming at identifying and characterizing tumor and non-tumor subpopulations, and conducting differential gene expression (DGE).

Methods: Fresh tumor material from 4 different synchronous localizations was profiled using the 3'-end counting 10X Genomic Chromium® assay. After quality control, we performed read mapping and expression quantification with CellRanger 3.0 software. Downstream analyses were performed with R package Seurat 3.0.0 (R v3.5.1). Filtering of cells was done using % of mitochondrial genes and number of features, before log-normalization of the data, detection of variable features and dimensional reduction with principal component analysis (PCA). Clustering of cell subpopulations was done using a k-nearest neighbors graph method based on the euclidean distance in PCA space followed by Louvain algorithm optimization. Visualization and exploration of the data was obtained with non-linear dimensional reduction techniques such as t-SNE and UMAP. Integrated analysis of the 4 samples was done using the novel integration procedure from Seurat 3.0.0. DGE analysis was performed using the Mann-Whitney-Wilcoxon test. We identified most differentially expressed genes based on p-value and log fold change, and used Gene Ontology (GO) terms to characterize each subpopulation. Finally, we performed gene set enrichment analysis of gene ontology (gseGO) on the most differentially expressed genes (absolute Z-score ≥ 3 with p-value <1% and GO term gene ratio >30%) using R package clusterProfiler.

Results: We analyzed 4 samples from 4 distinct abdominal localizations collected simultaneously during a cytoreductive surgery in a 25-year-old male previously treated by polychemotherapy and pazopanib. For each sample, the distribution of the total cell population was homogeneous and constituted of a majority of tumor cells (90%). One minor population (5%) overexpressed genes implicated in PDGF and IGF-II binding, PDGFRA receptor activity, and extracellular matrix formation, consistent with being stromal cells (SCs). Two other populations were consistently identified across samples: CD68 and CD163-expressing cells, corresponding to tumor-associated macrophages (TAMs) (4%), and CD3D-CD8A expressing cells, corresponding to cytotoxic lymphocytes (1%). Integrated analysis of tumor cells from the 4 samples identified 11 subpopulations. In particular: population 0 was characterized by overexpression of transcription factors such as AP-1, EGFR2 and NFκB; population 1 was enriched in genes involved in glucose and NADH metabolic processes; and population 2 overexpressed genes involved in immune response (immunoglobulin receptor, haptoglobin and antigen binding). gseGO analysis showed that some molecular function terms were enriched across at least one subpopulation of each sample (e.g. enhancer sequence-specific DNA binding), whereas others were specific to a unique subpopulation of a single sample, suggesting some degree of intratumoral heterogeneity.

Conclusion: ScRNA-seq provides new insights into the understanding of DSRCT intratumoral heterogeneity. Identification of activated oncogenic pathways and possibly immunosuppressive SCs and TAMs may represent therapeutic targets for this deadly disease. Integration with clinical, pathological, immunohistochemical, bulk RNA-seq and whole exome sequencing data is ongoing and will be available by the time of the congress, together with results from the analysis of a 2d patient.

UMAP representation of the cell subpopulations in the 4 samples after Seurat integrated clustering



8:30 am - 9:30 am

– SESSION 6 –

Multi-Disciplinary Care

Paper #24 3253497

A PHASE III RANDOMISED CONTROLLED TRIAL COMPARING HISTOTYPE-TAILORED NEOADJUVANT CHEMOTHERAPY AND STANDARD CHEMOTHERAPY IN PATIENTS WITH HIGH-RISK SOFT TISSUE SARCOMAS (ISG-1001): A SARCULATOR-BASED PROGNOSTIC RISK STRATIFICATION ANALYSIS

Sandro Pasquali[1]*; Emanuela Palmerini*[2]*; Vittorio Quagliuolo*[3]*; Javier Martin-Broto*[4]*; Antonio López Pousa*[5]*; Giovanni Grignani*[6]*; Antonella Brunello*[7]*; Jean-Yves Blay*[8]*; Oscar Tendero*[9]*; Roberto D. Beveridge*[10]*; Virginia Ferraresi*[11]*; Iwona Lugowska*[12]*; Domenico Merlo*[13]*; Valeria Fontana*[13]*; Emanuela Marchesi*[14]*; Davide M. Donati*[2]*; Elena Palassini*[1]*; Silvia Stacchiotti*[1]*; Silvia Baguè*[15]*; Jean M. Coindre*[16]*; Angelo Paolo Dei Tos*[17]*; Piero Picci*[14]*; Paolo Bruzzi*[13]*; Paolo Casali*[1]*; Alessandro Gronchi*[1]

[1]*Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy;* [2]*Istituto Ortopedico Rizzoli, Bologna, Italy;* [3]*Humanitas Cancer Centre, Rozzano, Italy;* [4]*Virgen del Rocío University Hospital, Valencia, Spain;* [5]*Hospital Sant Pau, Barcellona, Spain;* [6]*Candiolo Cancer Institute - FPO, IRCCS, Candiolo, Italy;* [7]*Veneto Institute of Oncology, Padova, Italy;* [8]*Centre Léon Bérard, Lyon, France;* [9]*Hospital Universitario Son Espases, Palma de Mallorca, Spain;* [10]*Hospital Universitario y Politécnico La Fe, Valencia, Spain;* [11]*istituto Nazionale Tumori Regina Elena, Rome, Italy;* [12]*Instytut im. Marii Sklodowskiej-Curie, Warsaw, Poland;* [13]*IST Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy;* [14]*Italian Sarcoma Group, Bologna, Italy;* [15]*Hospital de la Santa Creu i Sant Pau, Barcelona, Spain;* [16]*Institut Bergonie, Bordeaux, France;* [17]*University of Padova, Padova, Italy*

Objective: The ISG-STS 1001, which was a randomised controlled trial (RCT) compared 3 cycles of epirubicine plus ifosfamide (EI) and a histology-tailored (HT) neoadjuvant regimen in selected localized high-risk STS, did not meet the primary end-point of a disease-free survival (DFS) benefit for EI although this regimen resulted in a overall survival (OS) advantage. This study was aimed at determining if higher risk patients, as identified using the nomogram Sarculator, benefitted from EI compared to HT neoadjuvant chemotherapy.

Methods: The ISG-1001 compared EI and the following HT regimens: gemcitabine+docetaxel in undifferentiated pleomorphic sarcoma (UPS); trabectedin in high-grade myxoid liposarcoma (HG-MLPS); high-dose prolonged-infusion ifosfamide in synovial sarcoma (SS); etoposide+ifosfamide in malignant peripheral nerve sheath tumours (MPNST); gemcitabine+dacarbazine in leiomyosarcoma (LMS). Patients had localized high-risk (grade = 3; size ≥5 cm) sarcoma of extremities or trunk wall. In this retrospective analysis 10-yr predicted probability of overall survival (pr-OS) was estimated for each patient using the prognostic nomogram Sarculator. Patients were grouped into two categories of predicted pr-OS: high (pr-OS≥60%) and low (pr-OS<60%). OS and DFS were calculated.

Results: There were 125 (43.5%) and 162 (56.5%) patients in the pr-OS <60% and ≥60%, respectively. Majority of patients with HG-MLS (N=55/65, 84.6%) and UPS (N=63/97, 64.9%) had Pr-OS≥60%. Conversely, Pr-OS<60% was more common in synovial sarcoma (N=43/70, 61.4%), leiomyosarcoma (N=25/28, 89.3%). MPNST were similarly distributed across the two risk categories (pr-OS<60% 13/27, 48.1%; Pr-OS≥60% 14/27, 51.9%). After a median follow-up of 51.75 months, 5-yr DFS was 0.61 (95%CI 52.8-68.8) and 0.39 (95%CI 0.30-0.49) in patients with pr-OS ≥ 60% and <60% (HR=1.95, 95%CI 1.22-3.10, P=0.004). 5-yr OS was 0.78 (95%CI 0.71-0.85) and 0.66 (95%CI 0.55-0.77) in patients with pr-OS≥60% and <60% (HR=1.65, 95%CI 1.17-2.33, P=0.004). These prognostic differences were maintained also when study treatment arm was factored in the analysis (log-rank test for OS and DFS P=0.002 and P=0.009, respectively). Study participant with a low pr-OS (<60%) did better when treated with EI (5-yr OS=0.66; 95%CI 0.51-0.85; 5-yr DFS=0.45; 95%CI 0.33-0.62) compared to HT (5-yr OS=0.55, 95%CI 0.44-0.70; 5-yr DFS=0.34; 95%CI 0.23-0.50), resulting in a statistically significant benefit for OS (HR=1.91, 95%CI 1.00–3.70, P=0.044) but not for DFS (HR=1.51, 95%CI 0.75–3.05, P=0.246). Patients with a high pr-OS (≥60%) had also better OS in the EI arm (5-yr OS=0.81; 95%CI 0.72-0.91) compared to the HT arm (5-yr OS=0.74; 95%CI 0.64-0.87), though with a non-statistically effect (HR=1.47, 95%CI 0.92–2.37), but similar DFS (EI: 5-yr DFS=0.61;95%CI 0.51-0.73; HT: 5-yr DFS=0.60, 95%CI 0.49-0.73; HR=1.01, 95%CI 0.62–1.67).

Conclusion: Patients of the ISG-1001 with low predicted pr-OS (<60%, i.e. high-risk patients) had better DFS (5-yr difference: 11%) and OS (5-yr difference: 10%) when treated with neoadjuvant EI chemotherapy, although a statistical significance was detected only for OS. These results support anthracycline-based neoadjuvant when chemotherapy is used in primary high-risk localized STS and the prognostic stratification of such patient group with the prognostic nomogram Sarculator.

Paper #25 3253041

THERAPEUTIC RELEVANCE OF MOLECULAR SCREENING PROGRAM FOR PATIENTS WITH SARCOMA? ANALYSIS FROM THE PROFILER TRIAL

Armelle Dufresne; *Patrick Arnaud-Coffin; Mehdi Brahmi; Olivier Tredan; Pierre Meeus; Daniel Pissaloux; Valery Attignon; David Perol; Jean-Yves Blay*
Centre Leon Berard, Lyon, France

Objective: This study describes the frequency and distribution of actionable alterations identified in locally advanced or metastatic sarcomas, consider their use for guiding molecular targeted-agents in molecular tumor board, and reports the outcome of patients treated with molecular-based therapy (MBT).

Methods: Patients with metastatic or advanced sarcoma included in the ProfiLER ("Profilage Lyric Et Region") program, dedicated to "establish the genetic profile of patient's tumor for all types of advanced cancer" were studied. FFPE tumor specimen containing ≥10% of tumor cells were used to determine genetic molecular profiles by NGS using a 69 genes panel and CGH array. A weekly board reviewed NGS and aCGH reports to select relevant genomic molecular alterations (amplifications (gene copy number ≥6) or single nucleotide variant of oncogenes, homozygous deletions of tumor suppressor genes) guiding recommendations for MBT.

Results: 164 patients were included, genomic profiling was available for 158 patients. 101 (64%) had a sarcoma with a complex genomic profile whereas 57 (36%) presented a sarcoma with a known single driver genomic abnormality. Histological sub-types were distributed as follow: 21% LMS, 18% bone sarcoma, 12% UPS, 10% LPS, 6% GIST, 7% rhabdomyosarcoma, 6% endometrial stromal sarcoma, and others. The median age at inclusion was 51.3 [6.8-84.6], the median overall survival after diagnosis of metastases was 4.34 years (CI 95% [3.73-5.15]). 74% of patients had a good performans status of 0 or 1.

At least 1 molecular alteration was reported for 111 patients (70%). Majority of patients had multiple alterations (76 out of 111: 68%). In total, 339 molecular alterations were identified: 87 amplifications, 113 SNV and 139 homozygous deletions. Gene breakpoint was also reported by CHG array for 16 patients, suggesting an underlying rearrangement. Amplified genes related to cell cycle, tyrosine kinase receptor and p53 pathway in 33%, 24% and 17% of cases, respectively. Genes with SNV related to tyrosine kinase receptor, NF1/Ras pathway and PI3K/Akt/mTor pathway in 53%, 21% and 11% of cases, respectively. Genes with homozygous deletion related to cell cycle and PI3K/Akt/mTor pathway in 63% and 31% of cases, respectively.

Molecular board recommended a MBT for 50 patients: 1 MBT for 39 patients, 2 MBT for 8 patients and 3 MBT for 3 patients, corresponding to 64 recommendations in total (25 tyrosine kinase inhibitor, 19 cyclin kinase inhibitor, 12 mTor inhibitor, 6 MDM2 inhibitor, 2 PARP inhibitor). 10 patients were eventually treated with the MBT among which 7 in a clinical trial. Table describes characteristic and outcome of treated patients. The median progression free survival for these 10 patients was 1.9 months and the overall survival 5.5 months. Main reasons for no administration of the MBT were 1/ choice of the physician 2/ contraindication to MBT 3/death before MBT start.

Conclusion: The relevance of molecular screening of sarcoma is similar to that of other tumor types in terms of genomic alterations identified (high) and therapeutic recommendations associated (low), even for bone sarcoma. Patients with sarcoma included in such molecular screening program are selected ones with prolonged survival and good performans status. Identified molecular alteration may be found in any histological subtypes and relates to several signaling pathway. Recommended MBT was mainly started in GIST and sarcoma with complex genomic with no obvious clinical benefit. Molecular screening is feasible in sarcoma but didn't not demonstrate its clinical interest so far. To develop this strategy, scientific community will have to discuss the selection of patients who may benefit from such strategy (sarcoma with complex genomic at early stage of advanced disease?), the most relevant screening method to apply (next generation sequencing and RNAseq ?) and the objectives to reach (signal of efficacy for specific alteration).

Description and outcome of treated patients

Age (Inclusion)	PS (inclusion)	Histology	Genomic alteration	MBT	Best response	PFS(m)
58	1	GIST	CDKN2A homozygous deletion	Palbociclib	PD	0.8
43	1	Osteosarcoma	CDK4 amplification	Ribociclib	PD	1.7
57	0	Leiomyosarcoma	AKT2 amplification	Everolimus	PD	2.6
30	1	UPS	AKT2 amplification	Everolimus	PD	1.4
58	0	Chondrosarcoma	KDR mutation	Sorafenib	SD	33.6
47	1	MPNST	ERBB2 mutation	Lapatinib	SD	1.9
66	1	GIST	CDKN2A homozygous deletion	Palbociclib	PD	0.9
13	1	Osteosarcoma	KDR amplification	Regorafenib	PD	1.9
21	0	Osteosarcoma	PIK3CA amplification	Everolimus	PD	2.7
80	1	GIST	CDKN2A homozygous deletion	Palbociclib	SD	3.7

Paper #26 3253370

PERSONALISED MEDICINE FOR HIGH-RISK PAEDIATRIC AND AYA SARCOMA PATIENTS

Emmy D. Fleuren, PhD[1]*; Jinhan Xie*[1]*; Paulette Barahona*[1]*; Alexandra Sherstryuk*[1]*; Daniel Batey*[1]*; Jin Yi Lim*[1]*; Loretta Lau*[1]*; Dong Anh Khuong Quang*[1]*; Tim Failes*[1]*; Shu-Oi Chow*[1]*; Chelsea Mayoh*[1]*; Marie Wong*[1]*; Amit Kumar*[1]*; ZERO Omics Team*[1]*; ZERO Preclinical Drug Testing Team*[1]*; ZERO Senior Management Team*[1]*; David Thomas*[2]*; Toby Trahair*[1]*; Michelle Haber*[1]*; Emily Mould*[1]*; Richard Lock*[1]*; David Ziegler*[1]*; Vanessa Tyrrell*[1]*; Mark Cowley*[1]*; Paul Ekert*[1]
[1]*Children's Cancer Institute, Sydney, New South Wales, Australia;* [2]*Garvan Institute of Medical Research, Sydney, New South Wales, Australia*

Objective: Despite intensive multimodal treatment, outcomes of refractory, recurrent and/or metastatic paediatric and adolescents and young adult (AYA) sarcoma patients remain poor. Targeted therapies are high on the agenda, yet their clinical utility is limited due to inter-tumoural heterogeneity and a lack of recurrent and actionable mutations in these tumours. This is particularly the case for the translocation-associated Ewing sarcomas (ES),desmoplastic small round cell tumours (DSRCT), synovial sarcomas (SynS) and alveolar rhabdomyosarcomas (ARMS). Accurate prediction of individual patient responses to targeted therapies therefore remains a critical challenge in paediatric and AYA sarcomas.

Our objective is to implement a novel, comprehensive precision medicine platform incorporating molecular genomic, transcriptomic and epigenomic profiling with *in vitro* and *in vivo* drug testing to identify targeted therapeutic agents for high-risk (HR; expected survival <30%) paediatric and AYA sarcoma patients (0–21y). Here, we report for the first-time interim results of sarcoma patients enrolled in the currently active Zero Childhood Cancer (ZERO) National Clinical Trial (PRISM) (NCT03336931; 2017-2020).

Methods: We collected data of all sarcoma patients enrolled in the multicentre prospective ZERO PRISM trial, which combines molecular genomic (WGS (tumour, germline DNA), deep sequencing of a panel of cancer associated genes) and transcriptomic (whole transcriptome (RNASeq)) analysis. A subset of samples also had epigenomic (methylation) profiling. Where possible, we performed *in vitro* high-throughput drug screening (112 compounds) and patient-derived xenograft (PDX) drug efficacy testing (incl. combinations) for individual patients. Results are reviewed by an expert national Multidisciplinary Tumour Board (MTB) to assign personalised and tailored clinical recommendations (targeted and/or immunotherapy, change of diagnosis, and/or reportable germline cancer predisposition).

Results: HR sarcomas are the second largest patient group within ZERO PRISM to date (27%; *n=60)*. Complete genomic and transcriptomic molecular profiles were established for 56 sarcoma patients comprising a wide range of histologies, including 15 rhabdomyosarcomas (RMS; 9 alveolar, 6 embryonal RMS), 14 ES, 8 osteosarcomas, 5 malignant peripheral nerve sheath tumours (MPNST), 2 alveolar soft part sarcomas (ASPS), 2 angiosarcomas, 1 infantile fibrosarcoma, 1 DSRCT, 1 SynS, 1 leiomyosarcoma, 1 epithelioid sarcoma, 1 gastrointestinal stromal tumor (GIST) and 4 unspecified/other sarcomas. Through extensive clinical data curation, we identified reportable somatic SNVs, fusions, CNVs and aberrantly expressed genes (RNA) in 45% (*n=25*), 57% (*n=32*), 54% (*n=30*) and 57% (*n=32*) of patients, respectively, suggesting possible therapeutic strategies. Based on these profiles, 77% (*n=43*) of sarcoma patients received an MTB recommendation (75% targeted therapy, 4% diagnosis refinement and 7% germline mutation referral). Clinical follow-up of all these patients is ongoing, and interim clinical response data will be available within the coming months. In addition, we also describe as of yet unreported aberrations and present novel oncogenic signatures in a variety of sarcoma subtypes.

Conclusion: This study is one of the largest and most comprehensive clinical efforts ever undertaken in the field of precision medicine in paediatric and AYA sarcoma in the advanced setting. Our interim results highlight the feasibility, high clinical and research utility of precision medicine in HR sarcoma subtypes. This comprehensive dataset is therefore a unique and valuable source to understand the biology and pinpoint therapeutic opportunities in a wide range of sarcomas, particularly in the advanced setting.

Paper #27 3256280

RE-IRRADIATION FOR RECURRENT CHORDOMAS OF THE SPINE AND SACRUM WITH HIGH DOSE STEREOTACTIC BODY RADIATION THERAPY

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Objective: Chordomas are known to have high rates of local recurrence and potential for metastases, with limited options for effective salvage. Stereotatic body radiation therapy (SBRT) is an effective treatment for re-irradiation of even radioresistant malignancies. The goal of this study is to evaluate the safety and efficacy of SBRT to re-irradiate recurrent chordomas of the spine and sacrum.

Methods: Clinical records of patients with recurrent chordomas of the mobile spine and sacrum were reviewed from a prospectively maintained SBRT database. All patients who underwent salvage high dose SBRT (1-5 fractions) treated between December 2007 and August 2018 were evaluated. Radiographic local recurrence free survival (LRFS), overall survival (OS), symptom response and toxicity were assessed.

Results: A total of 16 patients underwent reirradiation with SBRTfor recurrent chordoma of the mobile spine or sacrum. The median follow up (FU) from reiirradiation was 2.3 yrs(0.7-5.8). Dedifferentiated or poorly differentiated chordoma was noted in 3 patients. SBRT alone was used in 10 patients (62%), separation surgery and post op SBRT in 6 cases (38%). Median gross tumor volume at the time of re-irradiation was 88.7 cm^3 (25.6-1329.9 cm^3). The salvage SBRT doses utilized were 2400cGyx1 (N = 3), 800cGy-1000cGy x 3 (N = 9), or 570cGy-800Gy in 5 fractions (median 3250cGy) in 4 patients. The median V95 (volume receiving 95% of prescription) was 98% of the prescribed dose. Proton/photon radiation was initially given to 12 patients in conventional fractionation (4500-8000cGy) and SBRT in 4 patients (2850cGy - 3600cGy). In 2 patients, re-riiradiation was given after 2 prior courses of radiation. LRFS was 2.7 yrs (95% CI: 0.6 - 5.1) and the median OS was 3.2 yrs (0.6-6.4). The LRFS and OS rates were 75% at 1 year and 60% at 2 years (figure 1). The cumulative incidence of local failure is shown in figure 2. For conventional chordoma, the LRFS and OS rates were 85% (95% CI 65-100%) at 1 year and 76% (52-99.8%) at years. Poorly differentiated or de differentiated chordoma patients had all succombed to disease at 2 years. For patients who presented with only local recurrence (N = 10), the LRFS/OS was found to be 90% (1 year) , 80% (2 years), 64% (3 years) and 64% at 4 years respectively. Among the 6 patients with metastases, LRFS/OS rates were 50% at 1 year, 25% at 2 years and none at 3 years of follow up. Volume or disease, time from prior RT to progression, number of courses of prior radiation were not associated with LRFS or OS. Symptom response after re-irradiation was 88% for pain and radiculopathy (25% CR). No grade 3 or higher acute toxicity (CTAE v 4) was encountered. Long term grade 3 toxicity was noted in 38% (neuropathy or fracture or rectosigmoid ulceration). No patient had grade 4 or higher late toxicity.

Conclusion: Recurrent chordomas are clinically challenging. Re-irradiation with high dose SBRT is a reasonable salvage option for patients who have recurrent chodromas of the spine or sacrum, even for patients who have undergone a full course of radiation. Salvage SBRT can provide long term local control and effective symptom relief, with acceptable morbidty in the long term. Metastases remain a significant challenge in this cohort of patients.

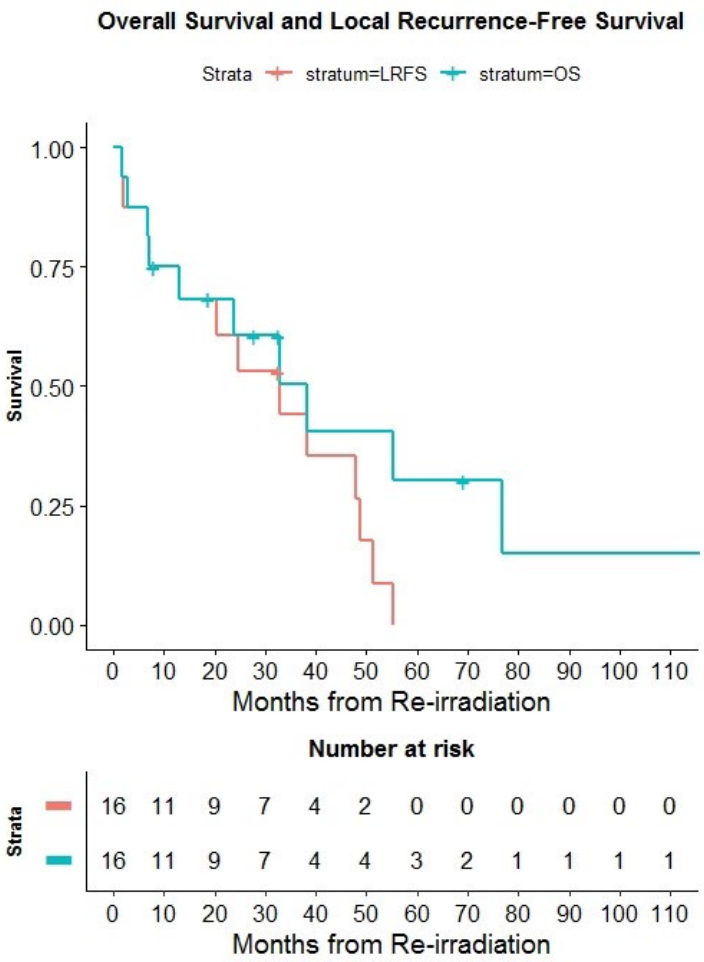

figure 1. Local replase free survival and overall survival

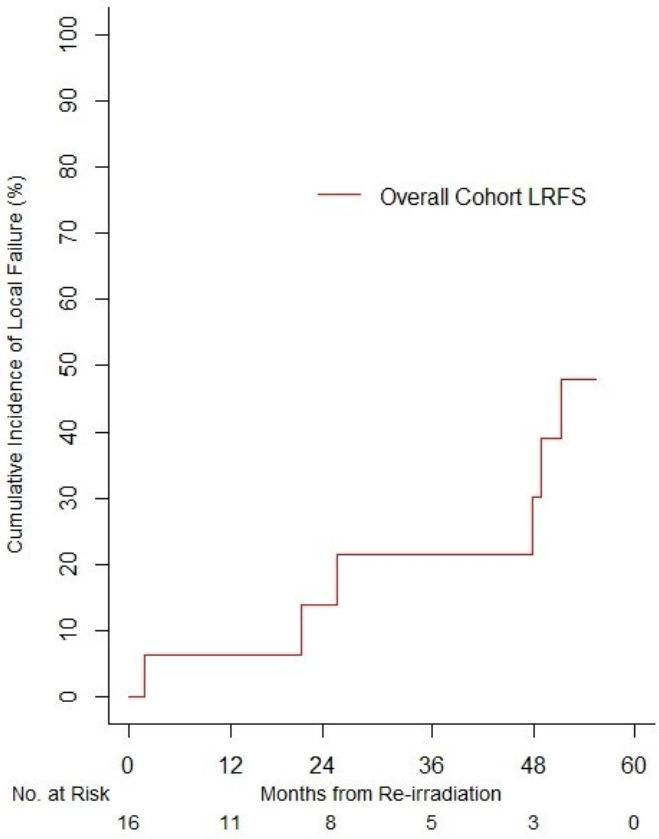

figure 2. Cumulative incidence of Local Failure

10:00 am - 11:00 am

– SESSION 7 –

Radiation Oncology

Paper #28 3242507

SPATIALLY-FRACTIONATED STEREOTACTIC BODY RADIOTHERAPY FOR LOCALIZED UNRESECTABLE, OLIGO-METASTATIC OR WIDELY-METASTATIC CONVENTIONAL TYPE CHONDROSARCOMA: A PROSPECTIVE PHASE I TRIAL

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Objective: Unresectable or metastatic conventional chondrosarcoma represents a treatment challenge. Since cytotoxic chemotherapy is generally ineffective, there is no standard of care for treatment of these tumors. Thus, aggressive local therapy with definitive radiotherapy is an attractive option. However, given the radioresistance of chondrosarcoma, protracted courses of high-dose radiotherapy, which can be toxic, are traditionally used to achieve local control. Early investigations of stereotactic body radiotherapy (SBRT) demonstrated that small lesions can be treated effectively with acceptable toxicity.Spatially fractionated radiotherapy (SFRT) (also known as "Lattice radiotherapy") allows for dose-escalation of large targets while also preventing excessive toxicity to organs at risk (OARs). Beam collimation creates high-dose "peaks," organized throughout a target volume with intervening low-dose "valleys". This heterogeneous peak and valley dose distribution is felt to increase tumor cell death, immunogenicity, and OAR sparing compared to traditional homogeneous radiotherapy plans. High quality SFRT plans can be delivered using widely-available RT equipment, but the treatment planning and quality assurance (QA) process are not well described. Our goal was to design and QA SFRT plans intended to treat large sarcoma lesions using volume-modulated arc therapy (VMAT) on a commercially available treatment planning system. The SFRT design and QA techniques will be used in a clinical trial of SFRT as definitive treatment for unresectable or metatstatic conventional chondrosarcoma.

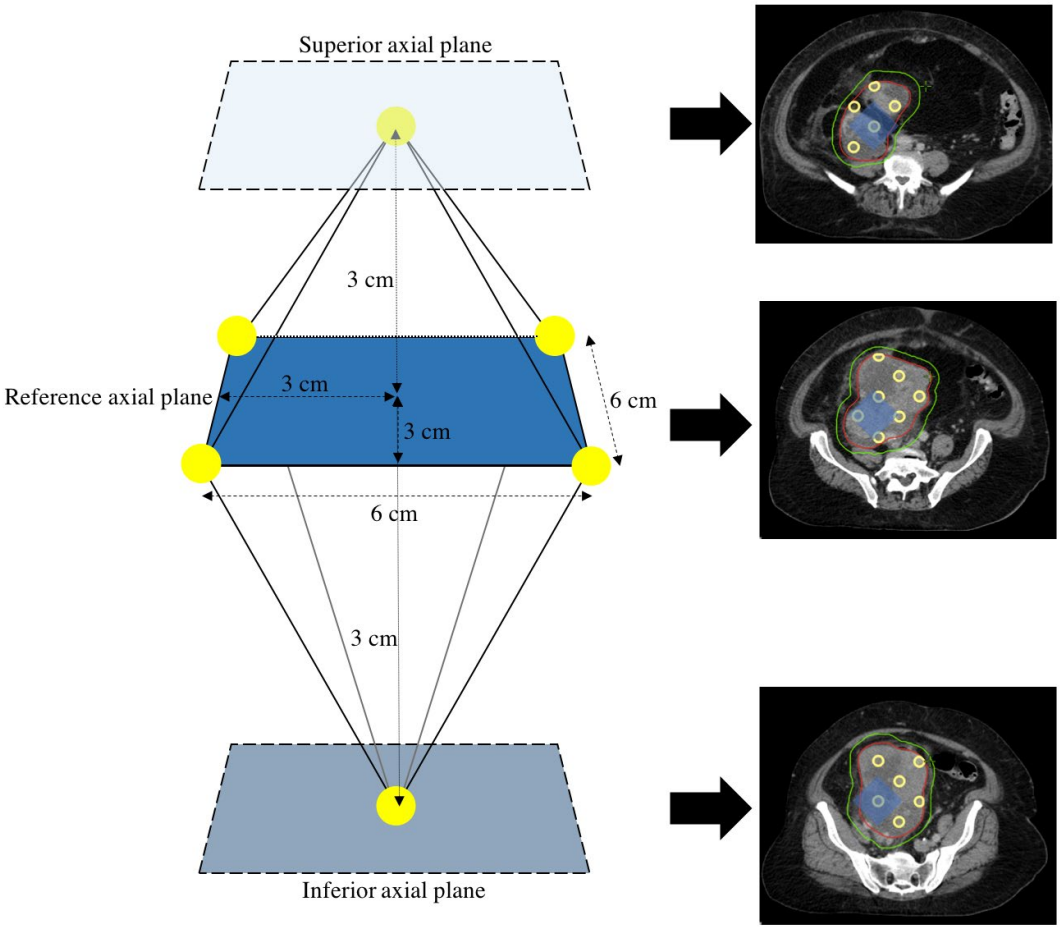
Methods: A planning and QA method for SFRT was designed using patients with bulky metastatic or unresectable sarcomas ≥ 10 cm in axial diameter. The planning tumor volume (PTV) was defined as the visible tumor (GTV) on planning CT with a 1 cm isotropic expansion. Spheres 1.5 cm in diameter were placed in a reference axial slice as shown in the accompanying figure. The prescription dose was 20 Gy to the PTV with a simultaneous integrated boost to 66.7 Gy to each sphere. Published OAR constraints for 5-fraciton SBRT were considered hard constraints for planning. SFRT plans were created using VMAT in Eclipse (Varian Medical Systems) with dosimetric specifications. A total of 5 tumors from patients with various sarcomas were assessed for plan deliverability. Two of these plans underwent QA with portal film and ion chamber dosimetry.

Results: SFRT plans achieved excellent coverage with acceptable dose to OARs. Dose characteristics are shown in the accompanying table. Coverage was optimal in locations where dose to OARs did not limit target coverage. In particular, spinal cord and bowel dose constraints limited target dose coverage goals. QA verified that plans could be delivered accurately, with ion chamber measurements within 2% of the expected dose within the high dose spheres and portal film gamma criteria pass rates (2%/2mm tolerance) greater than 98% for all treatment fields.

Conclusion: This process successfully planned and delivered SFRT using commercially available equipment. The process will be used in an upcoming phase 1 trial of the safety of 66.7 Gy/20 Gy in five fractions to all assessable lesions in patients unresectable or low-burden metastatic chondrosarcoma. The study will also assess tumor tissue and peripheral blood for changes to the immune-related microenvironment and serum. Given the hypothesized immunogenic effects, future work may evaluate combination treatment using SFRT and immunotherapy.

5 patients were evaluated for plan deliverability with SFRT SBRT. The target locations, size, coverage, and dose to OARs are shown above. GTV = gross tumor volume, defined by physician identifying the volume of interest for a minimum of 20 Gy in 5 fraction

Patient	Diagnosis	Location	AP x TV x CC (cm)	GTV/Spheres (cc)	V66.7 Gy / V63.4 Gy (Spheres)	PTV V20 Gy	Relevant OAR Dmax
1	Localized liposarcoma	Right Abdomen	15.5 x 11 x 12	1036/29.3	98% / 100%	100%	Kidneys: 6.3 Gy Bowel: 32.9 Gy Rectum: 37.9 Gy Cord: 1.3 Gy
2	Localized liposarcoma	Central Abdomen	9 x 13 x 12	825/22.5	72% / 93%	97%	Bowel: 27.3 Gy Kidneys: 1.3 Gy Cord: 0.7 Gy
3	Undifferentiated sarcoma	Right Neck	12 x 9 x 11	614/19.6	73% / 95%	99%	Cord: 29.2 Gy Brachial plexus: 30.0 Gy
4	Undifferentiated sarcoma	Left Lower Lung	11.5 x 9 x 9	449/19.5	96% / 100%	100%	LungV13.5 Gy: 21.6% Heart: 30.2 Gy Esophagus: 20.9 Gy Cord:17.3 Gy
5	Metastatic leiomyosarcoma	Right Abdomen	8.5 x 11 x 10.5	431/14.5	99% / 100%	99%	Cord: 16.4 Gy Bladder: 0.01 Gy Liver V21 Gy: negligible Kidneys V18 Gy: 0.05 cc



Paper #29 3250148

THE RADIO-ENHANCER HAFNIUM OXIDE NANOPARTICLE, NBTXR3 ACTIVATED BY RADIATION THERAPY IN PATIENTS WITH LOCALLY ADVANCED SOFT TISSUE SARCOMA: A PHASE II/III TRIAL

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Objective: A subset of locally advanced soft tissue sarcoma (STS) patients achieve significant therapeutic benefit from preoperative radiation therapy (RT) as shown by Pisters JCO 1996 and Yang JCO 2018. However, the impact of RT on pathological response (pR) and R0 resection is limited, highlighting the need for novel multimodal therapies aimed at local control.
NBTXR3 (hafnium oxide nanoparticles), injected intratumorally may represent such an option. Otherwise inert, NBTXR3 augments the effective RT dose deposited within tumor cells when activated by ionizing radiation to increase cancer cell death compared to RT alone.
We report here on the results of a phase II/III randomized clinical trial evaluating the preoperative efficacy and safety of NBTXR3 activated by RT in patients with locally advanced STS of the extremity and trunk wall [NCT02379845].

Methods: This is a multi-national phase II/III randomized, open-label clinical trial. Adults with locally advanced STS of the extremity or trunk wall, of any histologic grade, eligible for preoperative RT were randomly assigned 1:1 to receive NBTXR3 as a single intratumoral injection (volume corresponding to 10% of baseline tumor volume at 53.3g/L) followed by external beam RT (EBRT; 50 Gy as 25 fractions of 2 Gy, over 5 weeks) (arm A) or EBRT alone (arm B). Both arms had the chance to go on to receive post-RT surgical resection.

The primary objective was to compare the proportion of patients with pathological complete response (pCR; defined as <5% of residual viable cancer cells after surgery), as assessed by a Central Pathology Review Board based on the EORTC guidelines. Key secondary endpoints included negative surgical margin (R0), limb amputation rate and safety. Safety was evaluated in all subjects who received at least one puncture of NBTXR3 or at least one fraction of RT. Subjects are in continued long-term follow-up, focused on safety.

Results: Between March 3rd, 2015 and November 21st, 2017, 180 patients were randomized and 179 received treatment: n=89; arm A and n=90; arm B. The proportion of patients with pCR was 16.1% (14/87) compared with 7.9% (7/89) in arms A and B, respectively (p=0.044). The R0 resection rate was 77.0% (67/87) in arm A versus 64.0% (57/89) in arm B (p=0.0424). The most common grade 3-4 treatment emergent adverse event (AE) was post-operative wound complication, which occurred at a similar rate in each arm (8/89 and 8/90 in arm A and B, respectively). The most common grade 3-4 AE related to NBTXR3 administration was injection site pain (4/89, 4.5%) and hypotension (4/90, 4.4%). Skin injury was the most common grade 3-4 RT-related AE, which was shared between both arms (5/89, 5.6% and 4/90, 4.4% in arm A and B, respectively). Serious AEs were observed in 35 (39.3%) of 89 patients in arm A and 27 (30.0%) of 90 patients in arm B. There were no treatment-related deaths. Follow-up was conducted on 153 patients with a current median follow-up of 18.5 months. Currently 87 patients are still in long-term follow-up.

Conclusion: This registration trial of NBTXR3 combined with EBRT significantly achieved its primary and secondary endpoints of improving pCR and increasing R0 resection versus EBRT alone. NBTXR3 together with EBRT was well tolerated with a safety profile consistent with EBRT alone. Taken together, these results led to the EU approval (CE Mark) of NBTXR3 + RT for patients with locally advanced STS of the extremity and trunk wall.

Paper #30 3255664

SPATIALLY FRACTIONATED GRID RADIOTHERAPY PRIOR TO NEOADJUVANT CONVENTIONALLY FRACTIONATED RADIOTHERAPY FOR VERY HIGH-RISK SOFT TISSUE AND OSTEO- SARCOMAS: PROMISING PATHOLOGIC RESPONSE WITH SAFE DOSE ESCALATION

James W. Snider, MD[1]*; Jason Molitoris*[1]*; Susan Shyu*[2]*; Stephanie Rice*[2]*; Emily Kowalski*[2]*; Cristina Decesaris*[2]*; Jill Remick*[2]*; Lori Campbell*[2]*; Nader Hanna*[1]*; Vincent Ng*[1]*; William Regine*[1]

[1]*Department of Radiation Oncology, University of Maryland School of Medicine, Baltimore, MD, USA;*

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Objective: Bulky soft tissue (STS) and osteosarcomas (OSS), especially those over 10 cm, have relatively poor local control rates even when treated with neoadjuvant radiotherapy (RT) and wide local excision. Dose escalation efforts have been met with higher than expected rates of wound complication or major toxicity. Pathologic response rates, and especially complete response rates (pCR) (≥80% necrosis) in STS/OS have been correlated with improved clinical outcomes, including survival. Spatially Fractionated GRID RT (SFGRT) has been utilized in the megavoltage era as a safe, noninvasive, external beam form of dose-escalation with dose distributions similar to brachytherapy applications. We hypothesized that SFGRT followed by standard neoadjuvant RT would prove a safe method for dose escalation with the potential for improved pCR rates.

Methods: At our institution, patients standardly receive a single fraction of SFGRT (15 Gy) (Figures 1 and 2) followed immediately (start within 3 days) by conventionally fractionated RT (CRT) in the neoadjuvant setting for bulky sarcomas. On an IRB-approved protocol, we retrospectively reviewed demographics, histology, treatment characteristics, clinical outcomes, toxicity, and pathologic response rates for all patients receiving this regimen and undergoing surgical resection over the last 15 years. All pathologic response rates were retrospectively, formally reviewed by an expert pathologist and re-scored for approximate necrosis/pathologic response rates. Clinical outcomes of local control, progression free survival, overall survival, and rates of toxicity were also obtained.

Results: Twenty one patients have received 15 Gy SFGRT followed by CRT (range 45-50.4 Gy, 1.8-2.25 Gy/fx) prior to oncologic resection. Median follow-up was 33 months. Median tumor size by greatest dimension was 14.4 cm (range, 9.7-40cm; mean, 16.0cm). Histologies included the following: pleomorphic (n=7), leiomyosarcoma (n=2), myxofibrosarcoma (n=3), liposarcoma (n=3), spindle cell (n=1), extraskeletal OSS (n=2), OSS (n=2), and chondrosarcoma (CS) (n=1) (TOTAL: 16 STS, 4 OSS, 1 CS). Four patients received neoadjuvant chemotherapy of which 3 had progression/poor response prior to RT. Fifteen patients (71%) had negative resection margins, while 6 were R1/R2. Only 5 (24%) patients developed a major wound complication per NCIC standards. Four (19.0%) patients have failed locoregionally, 6 (29%) patients have progressed locally or distantly, and 7 (33%) have died. For 20 patients, full pathologic review was possible. High-grade STS (n=13) demonstrated a 39% (5/13) pCR rate. Osteosarcoma demonstrated a 50% pCR rate (2/4).

Conclusion: SFGRT followed by CRT is a safe and effective neoadjuvant regimen for very high-risk sarcomas. Pathologic response rates in this institutional series exceed those seen with Chemo-RT and CRT alone on prospective trials (RTOG 9514/0630) despite larger tumors in this series. These promising results deserve further prospective evaluation, and a multi-insitutional trial is planned.

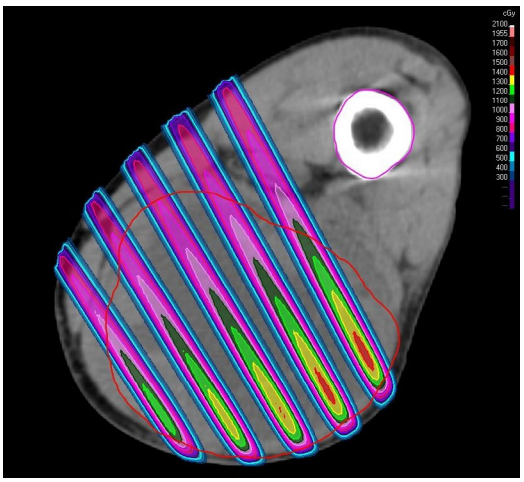

Figure 1. Axial CT slice of SFGRT 15 Gy dose distribution for thigh sarcoma.

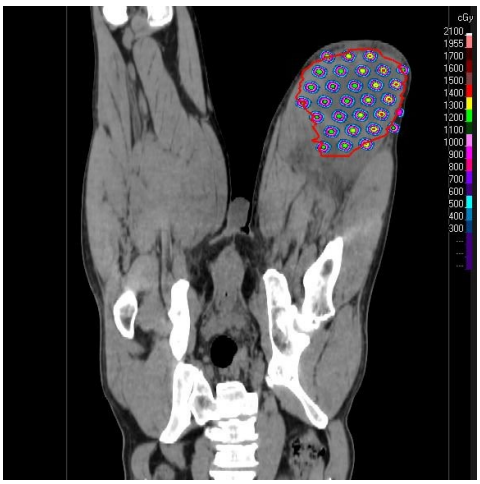

Figure 2. Coronal CT slice of SFGRT 15 Gy dose distribution for thigh sarcoma.

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To the Connective Tissue Oncology Society abstract review committee:

Dr. James William (J.W.) Snider, III, M.D. is an Assistant Professor radiation oncologist at the University of Maryland specializing in the management of patients with Head/Neck Cancer and Sarcomas. Dr. Snider also specializes in cutting edge technologies including Proton Therapy and Hyperthermia.

Dr. Snider's research focus at the University of Maryland centers on Head/Neck tumors, Sarcomas, Concurrent Thermoradiotherapy, Spine Tumors, Pencil Beam Scanning Proton Therapy, Stereotactic Radiotherapy, and unique treatment/device-development for increasing therapy efficacy with reduced side-effect profiles. Dr. Snider has numerous peer-reviewed publications in these arenas, and he has given many national/international presentations of this work. He has also received several awards for the presentations and content of his research including those from The Radiosurgery Society, International Congress for Hyperthermic Oncology, and the Radiological Society of North America Roentgen Resident/Fellow Research Award.

Dr. Snider has received research grant funding in the form of The Radiosurgery Society BEST Medical Fellowship Grant and funding for device development through the UM Ventures group. On a national level, Dr. Snider is an active member of the American Society for Radiation Oncology and the Society for Thermal Medicine.

I can confirm that Dr. Snider is within his first five years of practice following his residency completion at our institution. He is below the 35 years of age cutoff, and he is otherwise eligible for and very deserving of the Young Investigator Award from CTOS for his abstract on GRID (Spatially Fractionated Radiation Therapy) prior to conventionally fractionated, neoadjuvant radiotherapy for high grade resectable sarcomas. His findings have confirmed the utility of our current practice approach with this novel therapy in sarcomas, and this protocol is actively being explored for cooperative group activation on a multi-institutional level. I highly recommend Dr. Snider for this award.

Please feel free to contact me with any questions or concerns in this regard.

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Paper #31 3250473

ANGIOSARCOMA OF THE SCALP AND FACE: COMPARING RADIATION DOSE DISTRIBUTIONS BETWEEN HIGH-DOSE-RATE SURFACE APPLICATOR (HDR-SA) BRACHYTHERAPY AND VOLUMETRIC MODULATED ARC THERAPY (VMAT)

Devarati Mitra, MD, PhD[2]*; Yaguang Pei*[1]*; Ivan Buzurovic*[1]*; Philip Devlin*[1]*; Elizabeth Baldini*[1]*; Miranda Lam*[1]
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Objective: Angiosarcoma of the scalp and face is often a multifocal disease spanning a large area with critical adjacent normal structures. Radiation therapy (RT) can be used with good effect both definitively and in the adjuvant setting. The optimal RT approach for this disease has not been established. Our institutional practice has been to use high-dose-rate surface applicator (HDR-SA) brachytherapy. However, in the context of volumetric modulated arc therapy (VMAT) being a newer, more conformal external beam RT approach, this study was undertaken to compare the dose distribution of HDR-SA brachytherapy versus VMAT.

Methods: We identified 12 patients with either primary or recurrent angiosarcoma of the face or scalp who were treated in the department of radiation oncology at our institution between 2012-2018. All patients received HDR-SA brachytherapy as part of their local treatment. Prescription dose was 51 Gy in 17 fractions using Iridium-192 delivered to a depth of 3mm (or to the base of the lesion) and with at least a 5 cm clinical target margin radially (when feasible), with a goal of treating to the point of moist desquamation by the end of treatment. To compare the delivered HDR-SA brachytherapy plan to a deliverable VMAT plan, the delivered 100% isodose volume was designated as the planning target volume (PTV) and used to generate a VMAT plan that also delivered 51 Gy in 17 fractions to this same volume. Organs at risk visible on the brachytherapy planning CT scan were contoured, including the brain, eyes, lacrimal glands, lenses, cochlea and parotid glands. Dose-volume parameters were compared between the HDR-SA brachytherapy and VMAT plans by Student's t-tests.

Results: Ten of 12 patients received HDR-SA brachytherapy as part of their initial definitive cancer treatment with 8 patients initially receiving chemotherapy and 4 patients undergoing surgery (with positive margins) prior to RT. Two patients were treated for recurrent/progressive disease, 3 and 5 years after initial diagnosis. The scalp was the primary site for 10 patients while the cheek was the primary site for 2 patients.

By definition, for all patients, 100% of the PTV target received 100% of the prescription dose by the HDR-SA brachytherapy plan. Each patient's VMAT plan also resulted in 100% of the volume receiving at least 95% of the prescription dose (V95%=100%) which is our institution's traditional metric for adequate target volume coverage. Bolus was used in VMAT plans. An example plan comparison is shown in Figure 1.

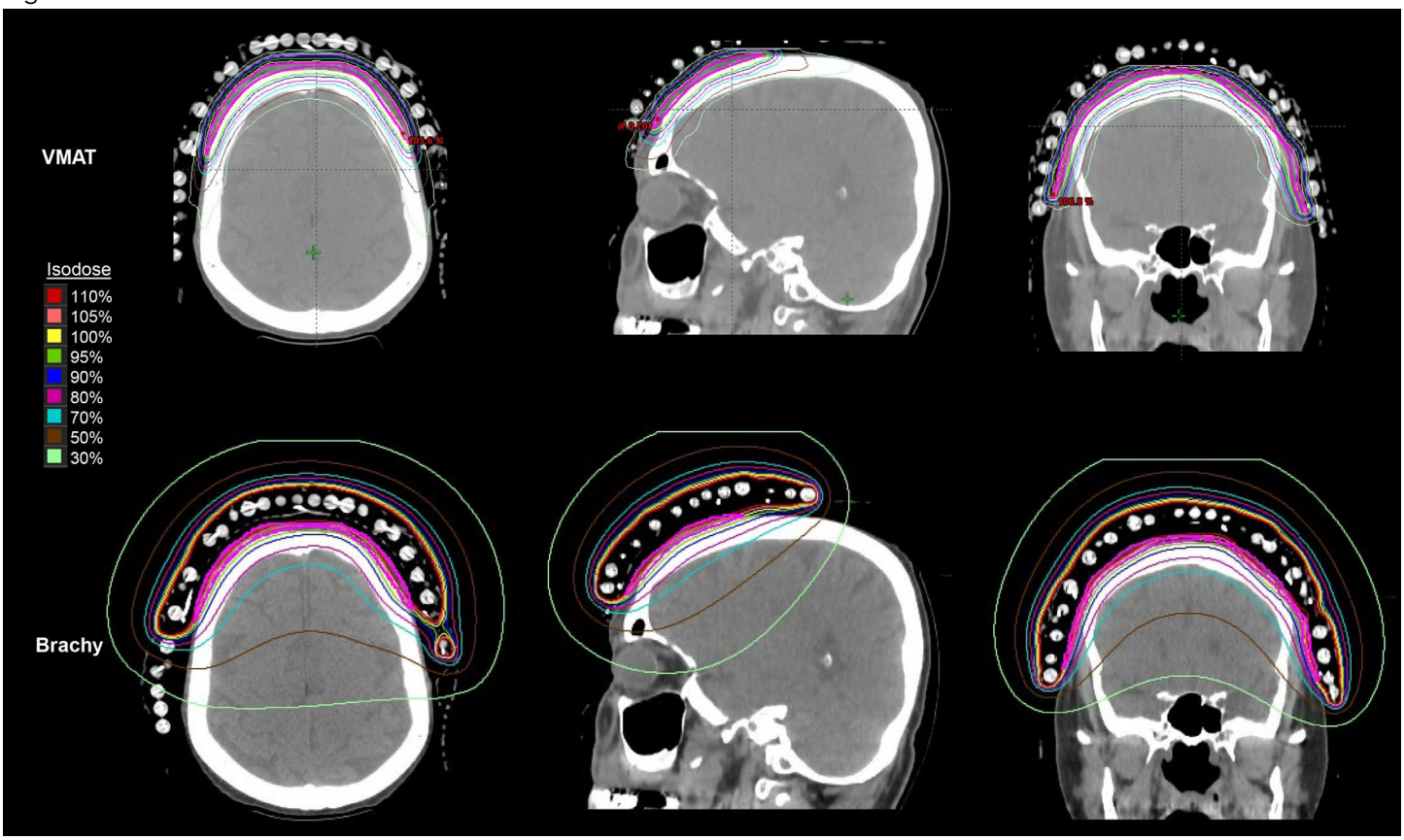
Dose metrics to various organs at risk are shown in Table 1. Because the entire brain was not included on all HDR-SA brachytherapy CT simulation scans, it was not possible to compare traditional dose volume histogram (DVH) metrics for the brain between the HDR-SA brachytherapy and VMAT plans. However, the Dmax for the brain was significantly higher in the HDR-SA brachytherapy plan (mean 41.8 Gy vs. 36.1 Gy, p=0.026), as was the absolute volume of brain receiving 50% of the prescription dose (25.5 Gy; mean 258 cc vs. 9.2 cc, p=0.027). The absolute volume of brain receiving 80% of the prescription dose was not significantly different. Mean dose to lacrimal glands, orbits, lenses and cochlea were all significantly higher with the HDR-SA brachytherapy plans. However, there was no significant difference in parotid gland dose for the 9 patients for whom the parotid gland was fully imaged on CT simulation scan.

Conclusion: While it has been our institutional practice to use HDR-SA brachytherapy as the RT modality of choice for scalp and face angiosarcoma patients, this study suggests that there may be dosimetric advantages to VMAT for many patients. While there are significant caveats to this conclusion, including whether a theoretical VMAT plan is deliverable (based on placement of bolus and patient anatomy), this study suggests a personalized approach to deciding RT modality may be the optimal treatment plan.

Table 1

	Brachy	VMAT	p-value
Brain Dmax	41.8 Gy	36.1 Gy	0.026
Brain V50% (25.5 Gy)	258 cc	9.2 cc	0.027
Brain V80% (40 Gy)	26.5 cc	0.06 cc	0.111
Mean lacrimal gland	15.9 Gy	6.7 Gy	0.020
Mean orbit	14.9 Gy	5.3 Gy	0.004
Mean lens	15.5 Gy	6.9 Gy	0.034
Mean cochlea	10.7 Gy	3.3 Gy	<0.0001
Mean parotid	8.1 Gy	6.3 Gy	0.546

Figure 1



11:00 am - 12:00 pm

– SESSION 8 –

East Meets West in Sarcoma Care

Paper #32 3247634

PREVALENCE AND PROGNOSTIC IMPACT OF COMORBIDITIES IN SARCOMAS: A POPULATION-BASED STUDY OF 3746 PATIENTS IN HONG KONG

Herbert H. Loong, MBBS, MRCP, FHKCP, FHKAM[1]*; Carlos K. Wong*[2]*; Chu-wa Ho*[2]*; Teresa Tse*[3]*; SC Sampson Kwan*[4]*; Linda K. Leung*[3]*; Yat Ming Lau*[3]

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Objective: The prognostic impact of comorbidities in patients (pts) with sarcomas is not well defined. The aims of this study were to examine the prevalence of comorbidities and its impact on overall survival in pts with sarcomas.

Methods: A population-based retrospective database was assembled to extract pts with sarcoma, as defined as ICD-9-CM codes of bone (170.x) or/and soft tissue (171.x) who have attended clinics or hospitals of the Hong Kong Hospital Authority between Jan 2004 and Mar 2018. Eligible pts with index presentation of bone or/and soft tissue sarcoma (STS) on or after Jan 2005 were analysed to allow 1-year window period. Comorbidities were obtained, and Charlson's Comorbidity Score (CCS) defined by 19 medical conditions according to risk of mortality at the time of sarcoma diagnosis was calculated. CCS score and prevalence of comorbidities at diagnosis were assessed. Rate of all-cause mortality according to level of CCS were computed. The prognostic value of CCS was estimated using Cox proportional hazard models.

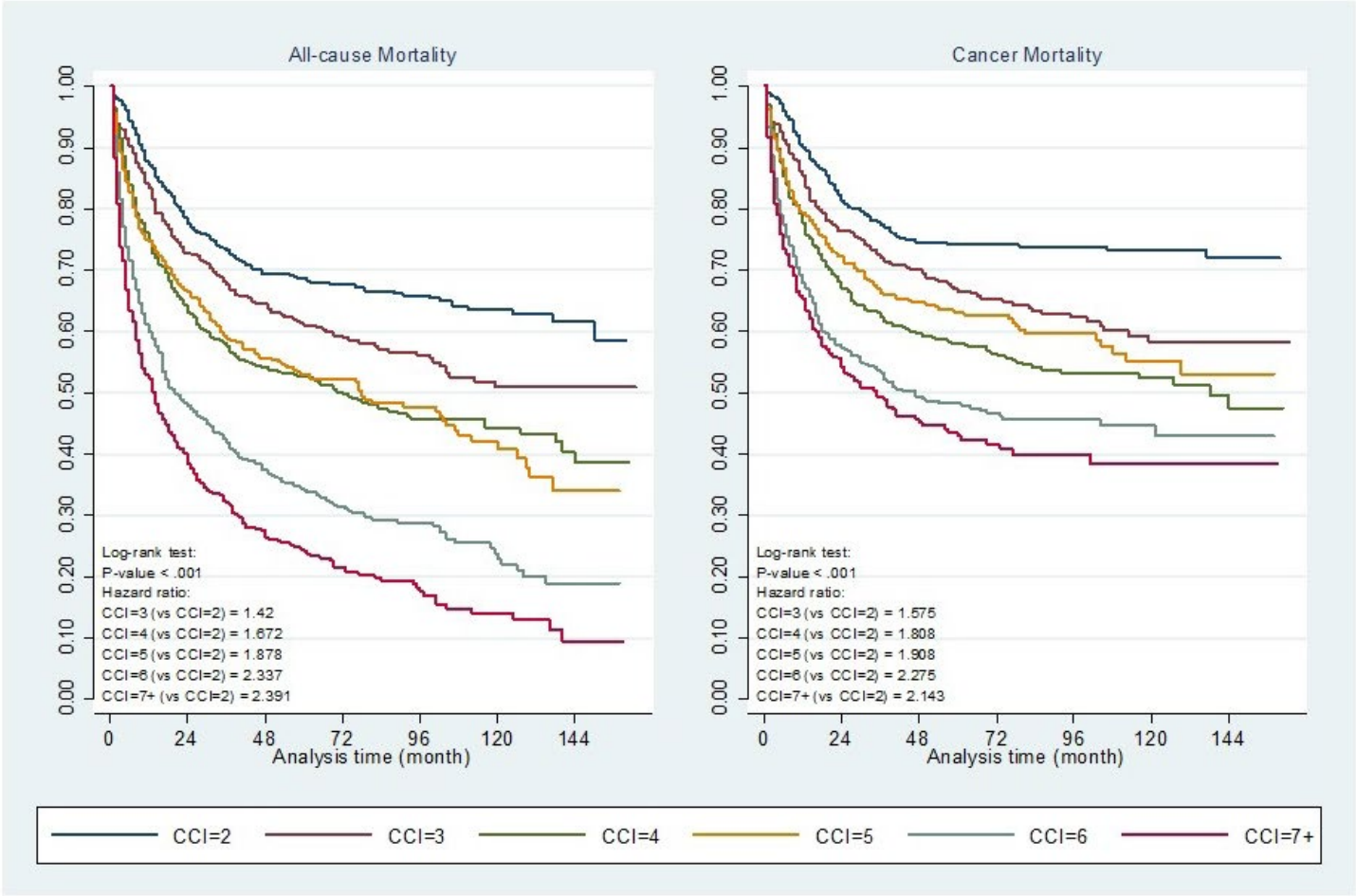
Results: Of 3746 pts identified, 3358 pts satisfied eligibility: bone: n=661, STS: n=2576; both: n=121. Male: Female 52.6% : 47.4%. Proportional age group: <18 years (y): 7.56% (n=254); 18<40y: 15.7% (n=529); 40<65y: 42.2% (n=1418); 65<80y: 23.4% (n=787); >/=80y: 11.0% (n=370). Top 5 common co-morbidities: diabetes mellitus 9.8%; cerebrovascular disease (4.8%), ischaemic heart disease (3.8%), chronic lung disease (2.9%), congestive heart failure (2.6%). Mean age at presentation: 54.2y (bone: 46.8y, STS: 56.5y). Mean CCS: 4.6. Pts with higher CCS had higher mortality (CCS3 vs. CCS2; HR 1.49; 95% CI 1.19-1.87; p<0.01; CCS>/=7 vs. CCS2; HR 3.20; 95% CI: 2.62-3.92; p<0.001).

Conclusion: This is one of the largest population-based sarcoma cohorts reported from Asia. Presence of comorbidities have significant negative prognostic impact on pts with sarcomas. Identification and treatment of relevant comorbidities may improve survival of sarcoma pts.

Comorbidities at Disease Presentation

Factor	Total (n=3358)	Bone & Articular Cartilage (n=661)	Connective and Other Soft Tissue (n=2576)	Borth (n=121)
Solid Tumour	100.0% (3358)	100.0% (661)	100.0% (2576)	100.0% (121)
Diabetes Mellitus	9.8% (329)	7.0% (46)	10.7% (275)	6.6% (8)
Cerebrovascular Disease	4.8% (161)	3.2% (21)	5.3% (137)	2.5% (3)
Other Chronic Ischaemic Heart Disease	3.8% (127)	3.0% (20)	4.1% (105)	1.7% (2)
Chronic Lung Disease	2.9% (99)	2.6% (17)	3.1% (80)	1.7% (2)
Congestive Heart Failure	2.6% (88)	2.0% (13)	2.8% (73)	1.7% (2)
Liver Disease	2.4% (82)	2.6% (17)	2.4% (63)	1.7% (2)
Peptic Ulcer Disease	2.4% (79)	2.0% (13)	2.5% (64)	1.7% (2)
Atrial Fibrillation	2.2% (74)	1.8% (12)	2.3% (60)	1.7% (2)

Charlson's Comorbidity Index Score correlating with All-cause and Cancer-specific mortality in entire sarcoma population



Paper #33 3255511

CLINICAL OUTCOME OF CLEAR CELL CHONDROSARCOMA: A MULTICENTER STUDY FROM JAPANESE MUSCULOSKELETAL ONCOLOGY GROUP

Robert Nakayama, MD, PhD[1]*; Keiko Hayakawa*[2]*; Makoto Endo*[4]*; Eisuke Kobayashi*[3]*; Shunsuke Hamada*[5]*; Tsukasa Yonemoto*[6]*; Hiroyuki Kawashima*[7]*; Kenichiro Hamada*[8]*; Itsuo Watanabe*[9]*; Hiroyuki Futani*[10]*; Takahiro Goto*[11]*; Toshifumi Ozaki*[12]

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Objective: Clear cell chondrosarcoma is an extremely rare subtype of chondrosarcoma and its clinical outcome has not been deeply assessed in the literature. The aim of this multicenter retrospective study was to investigate the clinical outcome of clear cell chondrosarcoma in Japan.

Methods: Information was collected retrospectively from the medical records of all patients with clear cell chondrosarcoma presenting to the registered hospitals between 1985 and 2018. The overall survival and disease-free survival were estimated using the Kaplan-Meier method.

Results: A total of forty-one patients from 12 JMOG hospitals were enrolled. There were 30 men and 11 women with an average age of 46.6 years (range: 19–79 years) at presentation. The median follow-up period was 69 months (range: 2-392). The sites of the primary lesions were the proximal femur in 25 patients (61.0%), proximal humerus in 5 patients (12.2%), ilium in 4 patients (9.8%) and others. Overall, 33 tumors (80.5%) occurred in the epiphysis of the long bones. The average size of the primary tumor was 6.3 cm (range: 2.5-12.5) in diameter. 18 patients (51.4%) were classified as StageIIA/B according to the AJCC staging, as no patients had metastatic lesions at presentation. As for first local treatment, 34 patients (82.9%) underwent wide resection of the tumor, 3 patients underwent simple excision, 3 patients underwent curettage and 1 had carbon iron radiotherapy. Endoprostheses were used in 29 of 33 patients (87.9%) who had primary tumors in the epiphysis of the long bones. Seven patients (17.1%) developed local recurrence and the 5- and 10-year local recurrence free survival were 90.5% and 70.0%, respectively. A total of 9 patients (22.0%) developed distant metastasis to the lung alone in 2 patients, bone alone in 4 patients, and both lung and bone in 3 patients. The 5- and 10-year metastasis free survival were 84.3% and 73.9%, respectively. Overall, the 5- and 10-year disease free survival were 81.8% and 53.5%, respectively. At the latest follow-up of the 41 patients, 4 died of the disease, 2 had died of unrelated causes, 3 were AWD, 5 were NED, and 25 were CDF. The 10- and 20-year overall survival were 88.8% and 79.0%, respectively.

Conclusion: Like the previous papers, there was a male predominance, the epiphysis of the long bones accounted for 80% of all cases and endoprosthetic replacement were performed in great majority of those patients. It is notable that bone metastasis was more common than pulmonary metastasis and many patients developed distant metastasis five years after the initial treatment. Long-term follow-up with surveillance of lung and bone metastasis is mandatory.

Paper #34 3255902

CHEMOTHERAPY UTILIZATION AND TIMING IN PRIMARY, LOCALIZED, HIGH-GRADE SOFT TISSUE SARCOMA: PATTERNS OF CARE IN THE NATIONAL CANCER DATABASE

Danielle S. Graham, MD, MBA[1]*; Mykola Onyshchenko*[2]*; Mark A. Eckardt*[3]*; Benjamin DiPardo*[1]*; Srirnam Venigalla*[4]*; Scott Nelson*[5]*; Bartosz Chmielowski*[6]*; Arun Singh*[6]*; Jacob Shabason*[4]*; Fritz C. Eilber*[7]*; Anusha Kalbasi*[8]
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Objective: Meta-analyses and prospective clinical trials provide conflicting evidence for the role and timing of chemotherapy for management of primary localized high-grade soft tissue sarcoma (STS) in adults. Given the absence of evidence-based consensus, we sought to characterize the patterns of chemotherapy utilization and timing at Commission on Cancer accredited facilities in the United States.

Methods: Using the National Cancer Database, we identified 19,087 patients ≥18 years of age who underwent surgical resection for primary localized high-grade STS from 2004-2016, notably excluding Ewing sarcoma, rhabdomyosarcoma, and GIST. Patients who had metastatic disease, received up-front palliative treatment, had significant treatment delays, or had primary head and neck disease were excluded. Using multivariable logistic regression analysis, we examined factors associated with utilization of chemotherapy, including clinical, patient, demographic, and facility characteristics. We also analyzed trends of chemotherapy utilization over time. This analysis was repeated by comparing utilization of single versus multi-agent chemotherapy as well as neoadjuvant versus adjuvant chemotherapy in patients treated after 2006, as neoadjuvant chemotherapy data was only available starting in 2006. The Bonferroni correction was used to adjust for multiple hypothesis testing; as such, statistical significance was set at $p < 0.001$.

Results: Baseline characteristics of the study cohort are shown in Table 1. Chemotherapy was administered to 21% (n=4,034) of the study population. Factors associated with chemotherapy use were younger age, larger tumor size, and histology. Among histologies, chemotherapy utilization was highest for synovial sarcoma (49%) and myxoid liposarcoma (30%), and lowest for fibrosarcoma (16%) and fibromyxosarcoma (14%). Chemotherapy utilization was also associated with commercial health insurance, higher patient income, treatment facility location, academic facilities, high-volume facilities, good performance status, cardiac tumor site, and use of radiation (Table 2). Of patients receiving chemotherapy, neoadjuvant therapy data was available for 3,701 patients, 47% (n=1,579) of whom received neoadjuvant chemotherapy. Histology and tumor site were associated with neoadjuvant chemotherapy use. Among histologies, neoadjuvant chemotherapy utilization was highest for fibromyxosarcoma (55%) and UPS (52%), and lowest for epithelioid sarcoma (34%) and angiosarcoma (29%). Patients with extremity tumors were most likely to receive neoadjuvant chemotherapy (55%). Neoadjuvant chemotherapy use was also associated with higher income, academic facilities, high-volume facilities, farther distance from treatment facility, larger tumor size, deep tumors, positive surgical margins, and radiation treatment (Table 3). Of those receiving chemotherapy, data regarding number of agents used was available for 4,112 patients, and 85% (n=3,506) of whom received multi-agent chemotherapy. Among histologies, multi-agent chemotherapy was highest in leiomyosarcoma (90%) and lowest in angiosarcoma (49%). The use of multi-agent chemotherapy was also associated with younger age and high-volume facility (99th percentile). We did not observe a temporal trend for utilization, timing, or number of agents of chemotherapy.

Conclusion: In the absence of level I evidence-based guidance, the variability in chemotherapy utilization is driven not only by clinical factors but patient, demographic and facility factors as well. There is a notable discrepancy in the use of chemotherapy – especially neoadjuvant chemotherapy and multi-agent chemotherapy – between high- and low-volume centers.

Table 1. Characteristics of study cohort (n = 20,969)

Characteristic		No.	Percent	Characteristic		No.	Percent	Characteristic		No.	Percent
Sex	Male	11,137	53.1	Facility type	Non-academic	8,575	40.9	Primary site	Extremity	12,952	61.8
	Female	9,832	46.9		Academic	10,185	48.6		Heart	157	0.7
Age	18-49yo	4,586	21.9		Unknown	2,209	10.5		Trunk	1,208	5.8
	50-69yo	8,641	41.2	Facility volume	Low-volume	16,043	76.5		Thorax	2,103	10.0
	≥70yo	7,742	36.9		High-volume	4,926	23.5		Abdomen/ pelvis	3,923	18.7
Race	Non-hispanic white	16,883	80.5	Distance to treatment	0-10 miles	8,060	38.4		Other	626	3.0
	Non-hispanic black	1,916	9.1		10-30 miles	6,095	29.1	Size	<5cm	5,635	26.9
	Hispanic	1,224	5.9		30-100 miles	4,385	20.9		5.1-10cm	6,533	31.2
	Other and Unknown	946	4.5		100+ miles	2,342	11.2		10.1-15cm	3,261	15.5
Insurance status	Commercial	9,270	44.2		Unknown	87	0.4		>15cm	2,659	12.7
	Medicare	9,228	44.0	Charlson-Deyo cormorbidity score	0	16,615	79.2		Unknown	2,881	13.7
	Medicaid	1,158	5.5		1	3,302	15.8	Depth	Superficial	5,145	24.5
	Uninsured	656	3.1		2+	1,052	5.0		Deep	9,473	45.2
	Other Government & Unknown	657	3.2	Histology	UPS	6,337	30.2		Unknown	6,351	30.3
Income	≥$63,333	7,788	37.1		High-grade myxoid LPS	603	2.9	Surgical margins	Negative	15,908	75.9
	$50,354-$63,332	4,900	23.3		Synovial sarcoma	1,058	5.0		Positive	3,708	17.7
	$40,227-$50,353	4,520	21.6		MPNST	788	3.8		Unknown	1,353	6.4
	<$40,277	3,416	16.3		Leiomyosarcoma	3,192	15.2	Radiation therapy	Yes	11,481	54.8
	Unknown	345	1.7		Liposarcoma	2,168	10.3		No	9,488	45.2
County size	Metropolitan	17,149	81.8		Angiosarcoma	767	3.7	Year	2004-2008	7,614	36.3
	Urban	2,921	13.9		Other undifferentiated / unclassified sarcoma	3,776	18.0		2009-2012	6,260	29.9
	Rural	361	1.7		Fibrosarcoma	328	1.6		2013-2016	7,095	33.8
	Unknown	538	2.6		Fibromyxosarcoma	1,681	8.0				
Facility location	South	6,439	30.7		Epithelioid sarcoma	271	1.3				
	East	4,049	19.3								
	Central	4,988	23.8								
	West	3,284	15.7								
	Unknown	2,209	10.5								

Table 2. Factors associated with chemotherapy use for the treatment of primary, localized, high-grade STS in the National Cancer Database from 2004-2016.

Characteristic		Chemotherapy (n)	Chemotherapy (%)	Unadjusted OR	p	Adjusted OR	p	Characteristic		Chemotherapy (n)	Chemotherapy (%)	Unadjusted OR	p	Adjusted OR	p	Characteristic		Chemotherapy (n)	Chemotherapy (%)	Unadjusted OR	p	Adjusted OR	p
Sex	Male	2,434	21.86	Reference	Reference	Reference	Reference	Facility type	Non-academic	1,432	16.70	Reference	Reference	Reference	Reference	Primary Site	Extremity	2,660	20.54	Reference	Reference	Reference	Reference
	Female	2,115	21.51	0.98	0.547	1.00	0.975		Academic	2,213	21.73	1.38	<0.001	1.17	0.001		Heart	85	54.14	4.57	<0.001	2.86	<0.001
Age	18-49yo	1,755	38.27	1.82	<0.001	1.49	<0.001		Unknown	904	40.92	3.46	<0.001	-	-		Trunk	198	16.39	0.76	0.001	0.85	0.059
	50-69yo	2,188	25.32	Reference	Reference	Reference	Reference	Facility volume	Low-volume	3,246	20.23	Reference	Reference	Reference	Reference		Thorax	493	23.44	1.18	0.002	1.23	0.002
	≥70yo	606	7.83	0.25	<0.001	0.31	<0.001		High-volume	1,303	26.45	1.42	<0.001	1.28	<0.001		Abdomen/ pelvis	976	24.88	1.28	<0.001	1.07	0.190
Race	Non-hispanic white	3,542	20.98	Reference	Reference	Reference	Reference	Distance to treatment	0-10 miles	1,589	19.71	Reference	Reference	Reference	Reference		Other	137	21.88	1.08	0.416	1.02	0.833
	Non-hispanic black	454	23.70	1.17	0.006	0.93	0.262		10-30 miles	1,372	22.51	1.18	<0.001	1.01	0.840	Size	<5cm	597	10.59	0.38	<0.001	0.36	<0.001
	Hispanic	344	28.10	1.47	<0.001	1.14	0.079		30-100 miles	1,002	22.85	1.21	<0.001	1.01	0.828		5.1-10cm	1,564	23.94	Reference	Reference	Reference	Reference
	Other & Unknown	209	22.09	1.07	0.414	0.85	0.064		100+ miles	568	24.25	1.20	<0.001	0.97	0.673		10.1-15cm	1,003	30.76	1.41	<0.001	1.50	<0.001
Insurance status	Commercial	2,821	30.43	Reference	Reference	Reference	Reference		Unknown	18	20.69	1.06	0.820	1.16	0.670		>15cm	830	31.21	1.44	<0.001	1.55	<0.001
	Medicare	1,032	11.18	0.29	<0.001	0.67	<0.001	Charlson-Deyo Comorbidity Score	0	3,860	23.23	Reference	Reference	Reference	Reference		Unknown	555	19.26	0.76	<0.001	0.75	<0.001
	Medicaid	360	31.09	1.03	0.647	0.86	<0.001		1	565	17.11	0.68	<0.001	0.83	<0.001	Depth	Superficial	643	12.50	Reference	Reference	Reference	Reference
	Uninsured	176	26.83	0.84	0.052	0.70	<0.001		2+	124	11.79	0.44	<0.001	0.63	<0.001		Deep	2,457	25.94	2.45	<0.001	1.70	<0.001
	Other Government & Unknown	160	24.35	0.74	0.001	0.85	0.118	Histology	UPS	1,183	18.67	Reference	Reference	Reference	Reference		Unknown	1,449	22.82	2.07	<0.001	1.63	<0.001
Income	≥$63,333	1,767	22.69	Reference	Reference	Reference	Reference		High-grade myxoid LPS	188	31.18	1.97	<0.001	0.95	0.650	Surgical Margin	Negative	3,377	21.23	Reference	Reference	Reference	Reference
	$50,354-$63,332	1,092	22.29	0.98	0.597	0.96	0.368		Synovial sarcoma	515	48.68	4.13	<0.001	2.22	<0.001		Positive	765	20.63	0.96	0.422	1.11	0.042
	$40,227-$50,353	972	21.50	0.93	0.128	0.94	0.230		MPNST	214	27.16	1.62	<0.001	0.79	0.014		Unknown	407	30.08	1.60	<0.001	1.61	<0.001
	<$40,277	657	19.23	0.81	<0.001	0.78	<0.001		Leiomyosarcoma	634	19.86	1.08	0.161	0.98	0.727	Radiation Therapy	Yes	2,674	23.29	Reference	Reference	Reference	Reference
	Unknown	61	17.68	0.73	0.030	0.63	0.011		Liposarcoma	394	18.17	0.97	0.609	0.71	<0.001		No	1,875	19.76	0.81	<0.001	0.83	<0.001
County size	Metropolitan	3,778	22.03	Reference	Reference	-	-		Angiosarcoma	231	30.12	1.88	<0.001	2.49	<0.001								
	Urban	579	19.82	0.87	0.007	-	-		Other undifferentiated / unclassified sarcoma	845	22.38	1.26	<0.001	1.14	0.018								
	Rural	84	23.27	1.07	0.575	-	-		Fibrosarcoma	50	15.24	0.78	0.120	0.70	0.036								
	Unknown	108	20.07	0.89	0.281	-	-		Fibromyxosarcoma	235	13.98	0.71	<0.001	0.73	<0.001								
Facility location	South	1,154	17.92	Reference	Reference	Reference	Reference		Epithelioid sarcoma	60	22.14	1.24	0.153	0.91	0.581								
	East	706	17.44	0.97	0.526	0.92	0.145																
	Central	1,104	22.13	1.30	<0.001	1.30	<0.001																
	West	681	20.74	1.20	0.001	1.18	0.008																
	Unknown	904	40.92	3.17	<0.001	1.40	<0.001																

Unadjusted and adjusted OR presented. Unknown facility type omitted from multivariate analysis due to collinearity. OR = odds ratio; CI = confidence interval

Paper #35 3217091

CLINICIANS' ADHERENCE TO PRACTICE GUIDELINES FOR SOFT TISSUE SARCOMA ANALYZED WITH QUALITY INDICATOR

Shintaro Iwata[1]*; Tomone Watanabe*[2]*; Yoko Kato*[3]*; Fumihiko Nakatani*[1]*; Eisuke Kobayashi*[1]*; Naoyo Takakura*[3]*; Naohiro Higashi*[2]*; Akira Kawai*[1]

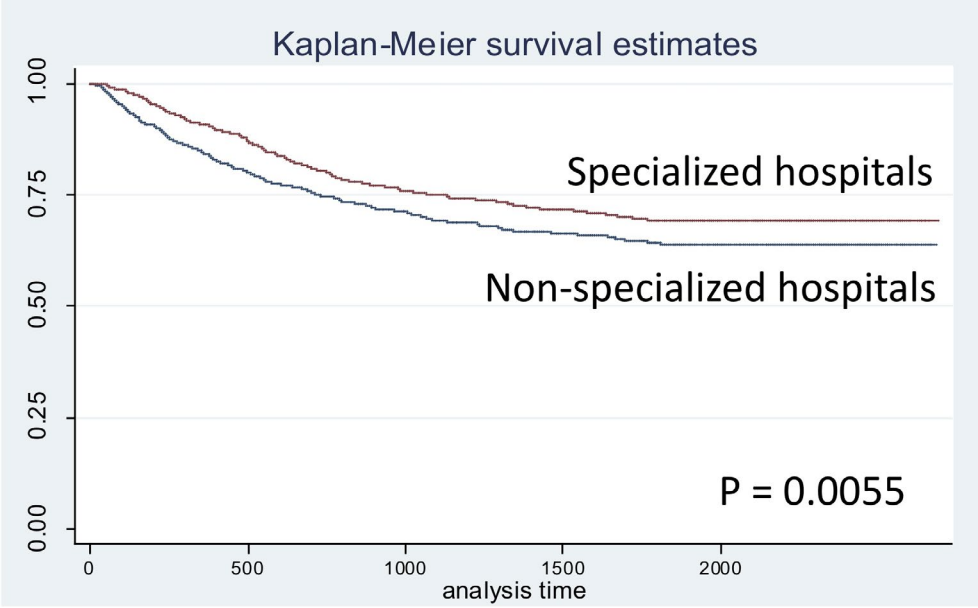
[1]*Dept. Musculoskeletal Oncology and Rehabilitation, National Cancer Canter Hospital, Tokyo, Japan;*
[2]*Center for Cancer Control and Information Services, National Cancer Center, Tokyo, Japan;*
[3]*Rare Cancer Center, National Cancer Center Hospital, Tokyo, Japan*

Objective: As a part of the Ministry of Health, Labor and Welfare project "Rare cancer control act", 53 facilities were designated as specialized hospitals (SH) for soft tissue sarcoma (STS) treatment in 2017, which can provide expert treatment of extremity or trunk STS. On the other hand, 382 facilities performed treatment of STS in Japan according to the population-based cancer registry. Clinicians' adherence to clinical practice guidelines (CPGs) was shown as an implementation rate of standards of care, which has been used as a quality indicator for hospitals. The purpose of this study is to clarify the difference of implementation rate of standards of care based on the CPGs for STS and overall survivals between SH and non-specialized hospital (NSH).

Methods: DPC data of 2,974 patients with extremity or trunk STS treated in designated cancer hospitals from 2013 to 2015 were extracted by topography and morphology code of ICD-O. Five standards of care based on the three CPGs for STS (R1: Appropriate local imaging before treatment, R2: Biopsy before treatment, R3: Wide resection as a definitive surgery, R4: Postoperative radiotherapy for the patient with a positive margin, R5: Postoperative radiotherapy for high-risk groups) were determined. Each implementation rate and 5-year overall survival were calculated, and a comparison between SH and NSH was performed by Pearson's chi-square test.

Results: Implementation rate of R1 to R3 were significantly higher in SH (R1, 81% vs 71%, p <.0001; R2, 80% vs 63%, p <.0001; R3, 85% vs 82%, p = .049). However, in R4 (19% vs. 22%, p = .52) and R5 (10% vs. 10%, p = .96), there was no significant difference in the implementation rate. 5-year overall survival was superior in SH comparing with NSH (69% vs 64%, p = .0055).

Conclusion: Regarding diagnosis and surgery, the implementation rate of standards of care for STS was significantly higher in SH comparing to NSH. This can result in a better outcome of STS patients treated in SH.



1:00 pm - 2:00 pm

– SESSION 9 –

GIST

Paper #36 3254072

INVICTUS: A PHASE 3, INTERVENTIONAL, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO ASSESS THE SAFETY AND EFFICACY OF RIPRETINIB (DCC-2618) IN PATIENTS WITH ADVANCED GASTROINTESTINAL STROMAL TUMORS (GIST) WHO HAVE RECEIVED TREATMENT WITH PRIOR ANTICANCER THERAPIES (NCT03353753)

Jean-Yves Blay[12]; Steven Attia[1]; Sebastian Bauer[13]; Ping Chi[2]; Gina D'Amato[3]; Suzanne George[4]; Hans Gelderblom[14]; Michael Heinrich[5]; Robin L. Jones[6]; Peter Reichardt[15]; Patrick Schöffski[7]; César Serrano[8]; John Zalcberg[9]; Julie Meade[10]; Kelvin Shi[10]; Rodrigo Ruiz Soto[10]; ***Margaret von Mehren****[11]*

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Objective: Progression of GIST following 1st-line therapy with imatinib generally is managed with the approved 2nd- and 3rd-line therapies sunitinib and regorafenib, respectively. Despite the effectiveness of these agents, heterogenous resistance mutations develop, driving further disease progression. No other approved treatment options exist, thus creating an area of high unmet medical need. We evaluated the safety and efficacy of ripretinib (DCC-2618), a novel, oral, broad-range inhibitor of primary and secondary imatinib-resistant mutants of KIT and PDGFR**α** kinases, as a ≥4th-line therapy in advanced GIST.

Methods: This global, phase 3, randomized, placebo-controlled, double-blind study enrolled patients (pts) aged ≥18 y with GIST and ECOG PS 0–2 who received ≥3 prior therapies (imatinib, sunitinib, regorafenib). Pts were randomized in a 2:1 ratio to ripretinib 150 mg QD + best supportive care (BSC) or placebo + BSC. Randomization was stratified by prior therapies (3 vs ≥4) and ECOG PS (0 vs 1 or 2). Upon disease progression, as assessed by blinded independent central review (BICR), pts were permitted to dose escalate to ripretinib 150 mg BID (if randomized to ripretinib) or to cross over to ripretinib 150 mg QD (if randomized to placebo). The primary endpoint is progression free survival (PFS) per modified RECIST based on BICR. PFS will be compared between the two arms using a stratified log-rank test. The secondary endpoints include ORR as assessed by BICR, overall survival, and other clinically relevant measurements of benefit.

Results: Enrollment was completed in Nov 2018. 129 pts were randomized, and 128 pts received ripretinib or placebo. Study results are expected in mid-2019.

Conclusion: This study was designed to demonstrate a clinically meaningful improvement in PFS in ≥4th-line therapy for GIST using ripretinib. Currently, there are no approved agents for use in ≥4L; a positive study would support the use of ripretinib to treat this population, which currently has a high unmet medical need for new treatments.

Paper #37 3258046

CLINICAL RESPONSE TO AVAPRITINIB BY RECIST AND CHOI CRITERIA IN ≥4TH LINE (4L+) AND PDGFRA EXON 18 GASTROINTESTINAL STROMAL TUMORS (GIST)

Michael Heinrich, MD[1]; *Robin L. Jones*[2]; *Margaret von Mehren*[3]; *Sebastian Bauer*[4]; *Yoon-Koo Kang*[5]; *Patrick Schöffski*[6]; *Ferry Eskens*[7]; *Olivier Mir*[8]; *Philippe Cassier*[9]; *César Serrano*[10]; *William D. Tap*[11]; *Jonathan C. Trent*[12]; *Piotr Rutkowski*[13]; *Shreyaskumar Patel*[14]; *Sant Chawla*[15]; *Eyal Meiri*[16]; *Teresa Zhou*[17]; *Maria Roche*[17]; *Suzanne George*[18]

[1]*OHSU Knight Cancer Institute, Portland, OR, USA;* [2]*Royal Marsden Hospital and Institute of Cancer Research, London, United Kingdom;* [3]*Fox Chase Cancer Center, Philadelphia, PA, USA;* [4]*University of Duisburg-Essen, Essen, Germany;* [5]*Asan Medical Centre, Seoul, Korea (the Democratic People's Republic of);* [6]*University Hospitals Leuven Leuven Cancer Institute, Leuven, Belgium;* [7]*Erasmus MC Cancer Institute, Rotterdam, Netherlands;* [8]*Institut Gustave Roussy, Villejuif, France;* [9]*Centre Léon Bérard, Lyon, France;* [10]*Vall d' Hebron Institute of Oncology, Barcelona, Spain;* [11]*Memorial Sloan Kettering Cancer Center, New York, NY, USA;* [12]*Sylvester Comprehensive Cancer Center University of Miami, Miami, FL, USA;* [13]*Maria Sklodowska-Curie Institute–Oncology Center, Warsaw, Poland;* [14]*MD Anderson Cancer Center, Houston, TX, USA;* [15]*Sarcoma Oncology Center, Santa Monica, CA, USA;* [16]*Cancer Treatment Center of America, Atlanta, GA, USA;* [17]*Blueprint Medicines Corporation, Cambridge, MA, USA;* [18]*Dana Farber Cancer Institute, Boston, MA, USA*

Objective: Avapritinib is an investigational, potent, and selective kinase inhibitor with broad activity against oncogenic KIT/PDGFRA mutants, including PDGFRA Exon 18 (Ex 18) D842V and other primary or secondary resistance mutations. We present previously unreported data from the phase 1 NAVIGATOR (NCT02508532) study of avapritinib in advanced gastrointestinal stromal tumors (GIST).

Methods: Adult patients (pts) with unresectable PDGFRA D842V-driven GIST, or other mutant GIST who progressed on imatinib and ≥ 1 other tyrosine kinase inhibitor (TKI), were treated with oral, once daily avapritinib. Efficacy per central radiology as per mRECIST 1.1 was assessed for patients who had received at least 3 prior therapies (4L+) and PDGFRA Ex 18 pts treated at the maximum tolerated dose (400 mg) or recommended Phase 2 dose (300 mg). Adverse events (AE) were analyzed for the overall safety population across the MTD/RP2D doses according to NCI CTCAE version 4.03.

Results: As of 16 Nov 2018, 237 pts [172 KIT, 62 PDGFRA Ex 18 (56 D842V, 6 non-D842V), 2 PDGFRA other (N659K, 1 missing) were enrolled including 111 in the response evaluable (RE) ≥4th Line (4L+) population (primarily KIT, median 4 prior TKIs) and 43 in the RE Ex 18 population (median 1 prior TKI). The 4L+ overall response rate (ORR) was 22% (1 complete response [CR], 23 partial responses [PR] [1 pending]), and 47% (n = 52) with stable disease (SD). Median duration of response (mDOR) was 10.2 months (95% CI: 7.2 - not evaluable [NE]). Among the 23 responders, DOR rates at 6 and 12 months were 87% and 43%, respectively. Median overall survival was 12.3 (95% CI: 8.7 - 14.4) months. Using Choi criteria, the ORR was 38% and the Disease Control Rate (CR, PR, or SD for ≥4 cycles) was 41%.

The Ex 18 ORR was 86% [3 CR, 34 PR (1 pending)] and 5 SD; mDOR was not reached (95% CI: 11.5 - NE). Among the 36 responders, DOR rates at 6 and 12 months were 89% and 65%, respectively. Median overall survival was not reached. Using Choi criteria, the ORR was 97% and the DCR was 97%.

Most AE were grade 1-2 the most common being (regardless of causality): nausea (64%), fatigue (55%), anemia (50%), periorbital edema (41%), vomiting (38%), decreased appetite (38%), diarrhea (37%), increased lacrimation (33%), peripheral edema (31%), and memory impairment (most common cognitive AE, 29%). AEs of Special Interest included cognitive effects (grade 1 (28%), 2 (9%), or 3 (4%)) and intracranial hemorrhage (3 events, two Grade 3 and one Grade 1). Only 8.3% of pts discontinued treatment due to a drug-related AE. Grade 3-4 treatment-related AEs (≥ 5%) included anemia (16%) and fatigue (6%).

Conclusion: Avapritinib has important clinical activity in advanced GIST pts with no available effective therapies (PDGFRA D842V; KIT-mutant GIST failing all approved therapies). The safety profile is predictable and manageable. These results suggest that avapritinib has the potential to change the treatment paradigm of pts with advanced GIST and supports randomized evaluation in earlier lines of therapy.

Paper #38 3214982

GENOTYPE-SPECIFIC ACTIVITY AND SAFETY OF CABOZANTINIB IN PATIENTS WITH GASTROINTESTINAL STROMAL TUMOR AFTER FAILURE OF IMATINIB AND SUNITINIB. EARLY MOLECULAR DATA FROM EORTC PHASE 2 TRIAL 1317 "CABOGIST"

Patrick Schöffski[1]*; Olivier Mir*[5]*; Bernd Kasper*[9]*; Zsuzsanna Papai*[10]*; Jean-Yves Blay*[11]*; Antoine Italiano*[12]*; Charlotte Benson*[3]*; Katerina Kopeckova*[6]*; Nasim Ali*[4]*; Palma Dileo*[7]*; Axel Le Cesne*[5]*; Franka Menge*[9]*; Sophie Cousin*[12]*; Céline Charon-Barra*[13]*; Agnieszka Wozniak*[1]*; Sandrine Marreaud*[8]*; Saskia Litiere*[8]*; Axelle Nzokirantevye*[8]*; Hans Gelderblom*[2]

[1]General Medical Oncology, University Hospitals Leuven, Leuven, Belgium; [2]Department of Medical Oncology, Leiden University Medical Center, Leiden, Netherlands; [3]Sarcoma Unit, Royal Marsden Hospital, London, United Kingdom; [4]Clatterbridge Cancer Centre, Wirral, United Kingdom; [5]Department of Medical Oncology, Institut Gustave Roussy, Villejuif, France; [6]Department of Oncology of the 2nd Faculty of Medicine, Charles University and University Hospital in Motol, Praha, Czechia; [7]University College London, London, United Kingdom; [8]European Organization for Research and Treatment of Cancer, Brussels, Belgium; [9]Sarcoma Unit - Interdisciplinary Tumor Center, Mannheim University Medical Center, Mannheim, Germany; [10]State Medical Centre Budapest, Budapest, Hungary; [11]Centre Léon Bérard, Lyon, France; [12]Sarcoma Unit, Institut Bergonié, Bordeaux, France; [13]Centre Georges François Leclerc, Dijon, France

Objective: Gastrointestinal stromal tumor (GIST) is the most common mesenchymal malignancy of the gastrointestinal tract and is commonly driven by activating mutations in *KIT* or *PDGFRA*. Advanced GIST is treated with tyrosine kinase inhibitors, but most patients (pts) develop resistance over time, mainly due to the occurrence of secondary molecular changes. EORTC 1317 assessed the safety and activity of cabozantinib, a multi-kinase inhibitor, in GIST pts who had progressed on imatinib and sunitinib. The primary endpoint was reported at the ASCO Annual Meeting (Schöffski et al. 2019), the final analysis of the trial including molecular findings will be presented at the CTOS Annual Meeting.

Methods: In this multi-center, open label, single arm Phase 2 study eligible metastatic GIST pts received 60 mg cabozantinib per os daily. The primary endpoint was the progression-free survival rate at week (wk) 12, assessed by local investigator per RECIST 1.1. If at least 21 of 41 eligible and evaluable pts were progression-free at wk 12, the activity of cabozantinib was sufficient to warrant further exploration (A'Hern one-stage design). Archival tissue from either the primary GIST or a metastatic lesion was collected and local mutational data was compared with results obtained with centralized targeted next generation sequencing (tNGS) using a custom-made panel of 97 genes and hybrid capture approach (IDT XGen lockdown probes, Illumina Nextseq500 paired-end sequencing).

Results: A total of 50 pts were eligible and started treatment between 02/2017 and 08/2018, with 16 (32%) continuing cabozantinib at the first database cut-off in 01/2019. The number of 3 wk treatment cycles ranged from 2-28+. Among the first 41 eligible and evaluable pts, 24 (58.5%) were progression-free at wk 12 and the trial thus met its primary endpoint. Among all 50 pts, 30 were progression-free at wk 12 (60%, 95% confidence interval (CI) 45-74%). A total of 7 pts achieved a confirmed partial response (PR) (14%, 95%CI 6-27%) and 33 had stable disease (SD) (66%, 95%CI 51-79%), resulting in a disease control rate (PR+SD) of 80% (95%CI 66-90%). Median progression-free survival was 6.0 months (95%CI 3.6-7.7). Local *KIT/PDGFRA* mutational information was available from 39 pts; central molecular results as obtained so far were concordant in 76% of cases. Centralized tNGS revealed *SDHA* variants of unknown significance in two pts with *KIT/PDGFRA* wild type tumors, and a likely pathogenic *NF1* mutation in a tumor without local molecular data. More details on the molecular analysis and the genotype-specific activity of cabozantinib will be presented after the final analysis of the trial and completion of gene sequencing in all cases, scheduled after the 2019 CTOS abstract deadline and prior to the Annual Meeting.

Conclusion: EORTC 1317 met its primary endpoint, with 24/41 pts (58.5%) being progression-free at wk 12. Results warrant further exploration of cabozantinib in GIST. Patient selection in a more definitive trial should ideally be based on molecular results obtained in the current study. Clinical trial information: NCT02216578

Paper #39 3247216

GASTROINTESTINAL STROMAL TUMOR LOCATION WITHIN THE STOMACH CORRELATES WITH TUMOR MUTATION PROFILE

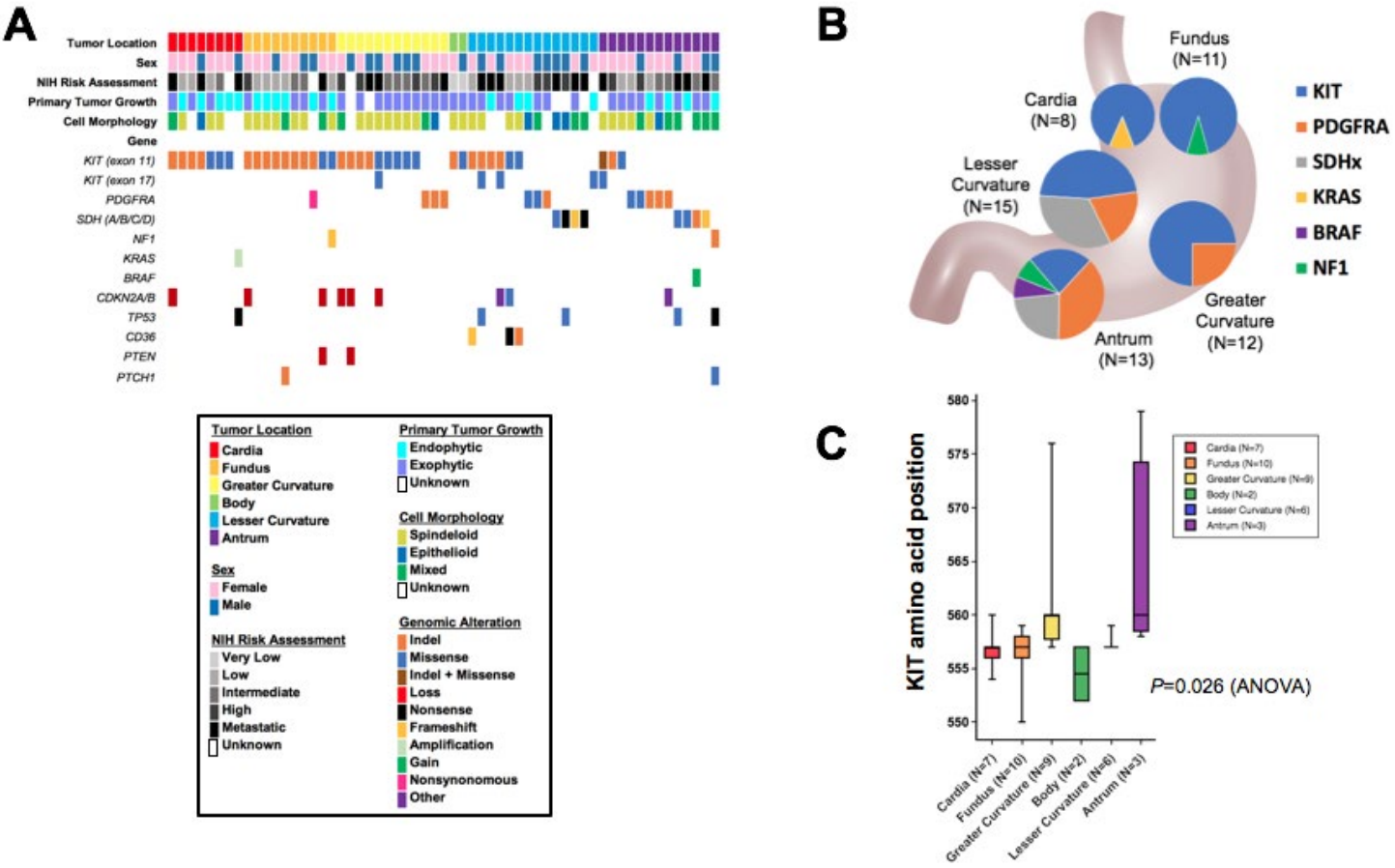
*Jason K. Sicklick[1]; **Jorge R. de la Torre Medina**[1]; Sudeep Banerjee[1]; Vi Nguyen[4]; Maha Alkhuziem[3]; Santiago Horgan[3]; Chih-Min Tang[1]; Mayra Yebra[1]; Hyunho Yoon[1]; Robert Mallory[1]; Hitendra Patel[2]; Shumei Kato[2]; Wilson Kwong[5]; Micheal Chang[5]; Syed Fehmi[5]; Thomas Savides[5]; Adam Burgoyne[2]; Paul Fanta[2]*
[1]Department of Surgery, Division of Surgical Oncology, University of California, San Diego, La Jolla, CA, USA; [2]Medical Oncology, UC San Diego, San Diego, CA, USA; [3]Department of Surgery, UC San Diego, San Diego, CA, USA; [4]Medical School, UC San Diego, San Diego, CA, USA; [5]Department of Gastroenterology, UC San Diego, San Diego, CA, USA

Objective: Gastrointestinal stromal tumor (GIST) most commonly occur in the stomach due to oncogenic mutations in *KIT* and *PDGFRA*, inherited mutations in *SDHx*, and less frequently from mutations in the RAS pathway (i.e., *KRAS, BRAF, NF1*). Outside of the stomach, *PDGFRA*and *SDHx*mutant GISTs are rare, suggesting that tumor location is associated with tumor mutation. We previously reported that the duodenal-jejunal flexure represents a hotspot for *NF1*mutant GIST (Burgoyne *et al.*, *JCO Precision Oncology*, 2017). Given this relationship between anatomy and tumor genetics, we hypothesized that GISTs arising from distinct regions of the stomach may possess unique genomic profiles.

Methods: An IRB-approved single institution database was analyzed (2001-2018, N=218). Study subjects were screened for gastric tumors (N=108) and next generation sequencing (NGS, N=110) performed during clinical work-up. Patients with multi-focal gastric GIST were excluded. Tumor locations were classified as 6 distinct regions including cardia, fundus, lesser curvature, greater curvature, body, and antrum. Tumor location was determined by review of cross-sectional imaging (JdlT and JKS) and operative notes (when available). Patient demographics, including age and sex, as well as tumor related factors (e.g., NIH risk assessment, pattern of tumor growth, and cell morphology) were retrospectively collected. Mutation status classification was performed for known genomic drivers including *KIT*, *PDGRFA*, *SDHx*, *KRAS*, *BRAF*, and *NF1*, as well as additional cancer-associated genes, based on NGS panels (Foundation Medicine, Tempus, and UC San Diego).

Results: Overall, there were 59 evaluable patients with gastric GIST and NGS (**Fig. 1A**). The median age was 60 and 61% were females. The median tumor size was 6.5 cm with median mitotic index of 2/5 mm^2. Tumors were most common in the lesser curvature (N=15; 23%), antrum (N=13; 22%) and greater curvature (N=12; 20%) (**Fig. 1B**). Females more frequently had cardia and fundus tumors (72%) versus males. These proximal tumors also tended to have an endophytic (vs exophytic) growth pattern (61% vs 38%). The overall genetic mutation distribution was 62% *KIT*, 18% *PDGFRA*, 13% *SDHx*, and 3% *NF1*, as well as 2% (each) *KRAS* and *BRAF*. Tumors in the proximal stomach (N=18; cardia+fundus) were almost uniformly *KIT* mutants (94%) (**Fig. 1A-B**). In contrast, *KIT* mutations were far less prevalent in tumors located in the lesser curvature (N=7; 46%) and antrum (N=3; 23%). Fewer *KIT*mutations in distal tumors were balanced by an increasing frequency of *PDGFRA* (greater curvature: 25%; lesser curvature: 20%; antrum: 38%) and *SDHx*(lesser curvature: 33%; antrum: 23%) mutations. All *KIT* mutations were in exons 11 and/or 17. Primary *KIT* exon 11 mutant tumors (N=37) in the proximal stomach (cardia+fundus) tended to have upstream mutations affecting amino acid positions 556-558 while distal tumors (greater curvature and antrum tumors) generally had downstream mutations affecting amino [SJ1] acid in the 559-561 position (**Fig. 1C**).

Conclusion: For the first time, we describe the anatomic-genomic landscape of gastric GIST. Our analysis revealed that tumors preferentially arise within five regions of the stomach. Furthermore, there are striking associations between gastric regions and driver mutations, as well as correlations between regions and sex. Proximal gastric GISTs (i.e., cardia and fundus) were overwhelmingly KIT mutant tumors, while tumors arising in the distal stomach displayed a much greater extent of genomic diversity. These findings suggest that: 1) gastric GIST is not a homogenous disease; 2) NGS of these tumors (especially in the distal stomach) has clear treatment implications for tailoring medical therapy; and 3) biological differences between tumor initiating cells in the proximal and distal stomach may exist.


A
Tumor Location
Sex
NIH Risk Assessment
Primary Tumor Growth
Cell Morphology
Gene
KIT (exon 11)
KIT (exon 17)
PDGFRA
SDH (A/B/C/D)
NF1
KRAS
BRAF
CDKN2A/B
TP53
CD36
PTEN
PTCH1
Tumor Location
Cardia
Fundus
Greater Curvature
Body
Lesser Curvature
Antrum
Sex
Female
Male
NIH Risk Assessment
Very Low
Low
Intermediate
High
Metastatic
Unknown
Primary Tumor Growth
Endophytic
Exophytic
Unknown
Cell Morphology
Spindeloid
Epithelioid
Mixed
Unknown
Genomic Alteration
Indel
Missense
Indel + Missense
Loss
Nonsense
Frameshift
Amplification
Gain
Nonsynonomous
Other
B
Fundus (N=11)
Cardia (N=8)
Lesser Curvature (N=15)
Greater Curvature (N=12)
Antrum (N=13)
KIT
PDGFRA
SDHx
KRAS
BRAF
NF1
C
KIT amino acid position
580
575
570
565
560
555
550
Cardia (N=7)
Fundus (N=10)
Greater Curvature (N=9)
Body (N=2)
Lesser Curvature (N=6)
Antrum (N=3)
P=0.026 (ANOVA)

3:30 pm - 5:30 pm

– SESSION 10 –

Retroperitoneal / Pelvic Sarcomas

Paper #40 3253011

PATTERNS OF RECURRENCE AND SURVIVAL PROBABILITY FOLLOWING SECOND RELAPSE OF RETROPERITONEAL SARCOMA: A STUDY FROM TARPSWG

Winan van Houdt[1]; Marco Fiore[2]; Francesco Barretta[2]; Piotr Rutkowski[3]; Jean-Yves Blay[4]; Guy Lahat[5]; Dirk Strauss[6]; Ricardo J. 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 P. Bagaria[16]; Robert Canter[17]; John Mullen[18]; Dario Callegaro[2]; Mark Fairweather[19]; Rosalba Miceli[2]; Chan Raut[19]; Alessandro Gronchi[2]; ***Rebecca Gladdy, MD, PhD****[15]*

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Objective: Data on oncologic outcomes following surgical management of recurrent retroperitoneal sarcoma (RPS) are limited, and clinical decision making remains complex. In this series from the Transatlantic Australasian Retroperitoneal Sarcoma Working Group (TARPSWG), we examined longitudinal outcomes of patients who experienced a second relapse of RPS to define predictors of recurrence and survival.

Methods: Data were collected from 22 sarcoma centers from January 2002 to December 2011 with institutional review board approval. All patients undergoing resection for a first local recurrence were included. Local recurrence (LR) was defined as recurrence in the ipsilateral retroperitoneum, peritoneal cavity, or pelvis. Primary outcome was overall survival (OS), defined as time from second relapse to death from any cause. Secondary outcomes included disease-specific survival (DSS) and crude cumulative incidence (CCI) of third recurrence (local or distant). OS was estimated using the Kaplan-Meier method and compared with the log-rank test. CCI curves of third events (LR or distant recurrence (DR)) after resection of LR were calculated in a competing risk framework. Multivariate analyses were performed with Cox and Fine & Gray regression models.

Results: Second recurrence occurred in 400 of 567 patients (70.5%) following an R0/R1 resection of first locally recurrent RPS. Patterns of failure were LR in 323 patients (80.75%), DR in 55 (13.75%), and concurrent LR and DR in 22 patients (5.5%) (Table 1). Median time (interquartile range) from resection of first local recurrence to second recurrence was 17 mo (8-32 mo) in the LR group, 9 mo (5-17) in the DR group, and 10 mo (4-18) in LR+DR group. The predominant histologic subtype with LR was liposarcoma (LPS) -31% were well-differentiated (WDLPS) and 46.1% were dedifferentiated (DDLPS). DR occurred most commonly in leiomyosarcoma (LMS) (43.6%). LR+DR was most common in DDLPS (54.5%). Chemotherapy was administered to the majority of patients with LR+DR (72.7%), but its use was limited in the DR (12.7%) and LR (36.8%) only groups. In contrast, radiation therapy was delivered to a minority of patients (LR: 14.2%, DR: 5.5%, and LR+DR: 4.5%). Resection was performed in 200 LR patients (61.9%), 8 DR patients (14.5%) and 5 LR+DR patients (22.7%). The 5-year OS for all patients with second recurrence (95% CI) varied significantly based on pattern of failure ($p<0.001$): 45.6% (39.4-52.8%) for the LR group, 25.5% (15.3-42.6%) for the DR group, and 0% for the LR+DR group. Factors associated with better OS by multivariable analysis included prolonged time to surgical intervention (32 vs 8 mo, HR 0.44; 95% CI 0.30-0.65, $p<0.001$) and surgery for second recurrence (yes vs no, HR 3.25; 95% CI 2.27-4.64, $p<0.001$). Histologic subtype and grade did not reach significance as predictors of OS. However, in patients with LR only, histologic subtype was statistically significant ($p<0.001$), with 5-year (95% CI) OS rates of 66.9% (56.1-79.9) for WDLPS, 31.6% (23.5- 42.5%) for DDLPS, 42.6% (26.7-67.9%) for LMS, 58.3% (34.0-100%) for solitary fibrous tumors (SFT), and 41.5% (24.6-70.2%) for other subtypes. Following resection of a second local recurrence, the CCI (95% CI) of LR (third LR) was 57.1% (50.2-64.9%) at 3 years and

65.6% (58.5-73.4%) at 5 years; the CCI of DR after resection of second LR was 9.2% (5.9-14.6%) at both 3 and 5 years. Strikingly, 48 patients (24%) were disease-free following resection for second local recurrence after a median follow up of 57 mo (30-83 mo).

Conclusion: In this comprehensive study of outcomes from TARPSWG after second recurrence in RPS patients, OS rates varied based on patterns of recurrence and surgical intervention was associated with improved survival. Although no survivors were identified for patients with a combined LR and DR as second relapse, durable disease free survivors were identified following surgery for second LR in patients highly selected for intervention.

Table 1. Demographic, Clinicopathological and Treatment Charactersitics of the Three Recurrent Disease Groups

Characteristic	LR	DR	LR+DR
Total patients, No.	323	55	22
At the time of surgery for the primary tumor			
Patient age, median (IQR), y	56 (47-64)	52 (47-65)	59 (52-64)
Sex, No. (%)			
Female	159 (49.2)	34 (61.8)	10 (45.5)
Male	164 (50.8)	21 (38.2)	12 (54.5)
Histologic subtype, No. (%)			
WDLPS	100 (31.0)	2 (3.6)	3 (13.6)
DDLPS	149 (46.1)	16 (29.1)	12 (54.5)
LMS	30 (9.3)	24 (43.6)	0 (0.0)
MPNST	10 (3.1)	1 (1.8)	1 (4.5)
SFT	1 (0.3)	2 (3.6)	1 (4.5)
Other	33 (10.2)	10 (18.2)	5 (22.7)
Follow-up after second recurrence, median (IQR), mo	50 (26-81)	71 (48-102)	31 (14-NA)
5 year Overall Survival	45.6%	25.5%	0%

Paper #41 3254877

POST-OPERATIVE MORBIDITY AFTER RESECTION OF RECURRENT RETROPERITONEAL SARCOMA: A REPORT FROM THE TRANS-ATLANTIC AUSTRALASIAN RPS WORKING GROUP (TARPSWG)

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Objective: Despite the increased discussion of recurrent retroperitoneal sarcoma (RPS) operations and their potential complexity, data concerning the safety of these procedures are lacking. Our aim was to evaluate perioperative outcome and identify predictors of severe adverse events after resection for recurrent RPS.

Methods: Data were collected from 22 sarcoma centers that are members of the Trans-Atlantic Australasian Retroperitoneal Sarcoma Working Group (TARPSWG), from January 2002 to December 2011 with institutional review board approval. All patients undergoing resection for a first local recurrence were included. Main outcome was to evaluate adverse events with surgery. A severe complication was defined as being classified as a Clavien-Dindo complication of grade ≥3. The resected organ score (ROS) is a devised weighted organ score to account for differences in surgical complexity[1]. Univariable and multivariable logistic models were fitted to study the association between Clavien-Dindo complications (grade ≥3 vs. no complications or<3) and patient and surgery characteristics. Survival end-points were overall survival (OS), (censoring for post-operative deaths, Clavien-Dindo=5) and local relapse and distant metastasis-free survival (LRFS, DRFS). Survival curves were estimated with the Kaplan-Meier method. Multivariable Cox models were fitted to study the association between the survival end-points and Clavien-Dindo complications (≥3 vs. no complications or <3) and other patient and tumor characteristics.

[1]MacNeill AJ, Gronchi A, Miceli R. et al. Postoperative Morbidity After Radical Resection of Primary Retroperitoneal Sarcoma A Report From the Transatlantic RPS Working Group. Annals of Surgery 2018; 267(5): 959-964.

Results: Six-hundred and eighty one consecutive patients were evaluated. Severe postoperative complications occurred in 109 patients (16.0%) and 3 patients (0.4%) died within 90 days. The most common complication was anastomotic leak at 6.0%. Median OR time was 3.8 hours and RO/R1 resections were achieved in 83.3% of cases. The median number of organs resected was 2 and only the recurrent tumor was resected in 22.5% of cases. Resections involving pancreaticoduodenectomy, major vascular resection and colon/kidney were found to entail higher operative risk for severe post-operative complications (odds ratio >1.9) but this was not found to be statistically significant in the multivariable analysis. In univariable analysis, tumor size, ROS and transfusion requirements were significant predictors of severe post-operative complications. However, on multivariable analysis only transfusion requirements remained a significant predictor. Importantly, having a severe complication was not associated with a worse OS, LRFS or DRFS.

Conclusion: Surgery for recurrent RPS can be quite complex, especially when a multi-visceral resection is performed, with risk for significant blood loss during an operation requiring transfusions. We note in this study that those patients requiring transfusion were at higher risk for severe complications. Future studies could look at how to mitigate the need for transfusion. This would include correlating if anemia at the time of surgery increases the risk of transfusion requirement. Specific strategies could be the focus of a future study in order to reduce the perioperative need of blood transfusion, including pre-habilitation and pre-operative optimization of hemoglobin. Overall, our results show that complication rates and mortality rates after resection of recurrent retroperitoneal sarcoma are very acceptable. Based on these data, a surgical

approach to recurrent RPS is reasonably safe and comparable to primary RPS when carried out at a specialized sarcoma center. High-risk resections should be carefully considered on an individual basis and weighed against anticipated disease biology. No association between severe surgical complications and long-term oncologic outcomes were identified.

Results univariable and multivariable logistic models for severe complications (Clavien-Dindo ≥3 Vs <3)

	Univariable models			Multivariable model		
	OR	95% CI	P	OR	95% CI	P
Age (years)			0.683			0.701
67 vs 50*	1.07	0.78-1.45		1.05	0.75-1.48	
Tumor size (cm)			0.070			0.542
18 vs 6*	1.21	0.80-1.83		0.77	0.49-1.23	
Resected organs score			0.003			0.411
3 vs 1*	1.58	1.19-2.10		1.24	0.89-1.73	
Transfusion requirement (blood units)			<0.001			<0.001
1-3 vs 0	2.94	1.66-5.23		2.82	1.53-5.18	
3+ vs 0	7.66	4.40-13.34		7.34	4.01-13.43	
Unknown vs 0	0.82	0.40-1.70		1.00	0.47-2.13	
Radiotherapy**			0.173			0.212
Pre-intraoperative† vs no	1.20	0.74-1.96		1.24	0.71-2.16	
Only postoperative vs no	0.46	0.18-1.18		0.44	0.15-1.30	
Chemotherapy**			0.184			0.668
Pre-postoperative§ vs no	1.48	0.91-2.4		1.28	0.75-2.20	
Only postoperative vs no	0.73	0.30-1.76		1.06	0.40-2.79	

Abbreviations: OR, odds ratio; CI: 95% OR confidence interval; P, two-sided Wald test p value; FNCLCC, French National Federation of the Centers for the Fight Against Cancer; DD LPS, dedifferentiated liposarcoma; WD LPS, well differentiated liposarcoma; LMS, leiomyosarcoma. * Third vs first quartile. **Not specified treatment not included. † including patients with preoperative, intraoperative, pre+intraoperative and intra+postoperative RT. § including patients with preoperative or pre+postoperative CT

Paper #42 3247745

COMPARISON OF TOTAL (IPSILATERAL) RETROPERITONEAL LIPECTOMY VERSUS STANDARD COMPLETE RESECTION IN PATIENTS WITH RETROPERITONEAL LIPOSARCOMA: A RETROSPECTIVE FIVE-INSTITUTION STUDY

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Objective: Retroperitoneal liposarcoma (RPLS) R_0/R_1 resection with co-resection of tumor-infiltrated organs is currently accepted to be standard complete resection (CR). As a more aggressive procedure, total (ipsilateral) retroperitoneal lipectomy (TRL) is to remove all the retroperitoneal fat tissue on the same side of the tumor in addition to standard CR. The objective of this study is to compare the outcomes of patients with RPLS treated with TRL versus CR.

Methods: Data of 165 de novo or first-recurrent RPLS patients was retrospectively drawn from prospectively maintained databases at 5 centers from December 2014 to June 2018. The patients were divided into TRL and CR on the basis of extent of surgical resection. Local recurrence (LR), local recurrence-free survival (LRFS) and overall survival (OS) rates were evaluated using Kaplan Meier and log-rank analyses. Univariate and Multivariate Cox regression analyses were used to determine the impact of demographic, operative and pathologic variables on the above mentioned endpoints.\

Results: Ninety-five patients underwent CR and seventy patients underwent TRL. The two groups were similar in age, gender, presentation (primary/recurrent), number of tumors (unifocal/multifocal) and FNCLCC grade. The TRL group had higher level of preoperative hemoglobin (p=0.031), higher percentage of larger tumors (cut-off of 21cm, p=0.010) and lower intraoperative blood loss (p=0.011). CR group had more severe postoperative complications than that of TRL group (p=0.026). After a median follow-up of 18 months, OS rate was significantly higher in the TRL group than in the CR group for multifocal tumors (p=0.013); however, it was not statistically significant for unifocal tumors. LR and LRFS rates were not significant between the two groups (all $p > 0.05$). On multivariate analysis, primary liposarcoma, low level of hemoglobin as well as low FNCLCC grade tumors were associated with decreased LR and improved OS.

Conclusion: TRL is a safe procedure with minor complications. It was associated with better OS in patients with multifocal RPLS; however, this did not translate into significantly better LRFS. This treatment strategy requires further investigation in prospective studies.

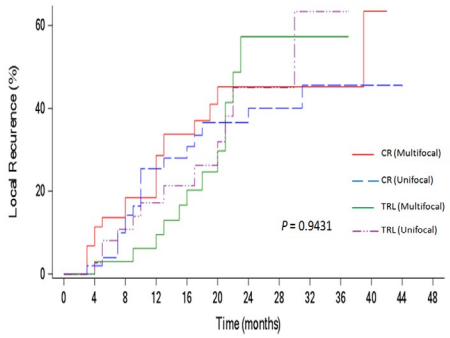

Figure 1. Local recurrence rate according to unifocality and multifocality of tumors in RPLS patients treated with TRL or CR. There was no statistically significant difference in the local recurrence rate between the two surgical techniques.

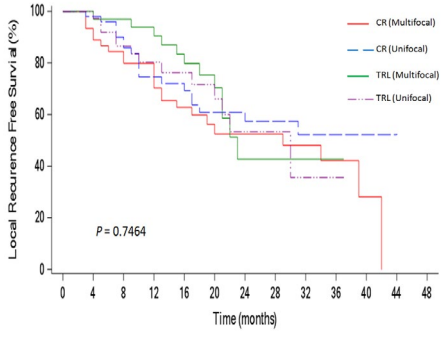

Figure 2. Local recurrence free survival according to unifocality and multifocality of tumors in RPLS patients treated with TRL or CR. There was no statistically significant difference in the local recurrence free survival between the two surgical techniques.

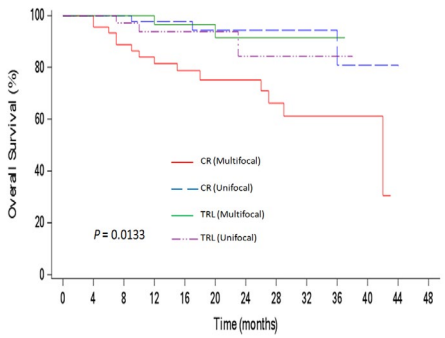

Figure 3. Overall survival according to unifocality and multifocality of tumors in RPLS patients treated with TRL or CR. TRL was associated with a statistically significant increase in overall survival for patients with multifocal tumors (p=0.0133).

Table 1. Demographic, Operative and Clinicopathologic Characteristics of Retroperitoneal Liposarcoma Patients. Data shown are number (%) or median (range).

Variable	All patients n = 165	CR n = 95	TRL n = 70	p value
Age, years	55 (29-81)	54 (29-81)	57 (36-77)	0.28
Gender				0.46
Male Female	88 (53%) 77 (47%)	53 (56%) 42 (44%)	35 (50%) 35 (50%)	
Presentation				0.15
Primary First Recurrence	93 (56%) 72 (44%)	49 (52%) 46 (48%)	44 (63%) 26 (37%)	
Hemoglobin, g/dl	12.70 (6.7-16.8)	12.5 (6.7-16.8)	12.95 (7.8-16.8)	0.031
Albumin, g/dl	3.9 (1.7-6.3)	3.8 (1.7-6.3)	3.9 (2.4-5.3)	0.35
Neoadjuvant therapy	7 (4%)	6 (6%)	1 (1%)	0.13
Tumor Size				0.010
 ≥21 cm	82 (50%) 83 (50%)	39 (41%) 56 (59%)	43 (61%) 27 (39%)	
No. of tumor				0.97
Unifocal Multifocal	87 (53%) 78 (47%)	50 (53%) 45 (47%)	37 (53%) 33 (47%)	
Operation time, minutes	245 (92-689)	241 (92-689)	245 (101-625)	0.86
Tumor site				0.67
Right retroperitoneum Left retroperitoneum	88 (53%) 77 (47%)	52 (55%) 43 (45%)	36 (51%) 34 (49%)	
Resected organs				0.30
None 1 2 ≥3	67 (41%) 46 (28%) 39 (24%) 8 (5%)	40 (42%) 29 (31%) 20 (21%) 5 (5%)	27 (39%) 17 (24%) 19 (27%) 3 (4%)	
Estimated blood loss, ml	500 (20-17000)	500 (20-17000)	400 (50-3000)	0.011
Clavien-Dindo classification				0.026
None <3 ≥3	69 (42%) 76 (46%) 19 (12%)	49 (52%) 34 (36%) 12 (13%)	20 (29%) 42 (61%) 7 (10)	
Length of stay, days	23 (4-64)	24 (4-64)	21 (7-45)	0.52
Histologic subtype				0.90
Well differentiated Dedifferentiated Others*	73 (45%) 59 (36%) 32 (19%)	39 (41%) 40 (43%) 15 (16%)	34 (49%) 19 (27%) 17 (24%)	
FNCLCC grade				0.64
Grade X Grade 1 Grade 2 Grade 3	8 (5%) 71 (49%) 28 (19%) 39 (27%)	6 (7%) 39 (48%) 14 (17%) 22 (27%)	2 (3%) 32 (49%) 14 (22%) 17 (17)	
Adjuvant therapy	10 (6%)	6 (6%)	4 (6%)	0.88

Paper #43 3256471

THE EFFECT OF PREOPERATIVE TREATMENT ON THE PERFORMANCE OF PREDICTIVE NOMOGRAMS IN PRIMARY RETROPERITONEAL SARCOMA (RPS)

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Objective: RPS-specific nomograms are used to calculate the risk of recurrence following resection, and probability of long-term survival, for the individual patient. Risk is calculated based on a group of weighted prognostic variables, validated in independent patient cohorts. Our aim was to evaluate the predictive accuracy of existing RPS-specific nomograms [1-4] in patients managed at our center, where the majority undergo preoperative XRT (preop XRT).

Methods: All patients who underwent curative treatment for primary RPS at Mount Sinai Hospital/Princess Margaret Cancer Centre between 1996 and 2016 were identified in a prospective database. Patients who had distant metastatic disease at presentation and/or did not undergo resection of their primary tumor were excluded. Survival functions were estimated by the Kaplan Meier methods. LR and DR were calculated within a competing risks framework. The performance of four existing nomograms was assessed by measuring the agreement between nomogram-predicted and actual outcomes, using Harrell's Concordance Index. Specific outcomes included in each of the nomograms (Overall Survival, OS; Disease-Free Survival, DFS; Disease-Specific Death, DSD; Local Recurrence, LR; Distant Recurrence, DR) at each of the specified post-resection time points (Table) were examined.

Results: 253 patients (119F, 134M; median age 60) with primary RPS underwent resection with curative intent (249 R0/R1; 4 R2) over the study period. Median postoperative follow-up time was 55 months (IQR 29-95), and 3-, 5-, and 10- yr OS were 81%, 71%, and 53%, respectively.
Comparing actual outcomes with those predicted by each of the nomograms for the entire cohort of 253 patients (Table), the Concordance Index ranged from 0.60 to 0.81. OS was underestimated by the INT nomogram (10yr OS predicted: 42%; actual: 53%), while LR was overestimated by the MSKCC nomogram (5yr LR predicted: 44%; actual: 25%).
We postulated that the high rate of preop XRT (203 of 253 patients, 80.2%) at our center might interfere with the predictive accuracy of existing nomograms. Indeed, LR in the preop XRT group was markedly notably overestimated by the MSKCC nomogram (5 yr LR predicted: 45%; actual: 24%), while the estimation for the no XRT group was more accurate (predicted: 41%; actual: 31%) (Table).

Conclusion: Preoperative radiotherapy appears to preclude the use of some components of existing prognostic nomograms for primary RPS, in particular with respect to the risk of LR. One potential interpretation of these results is that preop XRT reduces LR. Further exploration of histology-specific effects is warranted, in view of the recently released initial results of the STRASS1 RCT of preop XRT for RPS.

RPS-specific Nomogram	Outcome	Concordance Index		
		All (n=253)	Preop XRT (n=203)	No XRT (n=50)
MD Anderson [1]	OS – 3 yr	0.72	0.72	0.71
	OS – 5 yr	0.73	0.72	0.76
Istituto Nazionale Tumori, Milan (INT) [2]	OS - 5 yr	0.60	0.62	0.58
	OS - 10 yr	0.60	0.60	0.62
Tri-Institution (MDA, Milan, UCLA) [3]	OS – 7 yr	0.64	0.60	0.78
	DFS – 7 yr	0.66	0.67	0.73
MSKCC [4]	DSD – 5 yr	0.72	0.71	0.66
	LR – 5 yr	0.60	0.58	0.90
	DR – 5 yr	0.81	0.83	0.66

*OS- Overall Survival, DFS- Disease Free Survival, DSD- Disease Specific Death, LR- Local Recurrence, DR- Distant Recurrence [1] Anaya DA, Lahat G, Wang X, et al. Ann Oncol. 2010; 21:397 – 402. [2] Ardoino I, Miceli R, Berselli M et al. Cancer 2010; 116:2429–36. [3] Gronchi A, Miceli R, Shurell E, et al. J Clin Oncol 2013; 31:1649–1655. [4] Tan MCB, Brennan MF, Kuk D et al. Ann Surg 2016; 263:593–600.

Paper #44 3253843

PREOPERATIVE LEIOMYOSARCOMA RISK-SCORE FOR DISCRIMINATION OF LEIOMYOSARCOMA VS. LEIOMYOMA OF THE UTERUS

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Objective: From a country-wide register of uterine soft tissue malignancies in Germany, it turned out that surgery of uterine leiomyosarcoma (LMS) was performed in 69.8 % under the indication of presumed benign leiomyoma (LM). In consequence, 46.5 % of all LMS in stage pT1a/b have had an inadequate surgery with lesion of the tumor and/or uterus and morcellation takes place in 41.1 %. In this group local-relapse-free interval is significantly shorter than with adequate surgery. Therefore, prevention of inadequate surgery is a challenging problem. Here we demonstrate the results of obtaining a preoperative LMS-score for discrimination of LMS and LM prior to surgery.

Methods: From a nationwide prospectively collected registry (REGSA) intended to document the practice of treating gynaecological sarcomas and the counselling center on gynaecological sarcoma of the University of Greifswald data were retrieved. For development of the score we analysed and compared basic anamnestic, epidemiological, and clinical findings between LMS and LM. For the study the prospective cohort of 831 patients with LM and a predominantly retrospective cohort of 293 women with LMS were included. Based on the key features of both entities a preoperative LMS-score was developed by logistic regression. The logits of the logistic regression were translated into a score system for tumor classification and independently evaluated by analysing the area under the curve (AUC).

Results: Age, tumor diameter, postmenopause, postmenopausal bleeding, intermenstrual bleeding in premenopause, rapidity of LM/LMS growth, suspicion on pre-surgival ultrasound were different key features with $p<0.001$ for LMS vs. LM. Solitary tumor and failed medical therapy of previous LM were also higher in LMS but not significantly. In contrast, symptoms without bleeding disturbances, dysmenorrhea and hypermenorrhoea were significantly more observed in LM. By analysis the score achieved a cross-validated mean AUC of 0.964 (*SD*=0.019). The score ranges from -8 to + 13. No LMS are observed with a cut off <-4 and only 0.2 % false positive LM are observed with a score of +4 (Cut off - 3 only 1.9 % false negative LMS, and +1 only 2.3 % false positive LM). A score of -1 reveals a cumulative LMS-LM-ratio a of 1:1. Additional findings were that endometrial biopsy revealed in only 38.5 % an LMS. LDH-values, and anamnestic surgery for atypical smooth muscle tumors were significantly higher in LMS ($P < 0.01$) than in LM. In cases of an intermediate risk, subsequent diagnostics like endometrial biopsy (only with bleeding disturbances and/or suspicious intracavitary sonography), color-Doppler-sonography, LDH-recording, MRI and transcervical biopsy need to be discussed.

Conclusion: By using the proposed score, a prediction of an LMS in planned surgery of a uterine mass mostly LM is possible. The score is based only on basic preoperative clinical characteristics and well feasible by the gynaecological practitioner.

Paper #45 3253748

OUTCOMES ANALYSIS OF THE MULTIMODALITY TREATMENT OF PATIENTS WITH CAVAL LEIOMYOSARCOMA

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Objective: Caval leiomyosarcomas (cLMS) are rare soft tissue tumors originating from the smooth muscle layer of the inferior vena cava. Historically, patients with caval LMS have been associated with high recurrence rates and poor overall prognosis when compared to non-caval retroperitoneal LMS. While radical resection remains the mainstay of therapy for cLMS, recent improvements in systemic therapies have altered the landscape of sarcoma treatment and presented new opportunities for multimodality therapy. The aim of the current study was to examine the clinical outcomes of patients with cLMS treated with multimodality approaches and to compare their outcomes to those of patients with non-caval retroperitoneal LMS.

Methods: An IRB-approved, retrospective, single institution review of the Ohio State University cancer registry identified all patients with a diagnosis of primary retroperitoneal LMS from 2012-2018. Patients with non-retroperitoneal LMS (which includes primary uterine LMS) were excluded. Radiographic and pathologic review was undertaken to identify patients with cLMS and non-caval retroperitoneal LMS.
Standard clinicopathologic variables were collected retrospectively on all patients. For patients receiving neoadjuvant chemotherapy, radiographic response after 4 cycles was retrospectively assessed by standard RECIST 1.1 criteria. Primary endpoints were overall (OS) and progression-free survival (PFS) as estimated by Kaplan-Meier survival analysis.

Results: Eleven patients with cLMS were identified (Table). All patients with cLMS had pathologic Grade 2 (n=4) or Grade 3 (n=7) tumors and overall stage II (n=2) or stage III (n=9) disease. Median tumor size was 7.5cm (IQR, 5.0 – 14.3cm). Seven patients received neoadjuvant chemotherapy with adriamycin-based regimens, for a median duration of 6 cycles. Radiographic responses to neoadjuvant chemotherapy included one patient (14%) with partial response, 5 patients (72%) with stable disease, and one patient (14%) with progressive disease. Nine cLMS patients underwent successful R0/R1 resection, with 5 patients requiring en-bloc multivisceral resection. Two patients underwent attempted resection that was aborted intraoperatively. Six patients received adjuvant systemic therapy, including 5 who received targeted tyrosine kinase inhibitor therapy.
The 11 patients with cLMS were compared to the 20 patients with non-caval retroperitoneal LMS treated during the same period. No significant differences in average tumor size, pathologic grade, T-stage, overall stage, or resection margin status were observed between the two cohorts. Patients with cLMS were more likely to receive neoadjuvant (64% vs. 10%) and adjuvant chemotherapy (55% vs. 15%) than patients with non-caval retroperitoneal LMS. Two-year OS was comparable between patients with cLMS and those with non-caval retroperitoneal LMS, at 82% vs. 78% (p=NS), as was 2-year PFS (46% vs. 55%; p=NS).

Conclusion: Multimodality treatment with systemic therapy and an aggressive surgical approach may achieve equivalent survival outcomes for patients with caval LMS compared to those with similar non-caval retroperitoneal LMS. We recommend that all patients with caval leiomyosarcoma be evaluated for multidisciplinary treatment. Additional prospective data will be needed to confirm these findings.

Clinicopathologic features of patients with caval leiomyosarcoma (cLMS) and non-caval retroperitoneal (RP) LMS

Variable	cLMS (n=11)	Non-caval RP LMS (n=20)	p-value
Age (years)	64.7 +/- 11.0	53.9 +/- 13.4	0.03
Female gender	8 (73%)	16 (80%)	0.68
Neoadjuvant chemotherapy	7 (64%)	2 (10%)	0.04
Gross tumor size (cm)	9.6 +/- 5.9	11.6 +/- 5.5	0.45
Pathologic grade: Grade 2 Grade 3	- 4 (36%) 7 (64%)	- 6 (30%) 14 (70%)	0.67
T stage: T1 T2 T3 T4	- 2 (17%) 4 (36%) 4 (36%) 1 (9%)	- 0 7 (35%) 10 (50%) 3 (15%)	0.32
Overall stage: Stage II Stage IIIA Stage IIIB	- 2 (18%) 4 (36%) 5 (46%)	- 0 8 (40%) 12 (60%)	0.19
Margin status: R0/R1 R2	- 9 (82%) 2 (18%)	- 18 (90%) 2 (10%)	0.76
Adjacent organ resection	5 (45%)	13 (65%)	0.38
Adjuvant chemotherapy	6 (55%)	6 (30%)	0.26
Adjuvant radiation	0	4 (20%)	0.27

Values reported as mean +/- standard deviation or N (%)

Paper #46 3256534

FUNCTIONAL DURABILITY OF ACETABULAR RECONSTRUCTION FOLLOWING RESECTION OF PELVIC SARCOMAS

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Objective: Limb salvage for pelvic sarcomas involving the acetabulum remains a major surgical challenge. There is no consensus on what is an optimum acetabular reconstruction and little has been known about the functional durability of the reconstructive options. The purpose of this study was to assess functional outcomes according to the type of surgical treatment and associated factors with the outcomes.

Methods: A total of 91 patients with pelvic bone sarcoma involving the acetabulum who underwent surgical management between 1992 and 2017 were analyzed. Surgery consisted of limb-preserving procedure in 68 patients (75%) and hindquarter amputation in 23 (25%). Different reconstructive strategies were selected to address hip function/stability: allograft/APC in 24 (26%), pelvic prosthesis (custom-made 7; saddle 15; ice-cream cone 1; augmented THA 6) in 29 (32%), resection arthroplasty in 13 (14%), and arthrodesis in 2 (2%).

Results: A surgical complication occurred in 63 patients (69%) and 48 (53%) among them required further surgical treatment. A total of 16 patients (18%) experienced implant/graft failure; failure rate was 21%, 34%, 0%, and 50% in allograft/APC reconstruction, prosthetic reconstruction, resection arthroplasty, and arthrodesis, respectively. Major cause of failure was deep infection, which was most common in allograft/APC reconstruction (31%) followed by prosthetic reconstruction (21%), while no infection was observed with resection arthroplasty and arthrodesis. Tumor soft tissue extension significantly correlated with incidence of wound complication (p=0.029) and deep infection (p=0.035). The mean MSTS score at the final follow-up was 61%, 66%, 72%, and 53% in allograft/APC reconstruction, prosthetic reconstruction, resection arthroplasty, and arthrodesis, which were significantly superior to hindquarter amputation (33%; p<0.001). Lower MSTS scores were associated with deep infection (p=0.013), wound complication (p=0.005) and implant/graft failure (p=0.005). Among patients who were available for functional scores at various time points during follow-up, most patients (74%) had stable function after one year postoperatively. In patients with allograft reconstruction, 12 of 16 patients (75%) had stable function, ranging within ±20% of the MSTS score at the postoperative one year. The functional scores after saddle prosthetic reconstruction were relatively lower than other types of reconstruction, but were stable in 5 of 6 patients (83%). Patients who underwent resection arthroplasty experienced gradual improvement in function up to postoperative 10 years. The functional scores at the postoperative one year were significantly associated with the incidence of early complications within postoperative one year (p=0.004). Among patients who had implant/graft failure, 2 of 4 patients who had removal of implant/graft had improved function despite substantial leg-length discrepancy.

Conclusion: The functional outcome at one year postoperatviely reflected the final outcome in most patients. Overall functional outcomes were associated with early complications but not late complications. The functional outcome after implant/graft failure were not always pessimistic if limb-salvage was possible.

Paper #47 3256805

CARBON ION RADIOTHERAPY FOR SACRAL SARCOMAS

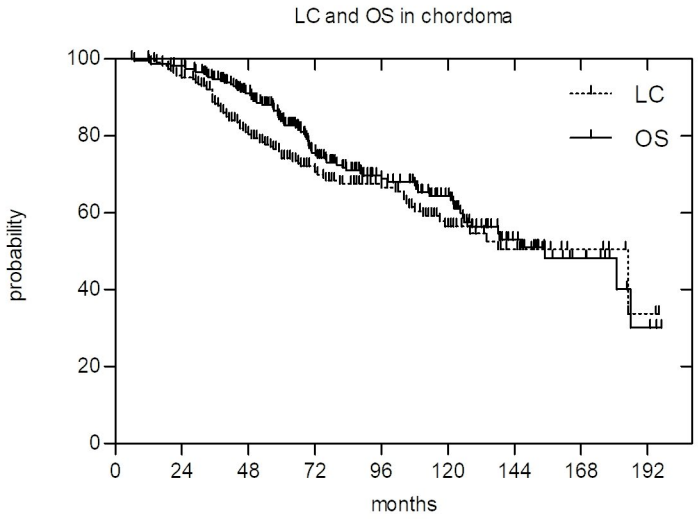
***Reiko Imai**; Hiroshi Tsuji; Tadashi Kamada*
QST NIRS Hospital, National Institutes for Quantum and Radiological Science and Technology, Chiba, Japan

Objective: Complete resection is essential for the treatment of sarcoma, however, it is sometimes difficult for patients with sacral sarcoma. Carbon ion radiotherapy(CIRT) makes the best use of the precise dose distribution and the high biological effectiveness of carbon ion beams and has been provided as a definitive treatment for inoperable sacral sarcoma. The objective is to report the results of CIRT in the treatment of patients with inoperable sacral sarcoma.

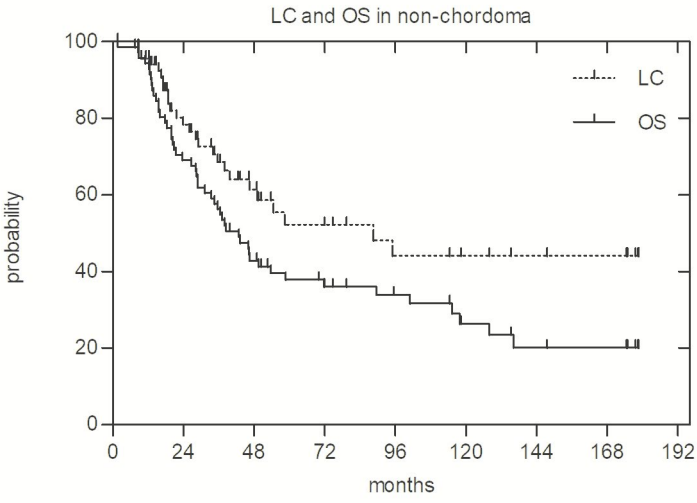
Methods: We retrospectively reviewed the records of patients who received CIRT for inoperable sacral sarcoma between April 2000 and March 2016.

Results: The cohort consisted of 306 patients aged 11-87 years (median 63 years of age) with inoperable sacral sarcoma. Median CIRT dose was 70.4 Gy RBE (relative biological effectiveness) delivered in 16 fractions. Median follow up for all patients was 70 months. In histology, chordoma was in 235 patients, chondrosarcoma in 13, osteosarcoma in 21, MPNST in 5, others in 32, respectively. In chordoma patients, median age was 66 years old. Median overall survival time was 75 months. Local control was 88%, 74% and 57% at 3, 5 and 10 years, respectively. Overall survival was 95%, 84% and 64% at 3, 5 and 10 years, respectively. The tumor location of the highest cranial level was L5 in 9 patients, S1 in 58, S2 in 87, S3 in 61 and S4 in 20. In 71 patients with other sarcomas median age was 36 years old. Median overall survival time was 38 months. Local control was 67%, 52% and 44% at 3, 5 and 10 years, respectively. Overall survival was 56%, 38% and 26% at 3, 5 and 10 years, respectively. The tumor location of the highest cranial level was L4 in 1 patient, L5 in 13, S1 in 46, S2 in 11, below S3 in 0. Compared to chordoma cases, tumors of non-chordoma cases located at higher cranial level. All patients tolerated the treatments well and there were only 11 grade 3-4 late toxicities.

Conclusion: CIRT was safe and efficacious in the treatment of inoperable sacral sarcoma with good local control, overall survival and low incident rate of adverse event.



Overall survival and local control in 235 patients with sacral chordroma



Overall survival and local control in 71 patients with sacral non-chordoma

8:00 am - 10:00 am

– SESSION 11 –

Paediatric Sarcomas

Paper #48 3253869

FIRST RESULTS OF THE EURO EWING 2012 TRIAL COMPARING TWO CHEMOTHERAPY REGIMENS IN NEWLY DIAGNOSED EWING SARCOMA

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Objective: Despite multiple randomized trials in newly diagnosed ES, over many years and involving several international co-operative groups, the outcomes for all stages of disease have plateaued. Internationally, a single standard chemotherapy schedule for ES is not defined. Therefore, a randomized comparison of the induction and consolidation chemotherapy regimens used most widely in Europe and the USA was undertaken. Based on an analysis in December 2018 of the first randomization of EUROEWING 2012, the independent Data Monitoring Committee recommended – and the Trial Steering Committee confirmed – that the randomization should close. Preliminary results for the first 584 patients are reported here.

Methods: Patients age 5 - 50 years old were eligible if they had newly diagnosed localised or metastatic ES. Patients were randomized to receive either the European regimen (Arm A) of VIDE induction and VAI/VAC (or VAI/BM) consolidation or the USA regimen (Arm B) of VDC/IE induction and IE/VC (or VAI/BM) consolidation [A=actinomycin D, B=busulfan, C=cyclophosphamide, D=doxorubicin, E=etoposide, I=ifosfamide, M=melphalan, V=vincristine]. The primary outcome measure was progression-free survival (PFS), with overall survival (OS) and toxicity as secondary outcomes. The trial had a Bayesian design with interpretation based on posterior probabilities (with non-informative priors) – i.e. probability that true hazard ratio (HR) is less than 1.0 given the data [Pr(HR<1.0|data)] – and 95% credible intervals (CrI) are reported. Analysis was intention-to-treat.

Results: Between 20 December 2013 and 10 December 2018, 284 patients were randomized to Arm A and 284 to Arm B. Baseline characteristics: 58% male; 40% <14 years old; 74% localized/loco-regional disease, 16% pleuro-pulmonary metastases, 10% other metastases. Median follow-up was 1.45 years, and 132 (23%) were still on treatment. Toxicity was not substantially different between the arms, with Arm B v. Arm A (adverse events [AEs] ≥ grade 3): number (percentage of total AEs) 236(84%) and 237 (84%) respectively. PFS at 2 years was 74% in Arm B and 65% in Arm A, HR=0.59, CrI=0.40-0.88. OS at 2 years was 88% in Arm B and 80% in Arm A, HR=0.56, CrI=0.32-0.98. There were 99.4% and 98% probabilities that PFS and OS respectively were better with Arm B compared to Arm A.

Conclusion: Arm B (VDC/IE/VC/VAI/BM) achieved both better PFS and OS than Arm A (VIDE/VAI/VAC/BM) with a high level of certainty, and with comparable toxicity.

This project has received funding from the European Union's Seventh Framework Programme for research; technological development and demonstration under grant agreement no 602856. This work was supported by Cancer Research UK [C5952/A14745].

Paper #49 3222400

RANDOMIZED PHASE 3 TRIAL OF GANITUMAB ADDED TO INTERVAL COMPRESSED CHEMOTHERAPY FOR PATIENTS WITH NEWLY DIAGNOSED METASTATIC EWING SARCOMA: A REPORT FROM THE CHILDREN'S ONCOLOGY GROUP (COG)

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Objective: Monoclonal antibodies directed against IGF-1R have shown activity in patients with relapsed Ewing sarcoma. The primary objective of COG trial AEWS1221 was to determine if the addition of the IGF-1R monoclonal antibody ganitumab to interval compressed chemotherapy improves event-free survival (EFS).

Methods: Patients with newly diagnosed metastatic Ewing sarcoma were randomized 1:1 at enrollment to Regimen A (interval compressed vincristine / doxorubicin / cyclophosphamide alternating every two weeks with ifosfamide / etoposide) or to Regimen B (same backbone as Regimen A, with ganitumab 18 mg/kg/dose administered intravenously at start of each cycle and then given as monotherapy every 3 weeks for 6 months after metastatic site radiation). Patients on both regimens received local control to primary tumor and metastatic sites. Randomization was stratified by age and metastatic site. A planned sample size of 300 patients was projected to provide 81% power to detect EFS hazard ratio of 0.67 or smaller for Regimen B compared to Regimen A with one-sided alpha of 0.025. Overall survival was a secondary endpoint.

Results: 299 eligible patients enrolled from December 2014 to March 2019 (148 in Regimen A and 151 in Regimen B; 254 patients < 21 years at diagnosis; 121 patients with isolated pulmonary metastasis). As of February 27, 2019, 50.5% of expected events had occurred. The 2-year EFS estimates were 39.8% (95% CI 29.0-50.4%) for Regimen A and 41.4% (95% CI 30.5-51.9%) for Regimen B (hazard ratio 0.95; 95% CI 0.65-1.39). The 2-year overall survival estimates were 73.8% (95% CI 62.0-82.4%) for Regimen A and 72.4% (95% CI 61.5%-80.6%) for Regimen B. More cases of pneumonitis post-radiation involving thoracic fields were reported on Regimen B vs. Regimen A (5 vs. 1). No other toxicity differences precluded administration of ganitumab along with interval compressed chemotherapy. Given the low likelihood of a significant efficacy result at the end of the study along with potential increased risk associated with ganitumab, the trial closed to accrual and no further ganitumab was administered as of March 2019.

Conclusion: Ganitumab added to interval compressed chemotherapy did not significantly improve EFS in patients with newly diagnosed metastatic Ewing sarcoma and may be associated with increased toxicity. Further follow-up after this interim analysis is ongoing with all active patients receiving interval compressed chemotherapy without ganitumab. New strategies are needed for this treatment-resistant population.

Paper #50 3279595

A PHASE III RANDOMIZED TRIAL OF ADDING VINCRISTINE-TOPOTECAN-CYCLOPHOSPHAMIDE (VTC) TO STANDARD CHEMOTHERAPY IN INITIAL TREATMENT OF NON-METASTATIC EWING SARCOMA – A REPORT FROM THE CHILDREN'S ONCOLOGY GROUP

Patrick Leavey[1]; Mark Krailo[2]; Steven DuBois[3]; Holcombe E. Grier[3]; Douglas S. Hawkins[4]; Bruce Pawel[5]; Helen Nadel[6]; Richard Womer[7]; Del Stringham[8]; Kenneth Brown[9]; Damon Reed[10]; Mark Bernstein[11]; Katherine A. Janeway[3]; Neyssa Marina[12]; Nadia Laack[13]; Lor Randall[14]; Richard Gorlick[15]; Leo Mascarenhas[5]

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Objective: Dose intensification by interval compression has improved outcomes for patients with non-metastatic Ewing sarcoma (EWS). We investigated whether the addition of VTC to interval compressed chemotherapy would further improve event-free survival (EFS).

Methods: Patients <50 years with newly-diagnosed EWS without distant metastases were eligible for enrollment on AEWS1031 (NCT01231906) and were scheduled to receive 17 cycles of alternating chemotherapy cycles administered every 2-weeks. Patients randomized to the standard arm with 5-drug therapy received 5 cycles of VDC (vincristine 1.5 mg/m2/day, days 1 and 8; cyclophosphamide 1,200 mg/m2, day 1; doxorubicin 37.5 mg/m2/day, days 1-2), 4 cycles of VC (vincristine 1.5 mg/m2/day, days 1 and 8; cyclophosphamide 1,200 mg/m2, day 1) and 8 cycles of IE (ifosfamide 1,800 mg/m2/day, days 1-5; etoposide 100 mg/m2/day, days 1-5). Patients randomized to the experimental therapy received 5 cycles of VTC (vincristine 1.5 mg/m2/day, days 1 and 8; topotecan 0.75 mg/m2/day, days 1-5; cyclophosphamide 250 mg/m^2/day, days 1-5), 5 cycles of VDC and 7 cycles of IE. Dexrazoxane was administered with the 4thand 5thdoxorubicin containing cycles. Myeloid growth factor support was administered at least 24-36 hours after each chemotherapy cycle. Primary tumor control with surgery, radiation or both was scheduled to be performed after 6 cycles in both arms. Chemotherapy was reinitiated following recovery from surgery and concomitantly with radiation therapy. Patients were randomized 1:1 between arms, with randomization stratified by age at diagnosis (<=17 years, >=18 years) and tumor site (pelvic, non-pelvic, extra-osseous). EFS was the primary endpoint and overall survival (OS) was a secondary endpoint. Risk for EFS and risk for death were compared between randomized groups by means of stratified log rank tests.

Results: 642 patients were enrolled between 2010 and 2016; 13 were ineligible. Among 629 eligible patients, 520 patients were <= 17-years and 357 were males; 115 patients had pelvic bone primaries, 401 had non-pelvic bone primaries, and 113 had extra-osseous primaries. After a median follow up of 59-months, 5-year EFS and OS for the cohort of eligible patients were 78% (95% CI, 74%-81%) and 87% (95% CI, 84%-90%), respectively. The 5-year EFS for those treated with experimental therapy was 79% (95% CI, 74%-83%) and for standard therapy was 77% (95% CI, 71%-82%). Experimental therapy did not significantly reduce the risk of event (EFS HR for experimental arm vs. standard arm of 0.83; 1-sided p = 0.13). The 5-year OS of patients treated with experimental therapy was 88% (95% CI, 0.84 to 0.91) and for standard therapy was 87% (95% CI, 0.82 to 0.90; 1-sided p=0.24). Toxicity between randomized groups was similar.

Conclusion: The addition of VTC to 5-drug interval compressed chemotherapy did not improve EFS and OS for patients with newly diagnosed non-metastatic EWS.

Paper #51 3223938

OUTCOME OF PATIENTS WITH RELAPSED OR PROGRESSIVE EWING SARCOMA ENROLLED ON PHASE 2 CLINICAL TRIALS: A REPORT FROM THE CHILDREN'S ONCOLOGY GROUP (COG)

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Objective: This analysis was undertaken to establish a benchmark for event-free survival (EFS) after enrollment on single agent trials for relapsed or progressive Ewing sarcoma. We performed a retrospective analysis of seven phase 2 trials of single agents for relapsed or progressive solid tumors, each with a Ewing sarcoma cohort, performed by the COG and its legacy groups.

Methods: Eligible patients with relapsed or progressive Ewing sarcoma enrolled on single-agent trials of docetaxol (CCG-0962), topotecan (CCG-09713), irinotecan (POG 9761), rebeccamycin analogue (POG 9963), imatinib (ADVL0122), oxaliplatin (ADVL0421), and ixabepilone (ADVL0524) from January 1997 until October 2007. The EFS (defined as time from study enrollment until first date of disease progression, date of detection of disease at a previously uninvolved site, date of death, or date of last follow-up) was estimated for the cohort of patients with Ewing sarcoma per study and for the entire cohort using the method of Kaplan and Meier.

Potential prognostic factors examined for their influence on risk of an EFS-event included: (1) age group at enrollment; (2) age group at initial diagnosis; (3) number of chemotherapy regimens received prior to enrollment on the particular study; (4) sex; and (5) enrolled on a trial where the agent was considered effective as described in the particular protocol.

Results: One hundred twenty-eight patients with relapsed or progressive Ewing sarcoma were enrolled on the included trials. Five patients were enrolled on more than one trial. One hundred twenty-four events (106 relapses and 18 deaths) occurred while the patients were enrolled. For all studies combined, the 6-month EFS was 12.7% (95% CI 7.6-19%). There was no difference in EFS based on age at relapse, age at diagnosis, number of prior chemotherapy regimens, or patient sex.

Only one trial achieved its protocol-specified goal for activity defined by radiographic response rate. CCG-0962 (docetaxel) had 3 partial responses among 26 patients (11.5%) with relapsed or progressive Ewing sarcoma. However, the 6-month EFS for this trial was 15% (95% CI: 4.8-31%). When the other 6 studies in aggregate are compared to CCG-0962, no difference in event free survival was identified (12%; 95% CI: 6.6-19.2%; p=0.253).

Conclusion: This analysis demonstrates the poor survival of patients with relapsed or progressive Ewing sarcoma with a pooled 6-month EFS for all seven single-agent studies of 12.7%. Although docetaxel was identified as active for relapsed or progressive Ewing sarcoma based upon radiographic response, EFS for docetaxel was similar to other agents without radiographic responses, indicating that a higher rate of radiographic response may not translate into superior disease control as assessed by EFS. The EFS benchmark identified in this analysis could be utilized in future trials conducted in recurrent Ewing sarcoma.

Paper #52 3253193

DO CHILDREN AND ADOLESCENTS WITH COMPLETELY RESECTED ALVEOLAR RHABDOMYOSARCOMA (RMS) REQUIRE RADIATION? A REPORT FROM THE CHILDREN'S ONCOLOGY GROUP (COG)

Jamie Aye, MD[1]*; Yueh-Yun Chi*[2]*; Jing Tian*[2]*; Suzanne Wolden*[3]*; Douglas S. Hawkins*[4]*; Abha Gupta*[5]
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Objective: Patients with RMS are risk-stratified based on their *FOXO1*-fusion status, histology (alveolar or embryonal), primary site (favorable or unfavorable), and post-surgical grouping (extent of upfront surgery). Patients with localized, completely resected (Group I) embryonal RMS (ERMS) without regional lymph node involvement do not require adjuvant radiation (RT). COG clinical trials have inconsistently included adjuvant RT for patients with Group I alveolar RMS (ARMS). To resolve this issue, we determined outcome in patients with Group I ARMS who were treated with or without RT.

Methods: Patients with Group I ARMS enrolled on 1 of 3 COG clinical trials (D9602, D9803, or ARST0531) were analyzed. All patients received intensive systemic chemotherapy and 36 Gy adjuvant RT (if given) to the primary site at week 12 or week 4 for D9602/D9803 and ARST0531, respectively. Event-free survival (EFS) and overall survival (OS) were estimated using the Kaplan-Meier method and the log-rank test was performed to assess statistical significance.

Results: 36 patients with Group I ARMS were treated on D9602/D9803 (n = 23) or ARST0531 (n = 13). Twenty-four (67%) patients were male. Median age was 4.1 years (range 0.8 to 45.8). Twenty-one (58%) patients had an unfavorable primary site and 10 (28%) had tumors > 5 cm. *FOXO1*-fusion status was negative, positive, and unknown in 28% (n = 10), 42% (n = 15), and 30% (n = 11), respectively. Twenty-two (61%) patients received RT. Overall, the 4-year EFS and OS were 70.8% (95% CI 55.5%, 86.1%) and 88.3% (95% CI 77.5%, 99.1%), respectively. There was no difference in EFS or OS by stage. Table 1 shows the relationship between *FOXO1*-fusion status, RT, and outcome.

Conclusion: Analysis of patients with Group I ARMS treated on D9602/D9803 or ARST0531 suggests that RT is necessary to improve outcomes in patients who are *FOXO1*+. Within the limits of our small study population, adjuvant RT is of uncertain value for Group I ARMS patients who are *FOXO1*-. Nonetheless, omitting adjuvant RT is rational for *FOXO1*- patients and similar to the standard for Group I ERMS.

Table 1. Outcome of patients with Group I ARMS based on *FOXO1*-fusion status and RT

	4-year EFS	4-year OS
FOXO1+ RT (n = 9) vs No RT (n = 6)	77.8% vs 16.7% (p = 0.03)	100% vs 50% (p = 0.08)
FOXO1- RT (n = 8) vs No RT (n =2)	87.5% vs 100% (p = 0.61)	87.5% vs 100% (p = 0.61)

Paper #53 3253900

ASSESSING THE PROGNOSTIC VALUE OF EARLY ANATOMIC RESPONSE TO INDUCTION CHEMOTHERAPY IN PEDIATRIC RHABDOMYOSARCOMA: A SYSTEMATIC REVIEW

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Objective: The prognostic value of early anatomic response, assessed by MRI or CT, in pediatric rhabdomyosarcoma (RMS) is still under debate. There is an urgent need to identify early biomarkers, that may serve as surrogate endpoints in RMS treatment. Early evaluation of treatment efficacy will facilitate early selection of promising treatment arms and their transition into phase III trials. A second unmet need, is the lack of biomarkers to identify patients at high risk for relapse, who should be selected early for innovative treatment strategies. The goal of this systematic literature review was to assess the evidence of the prognostic value of anatomic response to induction chemotherapy for patients with localized RMS, i.e. the association with event/failure-free (EFS/FFS) - and overall survival (OS).

Methods: The protocol was registered on PROSPERO (2017: CRD42017036060). We searched MEDLINE and EMBASE to 28 November 2018. Inclusion criteria: (1) the study population consisted of pediatric patients with IRSG stage III histologically proven RMS, (2) anatomic response assessment by MRI or CT was done after 2-4 courses of chemotherapy and (3) the prognostic value of early anatomic response for EFS/FFS and/or OS after at least 3 years was assessed. Two reviewers independently selected eligible articles, extracted data and critically appraised the methodological quality using the Quality in Prognosis Studies (QUIPS) instrument. In case of disagreement, consensus was reached by discussion with a third reviewer.

Results: The search identified 2810 records. After removal of duplicates, 2284 records were screened on title and abstract. We evaluated 61 full-text reports. Six studies were included, describing 2010 patients (table 1). Due to heterogeneity in response evaluation and treatment, a meta-analysis was not performed. Four studies found no difference in survival based on response; the studies of Burke et al. and Rosenberg et al. compared survival of patients with complete, partial and no response and found no significant difference in FFS and OS. Ermoian et al. compared FFS and OS between patients with complete response and patients with partial response/stable disease, again no significant difference in survival was found. In the study of Vaarwerk et al. a Cox proportional hazards regression analysis revealed no significant difference in FFS and OS for patients with partial or complete response compared to patients with no response. Two studies found a difference in survival; Dantonello et al. compared patients with partial response to patients with no response (including patients with progressive disease) and found a significant difference in EFS and OS. Ferrari et al. evaluated response in a multivariable analysis and found anatomic response to be prognostic for OS. Response was measured as a continuous variable and patients with progressive disease were included. Results are further specified in table 2. Quality assessment, see figure 1, revealed confounding as the most common limitation, as can be expected in observational studies; in three studies (Dantonello 2015, Ferrari 2010, Vaarwerk 2017) subsequent therapy was based on the response assessment; one study (Ferrari 2010) was a single institution cohort, which included patients over 26 years; one study (Dantonello 2015) merged patients with progressive disease and patients with objective response.

Conclusion: Current best available evidence shows no significant difference in survival between children in complete response versus any/no response at early response assessment. As known, progressive disease is prognostic for a worse outcome. Methodological analysis of two studies which concluded a positive prognostic value showed significant limitations. Therefore, we recommend that anatomic response assessment should not be used in future studies to guide treatment (de) escalation and treatment evaluation. There is an urgent need for early response markers.

Table 1. Summary of the studies included in this systematic review.

Study (year)	Country	Study design	Enrollment period	No. of patients included	Reason for excluding patients from response assessment analysis
Burke et al.(2007) [1]	Multinational	Multicentre prospective cohort	1991-1997	444	- Off therapy before completion of induction therapy/no response assessment (n=49) - Other histology than ERMS or ARMS (n=41) - Start date of RT could not be determined (n=14)
Dantonello et al. (2015) [2]	Multinational	Multicentre prospective cohort	1980-2005	529	In total n=229 excluded: - No documented response measurement at correct evaluation point - Tumour partly removed at primary surgery - Surgery/radiotherapy prior to evaluation of response
Ermoian et al. (2017) [3]	Multinational	Multicentre prospective cohort	2004-2010	53	- PD before week 12 evaluation (n=2) - Insufficient or missing week 12 evaluation (n=7)
Ferrari et al. (2010) [4]	Italy	Single centre retrospective study	1982-2008	205 (108 with response assessment)	In total n=216 excluded: - Metastatic disease - missing information on initial tumour size - Radiological diameter and volume not assessed
Rosenberg et al. (2014) [5]	Multinational	Multicentre prospective cohort	1999-2005	338	- Other histology than ERMS or ARMS (n=90) - Not IRS group III (n=139) - No response measurement documented (n=20) - PD at response assessment (n=6)
Vaarwerk et al. (2018) [6]	Multinational	Multicentre prospective cohort	1995-2003	432	In total n=194 excluded: - Unknown tumour size (n=64) - No response evaluation or at wrong time (n=116) - Tumour response was not evaluable (n=5) - Progressive disease at response assessment (n=7) - Lost to follow-up (n=2)

[1] Burke M, Anderson JR, Kao SC, et al. Assessment of response to induction therapy and its influence on 5-year failure-free survival in group III rhabdomyosarcoma: the Intergroup Rhabdomyosarcoma Study-IV experience - a report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group. J Clin Oncol. 2007;25(31):4909-4913. [2] Dantonello TM, Stark M, Timmermann B, et al. Tumour volume reduction after neoadjuvant chemotherapy impacts outcome in localised embryonal rhabdomyosarcoma. Pediatr Blood Cancer. 2015;62(1):16-23. [3] Ermoian RP, Breneman J, Walterhouse DO, et al. 45 Gy is not sufficient radiotherapy dose for Group III orbital embryonal rhabdomyosarcoma after less than complete response to 12 weeks of ARST0331 chemotherapy: A report from the Soft Tissue Sarcoma Committe e of the Children's Oncology Group. Pediatr Blood Cancer. 2017;64(9). [4] Ferrari A, Miceli R, Meazza C, et al. Comparison of the prognostic value of assessing tumor diameter versus tumor volume at diagnosis or in response to initial chemotherapy in rhabdomyosarcoma. J Clin Oncol. 2010;28(8):1322-1328. [5] Rosenberg AR, Anderson JR, Lyden E, et al. Early response as assessed by anatomic imaging does not predict failure-free survival among patients with Group III rhabdomyosarcoma: a report from the Children's Oncology Group. Eur J Cancer. 2014;50(4):816-823. [6] Vaarwerk B, van der Lee JH, Breunis WB, et al. Prognostic relevance of early radiologic response to induction chemotherapy in pediatric rhabdomyosarcoma: A report from the International Society of Pediatric Oncology Malignant Mesenchymal Tumor 95 study. Cancer. 2018;124(5):1016-1024.

Table 2. Summary of study methods and outcomes of included studies.

Study (year)	Response evaluation criteria	Timing response evaluation (after N courses of chemotherapy)	Response parameters	Treatment switch based on response	Outcomes
Burke et al. (2007)	Two-dimensional	3	CR: 100% decrease PR: ≥ 50% decrease NR: < 50% decrease or < 25% increase PD: ≥ 25% increase	No	5y-FFS: CR 75%, PR 71%, NR 78% p=0.57
Dantonello et al. (2015)	Volumetric measurement	3	PAR: ≥ 33% decrease NR: < 33% decrease OR: > 0-33% decrease SPD: no reduction or new lesions SD: stable disease (not defined) PD: overt progressive disease or new lesions	Patients with NR switched in chemotherapy	5-yr EFS: PAR; 68.1% ±4, NR; 59.2% ±13 p=0.03 5-yr OS: PAR; 76.4% ±4, NR; 62.6% ±13 p=0.004 Risk ratio: PAR+OR=1, SPD=4.8(2.8-8.2) Risk ratio: PAR=1, SPD+OR=2(1.3-3.2) 5y EFS: SD 47% ± 23, PD EFS 17%±30 p=0.04 5y OS: SD 47% ± 23, PD EFS 17%±30 p=0.03
Ermoian et al. (2017)	Volumetric measurement	4	CR: 100% decrease PR: ≥ 64% decrease SD: < 64% decrease or < 40% increase PD: ≥ 40% increase	No	5-yr FFS: CR 100, PR/SD 84 (71-96, p=0.11) 5-yr OS: CR 100, PR/SD 97 (91-100, p=0.52)
Ferrari et al. (2010)	One dimensional Volumetric measurement	3	Relative percentage reduction in tumour size (continuous variable)	Based on response, not further described	Tumour response significant predictor of survival (Wald test P V measure was 0.300 for diameter, 0.323 for volume.
Rosenberg et al. (2014)	Two-dimensional	4	CR: 100% decrease PR: ≥ 50% decrease NR: < 50% decrease or PD: ≥ 25% increase	No	5-yr FFS: CR 74% (64-82%), PR 76% (63-83%), NR 64% (47-82%) p=0.49
Vaarwerk et al. (2018)	Two-dimensional	3	CR: 100% decrease PR: ≥ 50% decrease OR: ≥ 25 - < 25% decrease or PD: ≥ 25% increase	Patients with OR/ NR/PD switched in chemotherapy	5-yr FFS: SR: 60% (55-65%), OR: 60 (44-75%), NR: 69% (51-87%) p=0.6 5-yr OS: SR: 74 (69-79%), OR: 73% (58-87%), NR: 72% (55-90%) p=0.9 Adjusted odds ratios for response: 5y FFS: SR: 1, OR: 1.09 (95% CI, 0.63-1.88), NR: 0.81 (95% CI, 0.39-1.67) 5y OS: SR: 1, OR: 0.91 (95% CI, 0.47-1.76), NR: 1.27 (95% CI, 0.61-2.64)

Abbreviations: CR, complete response; EFS, event-free survival; FFS, failure-free survival; HR, hazard ratio; IRS, Intergroup Rhabdomyosarcoma Group post-surgical staging; NR, non-response; OR, objective response; OS, overall survival; PAR, partial response; PR, partial response; RMS, rhabdomyosarcoma; RT, radiotherapy; SPD, stable/progressive disease; yrs, years.

Quality assessment	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis reporting
Burke et al (2007)	Low	Low	Low	Low	Moderate	High
Dantonello et al (2015)	Low	Low	Moderate	Low	High	Moderate
Ermoian et al (2018)	Low	Low	Moderate	Low	Low	Low
Ferrari et al (2010)	Moderate	High	Low	Moderate	High	High
Rosenberg et al (2014)	Low	Low	Low	Low	Moderate	Moderate
Vaarwerk et al (2018)	Low	Low	Moderate	Low	Moderate	Low

Paper #54 3256271

EUROPEAN PEDIATRIC SOFT TISSUE SARCOMA STUDY GROUP MTS2008 STUDY: RESULTS OF A PROTOCOL FOR METASTATIC RHABDOMYOSOSARCOMA

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Objective: Historically, patients with metastatic rhabdomyosarcoma have an event free and overall survival (EFS and OS) of respectively 27% and 34% (Oberlin et al, J Clin Oncol 26:2384-2389). The main goal of this study was to improve outcome by giving 9 3-weekly courses of intensive multiagent chemotherapy, followed by 1 year of maintenance chemotherapy.

Methods: Between August 2008 and December 2016, patients <21 years with metastatic rhabdomyosarcoma received 4x 21-day cycles of IVADo (ifosfamide, vincristine, actinomycin-D, doxorubicin) + 5 cycles of IVA with optional local therapy, followed by maintenance chemotherapy (12x 28-day cycles of cyclophosphamide + vinorelbine). Radiotherapy to locoregional disease and metastatic sites was advised after the sixth IVA cycle whenever feasible. Besides standard outcome analyses, patients were analyzed according to Oberlin prognostic risk factors for metastatic disease; these are defined as 1. age younger than 1 year or at least 10 years, 2.unfavorable site of primary tumor (i.e. extremity or 'other site'), 3. bone or bone marrow involvement, 4. three or more metastatic sites.

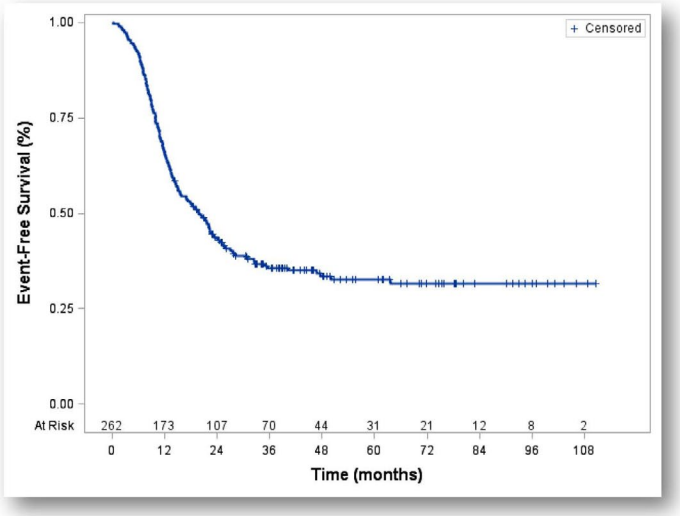
Results: 270 patients were enrolled in the study with a median follow up of alive patients (n=113) of 45.6 months (range 6.3-110.5). 53.3% of patients had a primary tumor at extremity or 'other sites'. Lung metastases were present in 47.1%, bone marrow metastases in 35.9%, and bone metastases in 38.2%.

The 3-yr EFS was 35.6 (95%CI 29.7-41.6), the 3-yr OS was 48.0% (95%CI 41.7-54.1%). Patients with 0, 1, or 2 Oberlin risk factors had a 3-yr EFS of respectively 55.7% (36.9-71.0), 50.0% (38.4-60.6), and 44.6% (32.0-56.4), where patients with 3, or 4 factors had dismal 3-yr EFS of 12.1 (4.8-22.9) and 11.1 (1.2-29.8) (p<0.0001) (Figures 1-3).

Treatment was well tolerated, and 56.4% of those that started maintenance therapy completed maintenance therapy. One-hundred and ninety patients (n=190) out of 203 (93.6%) were irradiated on the primary tumor with a median dose of 50.4 Gy (range 18-68.6 Gy). Eighty-four patients (n=84) out of 203 (41.4%) were irradiated on one or more metastatic sites with a median dose of 30 Gy (range 9-59.4 Gy).

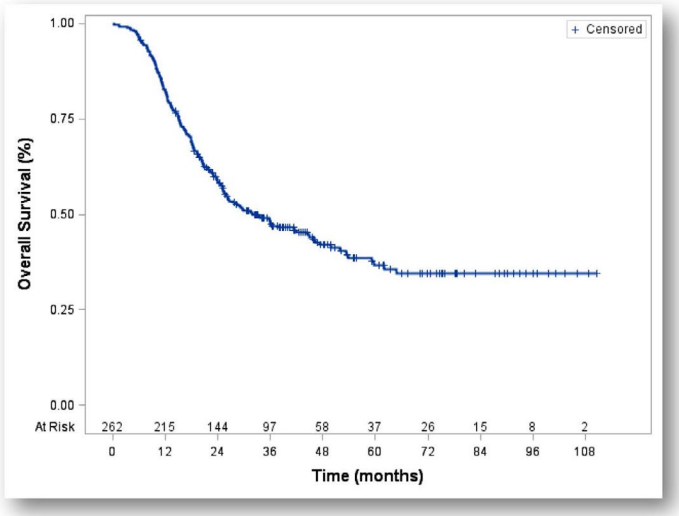
Conclusion: Patients with metastatic rhabdomyosarcoma with up to 2 Oberlin risk factors had improved survival compared to a cohort from pooled European and US studies. Survival for this group was comparable to the most recent reported COG study, ARST0431 (Weigel et al. J Clin Oncol 34:117-122), applying 54 weeks of dose-compressed intensive multiagent chemotherapy. For patients with ≥3 Oberlin risk factors prognosis remained dismal; new approaches are needed for this subgroup.

Figure 1 – Event Free Survival



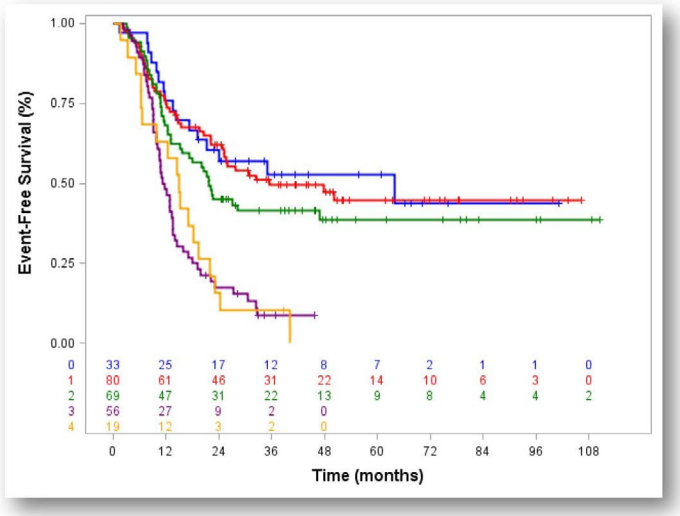
N	Failed	3yr-EFS
262	170	35.6 (29.7-41.6)

Figure 2 – Overall Survival



N	Deaths	3yr-OS
262	149	48.0 (41.7-54.1)

Figure 3 – Event Free Survival according to OO risk factors



	N	Failed	3yr-EFS	p-value
0 factors	33	16	52.7 (33.8-68.5)	<0.0001
1 factor	80	41	49.5 (37.8-60.1)	
2 factors	69	41	41.4 (29.6-52.8)	
3 factors	56	50	8.9 (3.0-18.8)	
4 factors	19	18	10.5 (1.8-28.4)	
Total	257	166		

Paper #55 3251949

SAFETY AND FEASIBILITY OF MAGNETIC RESONANCE-GUIDED HIGH INTENSITY FOCUSED ULTRASOUND (MR-HIFU) FOR THE ABLATION OF RELAPSED OR REFRACTORY PEDIATRIC SOLID TUMORS INCLUDING DESMOID TUMORS

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[1]Oncology, Childrens National Medical Center, Washington, USA; [2]Interventional Radiology, Children's National Medical Center, Washington, , USA; [3]The Sheikh Zayed Institute for Pediatric Surgical Innovation, Children's National Medical Center, Washington, USA; [4]Oncology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA; [5]Interventional Radiology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA; [6]Imaging Research Center, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA; [7]Profound Medical Inc., Mississauga, ON, Canada; [8]Surgery, George Washington School of Medicine, Washington, USA

Objective: Acute and late effects of current multi-modal therapy in pediatric cancer are substantial, and the prognosis for recurrent/refractory sarcomas and solid tumors remains dismal. Magnetic resonance guided high intensity focused ultrasound (MR-HIFU) is an ultrasound-based technology that can raise tissue temperature with millimeter spatial accuracy under MR thermometry guidance. Advantages over conventional local tumor control such as surgery or radiation therapy are that MR-HIFU is non-invasive, non-ionizing, and enables ablation of large tumor volumes under real-time image guidance. MR-HIFU has been studied in a variety of solid tumors in adults and for the relief of pain from bone metastases. There is evidence that MR-HIFU may improve systemic disease control by stimulating an anti-tumor immune response. The primary objective of this clinical trial is to determine the safety and feasibility of MR-HIFU ablation in children, adolescents, and young adults with relapsed/refractory solid tumors. Secondary objectives include the evaluation of changes in functional imaging, quality of life, and immune markers in children treated with MR-HIFU.

Methods: In this multi-institutional trial (NCT02076906), patients ≤ 30 years of age with relapsed/refractory solid tumors including desmoid tumors are eligible. Tumor target lesions are limited to those located in or close to bone at sites accessible to MR-HIFU. Patients with target lesions in the skull or spine or patients with any contraindication for MRI are excluded. Patient imaging and eligibility are reviewed by our multi-disciplinary HIFU team. Patients undergo MR-HIFU treatment of the selected lesion(s) under general anesthesia. Tolerability is defined during the 14 days following MR-HIFU ablation. Disease status is evaluated using standard imaging techniques post-treatment. Quality of life assessments using patient reported outcomes and immune pharmacodynamic markers are collected at baseline and during interval follow-ups post-treatment.

Results: Eleven evaluable patients [6M, 5F; median age 14 years (range 4-21)] with osteosarcoma (n=1), Ewing sarcoma (n=1), rhabdomyosarcoma (n=1), and desmoid tumor (n=8) have enrolled to date at two treatment centers. A total of 17 HIFU treatments were administered (2 patients underwent ablation of another target lesion, 2 patients underwent ablation of the same incompletely treated target lesion, one patient underwent ablation of the same target lesion 3 times). Only two HIFU treatments were technically unsuccessful due to the inability to achieve ablative temperature at the target location. There was no treatment limiting toxicities. One patient had a grade 3 skin burn requiring debridement. All other related toxicities were mild (grade 1/2) and reversible including transient pain (n=4), first or second degree skin burn (n=3); and transient paresthesia, neuropathy, skin discoloration, and gait disturbance due to pain (n=1 each). One target lesion was completely ablated; however, the patient progressed at other sites of disease. All other target lesions were partially ablated, either due to technical limitations or nearby critical structures.

Conclusion: MR-HIFU ablation of solid tumors in children, adolescents, and young adults appears to be safe and feasible. Changes in quality of life patient reported outcomes and immune markers' analyses are underway. Tumor volumetric analysis of perfusion for disease response post ablation therapy is being evaluated.

11:30 am - 12:00 pm

– SESSION 12 –

Young Investigator Awards

Paper #56 3256173

LONGITUDINAL PROGNOSTICATION IN PATIENTS WITH PRIMARY RETROPERITONEAL SARCOMA TREATED WITH SURGERY: DEVELOPMENT AND EXTERNAL VALIDATION OF A DYNAMIC PROGNOSTIC NOMOGRAM

Dario Callegaro, MD[1]*; Francesco Barretta*[2]*; Carol J. Swallow*[3]*; Dirk Strauss*[4]*; Sylvie Bonvalot*[5]*; Charles Honoré*[6]*; Eberhard Stoeckle*[7]*; Frits van Coevorden*[8]*; Rick Haas*[9]*; Piotr Rutkowski*[10]*; Yvonne Schrage*[11]*; Mark Fairweather*[12]*; Lorenzo Conti*[1]*; Nikolaos Vassos*[4]*; Rebecca Gladdy*[3]*; Deanna Ng*[3]*; Winan van Houdt*[8]*; Rosalba Miceli*[2]*; Chan Raut*[12]*; Alessandro Gronchi*[1]

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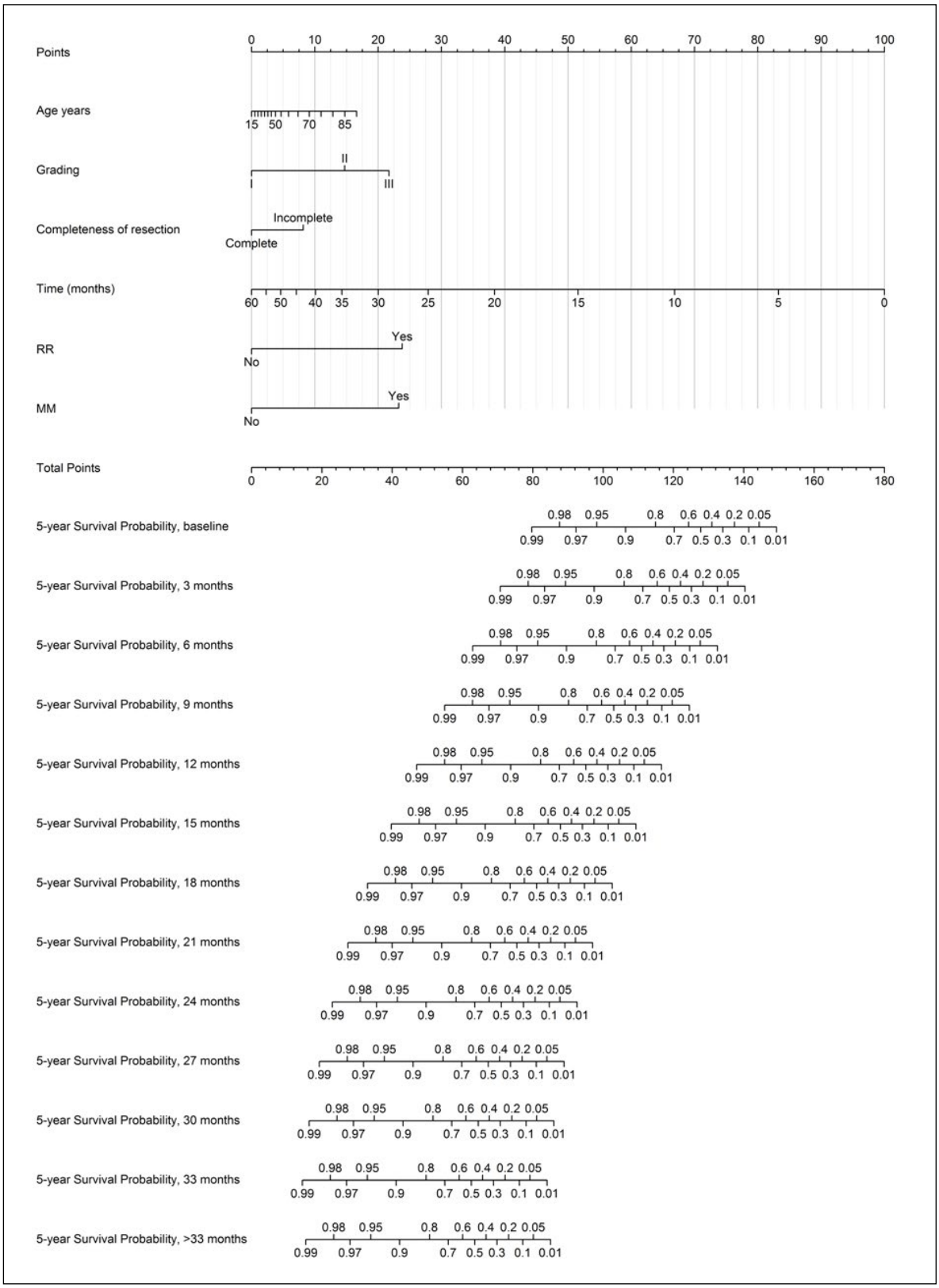
Objective: Available prognostic nomograms for patients with retroperitoneal sarcoma (RPS) predict survival or probability of tumor recurrence as of the time of surgery. After surgery, patient prognosis will change depending on time elapsed from surgery and event history (no events vs local recurrence vs distant recurrence). As such, available nomograms cannot be used during follow-up (FU) to accurately predict risk sequentially. We developed and externally validated a dynamic nomogram for overall survival (OS) to inform patient prognosis during FU.

Methods: Consecutive adult patients with primary, non-metastatic, RPS who underwent resection with curative intent between 2002 and 2017 at Istituto Nazionale Tumori (Milan, Italy), Royal Marsden Hospital, (London,UK), Institut Gustave Roussy, (Villejuif,France) and Mount Sinai Hospital (Toronto,Canada) were merged in the development cohort. Patients with the same characteristics treated in 6 other reference centers from Europe and USA formed the validation cohort. We used landmark analysis and a Cox model to create the nomogram. We established a 5-year fixed prediction window and landmark time points (T_{LM}) every three months for the first five years. The datasets at each T_{LM}, including patients at risk at that time (left truncated, with right censoring at TLM+5 years), were stacked in a unique super landmark dataset on which we fitted a multivariable Cox model with 13 T_{LM} strata (to account for different baseline hazards at different T_{LM}). Baseline covariates were age, tumor size, grade, histology, multifocality, completeness of surgical resection (R0/R1 vs R2), chemotherapy and radiotherapy administration. The model accounted for the possible occurrence of local recurrence (LR) and distant metastasis (DM) as first events (whichever occurred first), and included T_{LM} and its first order interaction with the covariates to test their time-varying effects. We applied a backward procedure based on the Akaike Information Criterion for variable selection.

Results: The multicenter series from which we extracted the two cohorts totaled 1946 patients. Two patients were excluded because survival time was missing and 151 patients were excluded because one or more covariates were missing. The development and validation cohorts included 1356 and 437 patients, respectively. Median FU was 63 months (IQR: 36-106 mo) in the development cohort and 57 months (30-107 mo) in the validation cohort. Five-year and 10-year OS were 69.3% (95%CI 66.6, 72.2) and 50.0% (45.9, 54.5) in the development cohort and 64.1% (59.0, 69,7) and 46.9% (39.9, 55.1) in the validation cohort, respectively. After the backward procedure, the following covariates were included in the final model: age, T_{LM}, grade, completeness of surgery, occurrence of LR and DM. None of the interactions between baseline covariates and T_{LM} was retained in the final model. The dynamic nomogram (**Fig 1**) allows calculation of the 5-year OS probability at different time points over the first five years of FU (e.g. at 1 year after surgery the user can obtain the predicted probability of being alive at 6 years after surgery).

In the development cohort the dynamic nomogram model showed good discrimination, with Harrell C indexes varying from 0.75 to 0.85 at different T_{LM}, and good calibration. Upon external validation, Harrell C indexes varied from 0.73 to 0.82 at different T_{LM} and once again the model showed good calibration, as proof of its generalizability.

Conclusion: This new prognostic tool fulfills a previously unmet need of the oncologist dealing with patients with retroperitoneal sarcoma to inform them of their residual risk over the duration of FU. This nomogram paves the way for the development of personalized FU strategies based upon the individual residual risk. Also, it allows the calculation of the prognostic impact of LR and DM in the individual patient, possibly aiding the decision making in the setting of recurrent disease. This nomogram will be incorporated in the 'Sarculator' app.



Paper #57 3254081

DISSECTING THE ROLE OF FUS-DDIT3 IN MYXOID LIPOSARCOMA RESPONSE TO RADIATION THERAPY

Mark Chen[1]*; Nathan Leisenring*[1]*; Andrea R. Daniel*[1]*; Joseph Foster*[2]*; Eric Xu*[1]*; Andrea Ventura*[3]*;*
Ian J. Davis[2]*; David Kirsch*[1]
[1]*Duke University, Durham, NC, USA;* [2]*University of North Carolina - Chapel Hill, Chapel Hill, NC, USA;*
[3]*Memorial Sloan Kettering Cancer Center, New York, NY, USA*

Objective: Myxoid liposarcoma is a malignant fusion-positive sarcoma that is notable for its dramatic response to radiation therapy relative to other sarcomas, but the mechanism for its radiosensitivity is unknown. Here we investigate a molecular mechanism of radiosensitization that couples ionizing radiation to inhibition of translocation-driven sarcomagenesis in myxoid liposarcoma.

Methods: We performed co-immunoprecipitation (co-IP) to identify proteins interacting with the pathognomonic fusion protein found in 95% of myxoid liposarcoma, FUS-DDIT3. Incucyte assays measured cell proliferation after knockdown of chromatin remodelers in fusion-positive and fusion-negative primary murine sarcoma cell lines. Soft agar assays were performed to identify the domains of FUS-DDIT3 that are necessary for oncogenic transformation. ChIP-seq mapped genome-wide binding sites of FUS-DDIT3 and identified DNA-binding motifs for the fusion oncoprotein. Co-IP of irradiated human MLPS cell lines were performed to evaluate post-translational modification of FUS-DDIT3 after irradiation, and to investigate regulation of protein-protein interactions by these modifications.

Results: We detected functionally important interactions between FUS-DDIT3 and multiple chromatin remodeling complexes via co-IP. Using knockdown systems, we demonstrated that these chromatin remodelers are functionally important for proliferation specifically in FUS-DDIT3-driven, but not Kras-driven murine sarcoma cells. ChIP-seq of human MLPS cell lines identified DNA-binding motifs and genomic loci targeted by FUS-DDIT3, which overlapped with H3K27ac marks of active chromatin. Soft agar transformation assays determined that both DDIT3 and the prion-like domain of FUS-DDIT3 are required for transformation. We further hypothesized that post-translational modification of the FUS-DDIT3 prion-like domain may regulate the protein-protein interactions between FUS-DDIT3 and chromatin remodelers. Using irradiated human MLPS cell lines, we show that FUS-DDIT3 is a target of phosphorylation by the DNA damage response kinases DNA-PK and ATM after radiation. Most importantly, we show that phosphorylation of the prion-like domain of FUS-DDIT3 diminishes protein-protein interactions with chromatin remodeling complexes.

Conclusion: Here we demonstrate a chromatin remodeler-dependent mechanism for FUS-DDIT3-driven sarcomagenesis in myxoid liposarcoma. Moreover, we present evidence for a novel mechanism of radiosensitivity where oncogenic interactions between the fusion oncoprotein FUS-DDIT3 and chromatin remodelers are diminished by ionizing radiation through phosphorylation of the prion-like domain.

1:30 pm - 3:30 pm

– SESSION 13 –

Soft Tissue Sarcomas: Biology

Paper #58 3255107

COMPREHENSIVE GENOMIC ANALYSIS OF EWSR1-NFATC2 FUSION SARCOMAS IDENTIFY DISTINCTIVE GENOMIC ALTERATIONS AND UPREGULATION OF THE MTOR PATHWAY

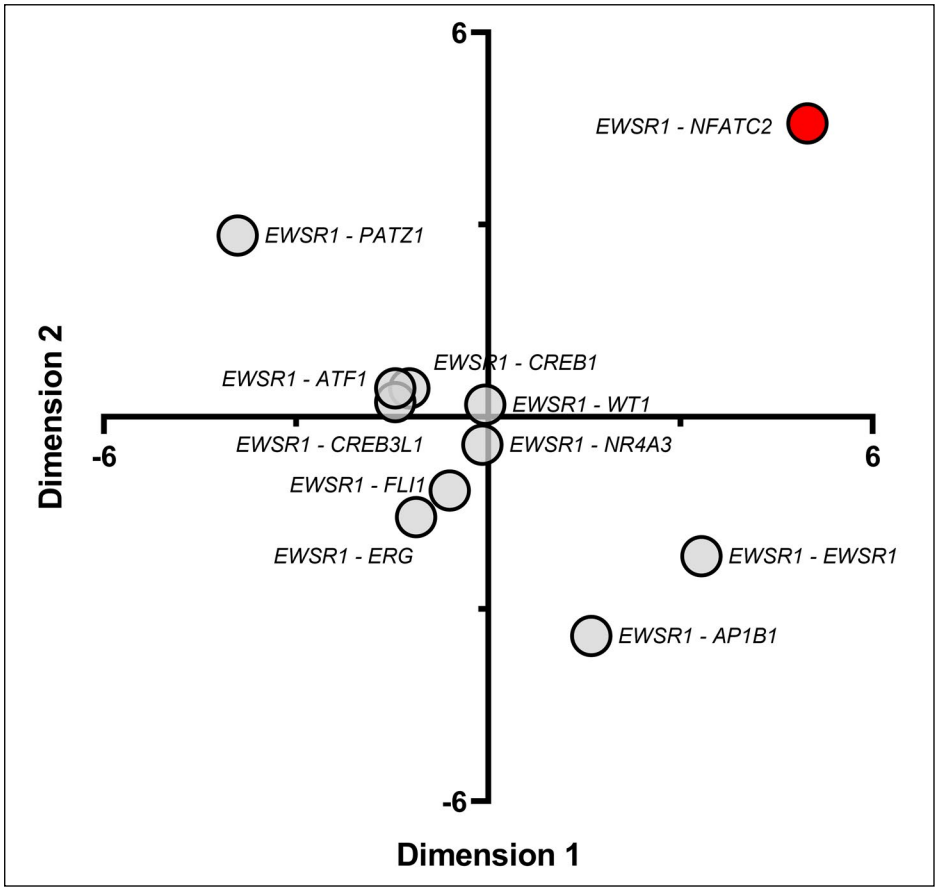
Nathan D. Seligson, PharmD[1]*; Richard Maradiaga*[2]*; John Hays*[2]*; Sherri Millis*[3]*; James L. Chen*[2]
[1]*University of Florida, Jacksonville, FL, USA;* [2]*Ohio State University, Columbus, OH, USA;*
[3]*Foundation Medicine, Phoenix, AZ, USA*

Objective: Sarcomas harboring *EWSR1-NFATc2* fusions are extremely rare and have historically been categorized and treated as Ewing's sarcomas; however, emerging evidence demonstrates unique molecular characteristics and chemotherapy sensitivities indicative of the *EWSR1-NFATc2* fusion. *NFATC2*, responsible for B-cell signaling, directly associates with the mTOR pathway; suggesting potential differences between *EWSR1-NFATc2* and other *EWSR1* fusion driven sarcomas. Here we review the molecular and treatment landscape of *EWSR1-NFATc2* fusion positive sarcomas and present additional molecular data suggestive of mTOR pathway dysregulation in *EWSR1-NFATc2* fusion positive sarcomas. We also present a follow-up for a long-term responder to mTOR targeted therapy.

Methods: Comprehensive genomic profiling of *EWSR1* fusion positive sarcomas was obtained through the Foundation Medicine's research database. Descriptive statistics were used to summarize the alterations, while principle component analysis (PCA) was used to demonstrate similarity between the secondary genomic landscapes of *EWSR1* fusion positive sarcomas. Differential expression and pathway analysis of transcriptomic data from subjects with *EWSR1-NFATc2* and *EWSR1-ETS* positive sarcomas was performed using R/Bioconductor. Consent was obtained from a subject with *EWSR1-NFATc2* fusion positive sarcoma treated with an mTOR inhibitor.

Results: Eleven patients with *EWRS1-NFATc2* and 593 patients with other *EWSR1*fusion positive sarcomas were identified. Secondary pathogenic genomic variants in *EWSR1-NFATc2* fusion positive sarcomas were identified in 13 unique genes; however, no one alteration was identified in more than two subjects. PCA demonstrated uniqueness of *EWSR1-NFATc2* fusion positive sarcoma compared to other *EWSR1*fusion positive sarcomas (**Figure 1**). Pathway analysis of historic *NFATc2* subjects suggests increased activity of the *mTOR* pathway ($p=3.5x10^{-8}$). We also present follow-up data in a case of extraordinary long-term disease stabilization in a 58yo male patient with metastatic intraabdominal *EWSR1-NFATc2* fusion positive sarcoma treated with mTOR inhibition.

Conclusion: *EWSR1-NFATc2* fusion positive sarcomas are molecularly distinct from traditional Ewing sarcomas. Increased mTOR signaling may be therapeutically targetable in this rare subtype of sarcoma. Further studies are required to confirm this finding.



Principle component analysis (PCA) demonstrates similarity between the secondary genomic landscapes of *EWSR1* fusion positive sarcomas.

Paper #59 3256379

EXPRESSION OF CIC-DUX4 IN HEK293FT CELLS INCREASES THE LEVELS OF THE ONCOMETABOLITES L-2-HYDROXYGLUTARATE AND D-2-HYDROXYGLUTARATE

Kelsi R. Willis[1]; Richard L. Boriack[2]; ***Dinesh Rakheja, MD[1]***
[1]Pathology, University of Texas Southwestern Medical Center, Dallas, TX, USA;
[2]Pathology and Laboratory Medicine, Children's Health, Dallas, TX, USA

Objective: Sarcomas characterized by the fusion CIC-DUX4 are a relatively recently recognized, aggressive, primitive round cell sarcomas that are distinct from Ewing sarcomas and affect children and young adults. The CIC-DUX4 fusion results from chromosomal translocations t(4;19)(q35;q13) or t(10;19)(q26.3; q13). The CIC gene resides on chromosome 19q13, is a human ortholog of Drosophila melanogaster capicua gene, and encodes a protein that is a member of the high mobility group (HMG)-box transcription repressor superfamily. In oligodendrogliomas, mutant CIC cooperates with mutant IDH1 to increase cellular levels of 2-hydroxyglutarate (2HG). 2HG exists in two enantiomeric forms: D2HG and L2HG, both of which are oncometabolites implicated in epigenetic dysregulation in various cancers. We hypothesized that CIC-DUX4 fusion gene product may also affect the levels of these oncometabolites.

Methods: We obtained the sequence of a CIC-DUX4 fusion construct from Takuro Nakamura (*Cancer Res. 2017 Jun 1;77(11):2927-2937*). The fusion gene was cloned into a lentiviral transfer vector downstream of an EF1a promoter. Then the transfer vector, along with envelope and packaging plasmids, was transfected into HEK293FT cells to generate the complete lentivirus. Fresh HEK293FT cells were infected with the complete virus and the infected cells were selected for by resistance to puromycin and monitored by GFP expression. HEK293FT cells and HEK293FT-CIC-DUX4 cells were harvested at 70-90% confluence and the cellular levels of L2HG and D2HG were measured by tandem mass spectrometry. Briefly, the cell extracts were derivatized with (+)-Di-O-acetyl-L-tartaric anhydride, a chiral derivatizing agent, followed by liquid chromatography-tandem mass spectrometry. Deuterated stable-isotope, D,L-[3,3,4,4-$^{2}H_{4}$]-2-hydroxyglutarate, was used as internal standard and the results were normalized to protein content of the cell extracts.

Results: Levels of L2HG were 15.56 ng/mg protein in HEK293FT cells and 77.76 ng/mg protein in HEK293FT-CIC-DUX4 cells (a 5-fold increase). Levels of D2HG were 9.23 ng/mg protein in HEK293FT cells and 77.08 ng/mg protein in HEK293FT-CIC-DUX4 cells (an 8-fold increase).

Conclusion: We established a human cell model for studying the effect of CIC-DUX4 fusion on cellular metabolism. Consistent with our hypothesis, we found a 5- to 8-fold increase in the cellular levels of 2HG in HEK293FT cells expressing CIC-DUX4. Since D2HG and L2HG are epigenetic modifiers by virtue of inhibiting 2KG-dependent dioxygenases, we predict that CIC-DUX4 expression leads to global DNA and histone hypermethylation. Further studies are ongoing to study the mechanism of 2HG increase and to confirm the predicted epigenetic changes, which may have therapeutic implications for CIC-DUX4 sarcomas.

Paper #60 3254542

GENE EXPRESSION CHANGES ASSOCIATED WITH DEDIFFERENTIATION IN LIPOSARCOMA PREDICT OVERALL SURVIVAL

Nicholas Shannon; *Xuan Qiu; Joey W. Tan; Josephine Hendrikson; Deanna Ng; Chin-Ann J. Ong; Grace Hwei Ching Tan; Claramae Shulyn Chia; Melissa Ching Ching Teo*
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Objective: Liposarcomas, despite being rare consist of a number 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 gene expression changes associated with dedifferentiation and whether these are informative of tumour biology within DDLS.

Methods: We analysed data from gene expression omnibus (GEO, ID = GSE30929) to identify genes differentially expressed between WDLS (n=52) and DDLS (n=39). We validated the signature on whole and laser capture microdissected samples from patients with tumour consisting of mixed WDLS and DDLS components. A subset of this signature representing 5 genes dysregulated in DDLS was then applied to an independent dataset, utilising data from The Cancer Genome Atlas (TCGA, n=58 DDLS) to segregate samples based on gene expression and groupings compared for recurrence and overall survival.

Results: A 15 gene signature was generated consisting of genes with increased expression in DDLS compared to WDLS. The signature was significantly enriched for genes involved in fatty acid metabolic processes (ADIPOQ, LPL, ACACB, LEP, PRKAR2B, $p<0.01$)

The signature was able to segregate WDLS and DDLS samples from patient with mixed component tumours as well as across multiple recurrence.

A further subset of this signature consistent 5 genes (AQP7, ACACB, FZD4, GPD1, LEP) was able to segregate DDLS in the TCGA cohort with a significant difference in overall survival ($p=0.019$) and recurrence free survival (0.061) and was independently prognostic compared to clinical factors in multivariate analysis ($p<0.01$).

Conclusion: A 5 gene model based on genes dysregulated between DDLS and WDLS is able to stratify DDLS into prognostic groups and outperforms clinical factors in existing models in retroperitoneal DDLS.

Paper #61 3255278

EXPLORING THE TP53 AXIS AS A THERAPEUTIC VULNERABILITY IN SYNOVIAL SARCOMA

Mushtaq Muhammad[1]; Jennifer Wilson[1]; Jamie Yu[2]; Ian Lock[3]; Toshihiko Nishisho[2,4]; Torsten O. Nielsen[2]; Kevin B. Jones[5]; ***Bertha Brodin, PhD***[1]

[1]Department of Microbiology, Tumor and Cell Biology, Karolinska Institutet; [2]Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, BC, Canada; [3]Huntsman Cancer Institute, Salt Lake City, Utah; [4]Department of Orthopedics, Tokushima University Graduate School, Tokushima, Japan; [3]Department of Oncology and Pathology, Karolinska Institutet, Stockholm, Sweden; [5]Department of Orthopedics, University of Utah School of Medicine, Salt Lake City, Utah, USA

Objective: *TP53* mutations, frequent in most cancers, are uncommon in pediatric and young adult cancers including synovial sarcomas. The function of p53 is nevertheless compromised in these tumors due to abnormal equilibrium of p53 synthesis and degradation regulated by HDM2. Consistently inhibition of HDM2 function can be therapeutically exploited in several pediatric cancers. The aims of this study are to explore the mechanism of TP53 inactivation in synovial sarcomas with intact *TP53* gene copies, and to assess treatments that can exploit this vulnerability.

Methods: We investigated the activity of three HDM2 inhibitors, RG7388, HDM201 and CGM097, alone or in combination with the DNA damaging agent doxorubicin on synovial sarcoma cell lines, and investigated the postrancriptional changes in TP53, the expression of TP53 target genes using Q-RT-PCR arrays, its association with the SS18/SSX fusion oncoprotein complex by proximity ligation assay and immunoprecipitation, and the genes targeted using chromatin immunoprecipitation.

Results: RG7388 and HDM201 displayed synergistic anti-proliferative effect in combination with doxorubicin. HDM2 inhibition led to increased levels and nuclear translocation of TP53. Following HDM2 inhibition, TP53 becomes phosphorylated at serine15 by the ATM kinase, and translocated to the nucleous for transcriptional function. The TP53 target genes *BAX, ATM, MyoD,* and *EGR1* become activated, whereas *WT1, IGF1R, MycN and Sox1* were repressed. TP53 forms a transcriptional complex with SS18/SSX and targets ATM to repress its transcription. Consistently, the knock-down of SS18-SSX in synovial sarcoma cell lines results in the re-expression of ATM. Supporting this data, we find ATM is repressed in synovial sarcoma tumors.

Conclusion: We propose that in synovial sarcomas, the SS18/SSX fusion oncoprotein forms a transcriptional complex with TP53 to dysregulate its transcription. This results in the transcriptional repression of the *ATM* gene, encoding a serine/threonine kinase that activates TP53 function. HDM2 inhibition in synovial sarcoma cells leads to increased levels of ATM and the reconstitution of the TP53 response to cell stress. HDM2 inhibition in combination with agents that induce cell stress in synovial sarcoma cells represents a vulnerability with potential therapeutic application.

Paper #62 3256131

ARGININE STARVATION AND DOCETAXEL INDUCE C-MYC DRIVEN HENT1 SURFACE EXPRESSION TO OVERCOME GEMCITABILE TRASPORTER LEVEL RESISTANCE IN ASS1 NEGATIVE SARCOMAS

Bethany C. Prudner; Richa Rathore; Angela Hirbe; ***Brian A. Van Tine***
Washington University in St. Louis, Saint Louis, MO, USA

Objective: As ~88% of sarcomas are deficient in the ability to make arginine due to the loss of argininosuccinate synthetase 1 (ASS1), we have been developing therapies based on this metabolic urea cycle defect. The response to acute and long-term arginine starvation results in a conditional adaptive metabolic reprogramming that can be harnessed for therapeutic opportunities in ASS1-negative tumors. Here, we investigate the underlying biology of priming ASS1(-) tumors with arginine deiminase (ADI-PEG20) before treatment with gemcitabine (GEM) and docetaxel (DTX) in sarcoma to define the mechanism by which ADI-PEG20, DTX and GEM are synergistic.

Methods: ASS1(-) tumor cell lines were treated to create LTAT (long term ADI treated) cell lines (ASS1+) and used for drug combination studies. Protein expression of ASS1, dCK, RRM2, E2F1, c-MYC and hENT1 were measured. c-MYC activity was determined, live-cell immunofluorescent studies for hENT1, uptake assays of FITC-cytosine probe and rescue studies with a c-MYC inhibitor were all determined in the presence or absence of the ADI-PEG20:GEM:DTX. Synergy and i*n vivo animal* testing was perfromed.

Results: Combination experiments showed that the addition of ADI-PEG20 to the standard GEM:DTX treatment was synergistic. The addition of Docetaxal to ADI-PEG20 translocates the stable c-MYC to the nucleus. The increased activity of stabilized c-MYC in the nucleus led to an increase in the transcription of SLC29A1(hENT1). Resulting in increased protein expression at the cell surface, shown by live cell immunofluorescence. The increase in hENT1 at the cell surface led to an increase uptake of a cytosine probe, which mimics Gemcitibine. An increase in hENT1 expression is diminished via a c-MYC inhibitor. Ultimately, in vivo studies strongly indicate that treatment in the triplicate combination decreased tumor growth as compared to any alone or in paired combination.

Conclusion: In examining modulations within the pyrimidine pathway, we identified that the addition of docetaxel (DTX) to cells treated ADI-PEG20 resulted in translocation of stabilized c-Myc to the nucleus. This resulted in an increase of hENT1 cell surface expression and rendered the cells susceptible to GEM. In vivo studies demonstrate that the combination of ADI-PEG20:GEM:DTX was optimal for tumor growth inhibition, providing the preclinical mechanism, synergy and justification for the ongoing clinical trial of ADI-PEG20, GEM, and DTX in sarcoma (NCT03449901 ADI-PEG 20 in Combination With Gemcitabine and Docetaxel for the Treatment of Soft Tissue Sarcoma). *Clinical Caner Reseach* 2019: PMID: 31113844.

Paper #63 3253588

ALTERATIONS IN DNA DAMAGE RESPONSE PATHWAY GENES ACROSS SARCOMA SUBTYPES

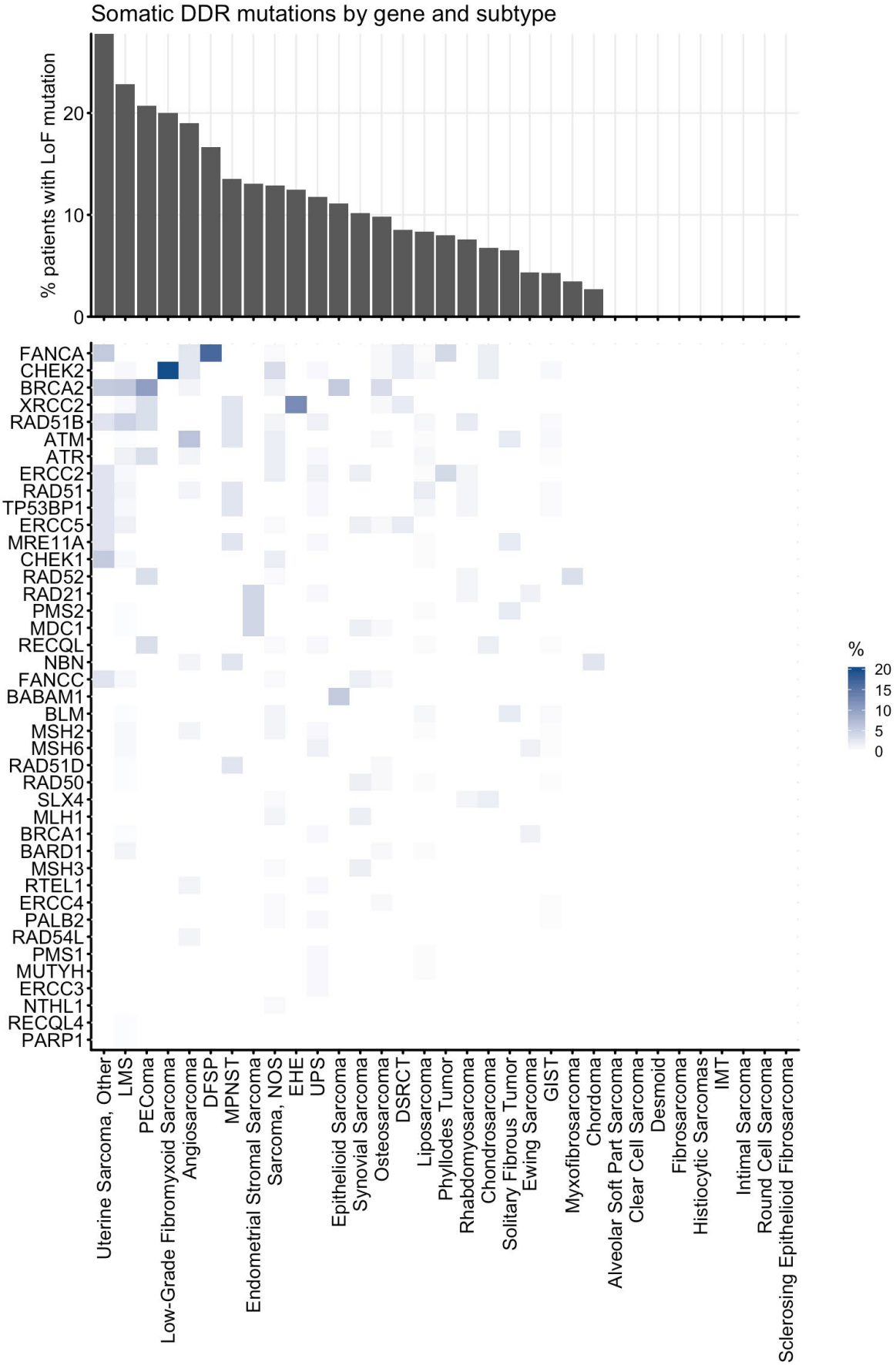
Evan J. Rosenbaum, MD[1]*; Philip Jonsson*[2]*; Viswatej Avutu*[1]*; Ping Chi*[1]*; Mark Dickson*[1]*; Ciara Kelly*[1]*; Mary Louise Keohan*[1]*; Mrinal M. Gounder*[1]*; Benjamin A. Nacev*[1]*; Jason E. Chan*[1]*; Sandra P. D'angelo*[1]*; Martee L. Hensley*[1]*; Diana Mandelker*[3]*; Mark Donoghue*[2]*; Zsofia K. Stadler*[3]*; Marc Ladanyi*[3]*; Cristina Antonescu*[4]*; Sam Singer*[5]*; William D. Tap*[1]*; Sujana Movva*[1]
[1]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]Center for Molecular Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [3]Department of Molecular Genetics, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [4]Clinical Genetics, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [5]Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Objective: DNA damage response (DDR) pathway genes are commonly altered in cancer and have lineage-specific prognostic and predictive potential. PARP inhibitors, immune checkpoint blockade, and other novel agents have demonstrated promise in select DDR deficient tumors. We determined the frequency of DDR gene alterations across the landscape of sarcoma to highlight subtype- and DDR-pathway specific differences with potential biological and clinical implications.

Methods: As part of an institution-wide research protocol, we prospectively sequenced tumor and matched-normal peripheral blood samples of sarcoma patients treated at MSKCC using the MSK-IMPACT platform, a targeted next-generation sequencing assay of up to 468 cancer-associated genes. Select patients were offered germline sequencing of up to 88 cancer-predisposing genes. Patients with an alteration in at least one of 46 DRR pathway genes (31 in the germline) representing six DDR pathways were identified. In addition, tumor mutation burden (TMB) and somatic copy number alteration (SCNA) burden were measured and correlated with DDR gene alteration status.

Results: Between March 2014 and February 2019, 2022 patients had MSK-IMPACT testing, 443 of whom consented to germline sequencing. Among those with germline data, 9% (n=39) carried a pathogenic or likely pathogenic mutation in at least one DDR gene, 10% of whom had two or more pathogenic DDR pathway mutations. *MUTYH* (n=10), *CHEK2* (8), and *BRCA2* (5) were the most common germline mutated DDR genes. One-fifth of patients with somatic tumor sequencing (n=403) had a DDR pathway gene alteration, 53% of whom had an oncogenic or likely oncogenic alteration (n=214; 11% of all patients). Oncogenic somatic alterations in *BRCA2* (n=28 patients), *RAD51B* (24), *CHEK2* (20), *ATM* (16), *RAD51* (14) and *ATR* (13) occurred most frequently. Homozygous deletions were more common than SNVs or indels (63% and 31% of all likely oncogenic variants, respectively; the remainder were structural variants). Among subtypes with more than 10 patient samples, uterine sarcoma (excluding leiomyosarcoma or PEComa; 28% of patients), leiomyosarcoma (23%), PEComa (21%), angiosarcoma (19%), and MPNST (14%) had the highest frequency of deleterious DDR gene alterations (**Figure**). Deleterious somatic *BRCA2* alterations were present in 10% of patients with PEComa and 6% of leiomyosarcoma, uterine sarcoma, and epithelioid sarcoma, respectively. Other notable potentially targetable somatic gene alterations included *ATM* in angiosarcoma (6%) and *CHEK2* in sarcoma NOS (4%). Patients with a loss-of-function DDR gene alteration had higher median tumor mutation burden and more SCNAs compared to wild type patients ($p<0.01$, respectively).

Conclusion: Overall, one-fifth of sarcomas harbor an altered DDR pathway gene, predominantly in the homologous recombination and DNA damage sensor pathways. Both germline and somatic DDR gene alterations were present across subtypes, including those with diploid and less complex genomes. Further investigation of synthetically lethal agents that can exploit DDR deficiencies across sarcoma subtypes are warranted.



Frequency of Somatic Loss-of-function Alterations in DNA Damage Response Genes by Sarcoma Subtype

Paper #64 3253095

SLFN11 IS NECESSARY - BUT NOT SUFFICIENT - TO SENSITIZE PEDIATRIC SARCOMAS TO DNA DAMAGING AGENTS

***Jessica Gartrell, MD**; Marcia Mellado-Largarde; Michael Clay; Jia Xie; Nathaniel Twarog; Nancy Martinez; Michele Connelly; Koon-Kiu Yan; Jiyang Yu; Shaina Porter; Shondra Miller; Lauren Hoffman; Hyekyung Plumley; April Sykes; Natasha Sahr; Kaley Blankenship; Armita Bahrami; Christopher Tinkle; Sara Federico; Elizabeth Stewart; Anang Shelat*

Oncology, St. Jude Children's Research Hospital, Southaven, MS, USA

Objective: Schlafen family member 11 (SLFN11) binds replication protein A1 at stalled DNA replication forks, impedes DNA repair checkpoint maintenance, and increases sensitivity to DNA-damaging agents (DDA). It is reported that SLFN11 transcript levels positively correlate with improved survival in several cancers, and reduction in SLFN11 expression through gene silencing has been implicated as a significant mechanism of resistance to DDA in adult cancers. Our previous work suggested that SLFN11 knock-out (KO) resulted in substantial loss of sensitivity to these agents *in vitro* and *in vivo*. However, we found that the protein is nearly universally expressed in Ewing sarcoma (ES) tumors, despite the fact that a subset of patients with these tumors fail to respond to DDA. We sought to evaluate the role of SLFN11 in tumorigenesis of pediatric sarcomas. Further we sought to evaluate if similar mechanisms of resistance seen in adult sarcomas are applicable to children. We hypothesize that SLFN11 is required but not sufficient to induce strong sensitivity to DDA in pediatric sarcomas.

Methods: Cell viability in a panel of 14 pediatric sarcoma cell lines including ES, desmoplastic small round cell tumor (DSRCT), clear cell sarcoma, osteosarcoma (OST) and rhabdomyosarcoma was quantified following exposure to talazoparib (TAL) and SN-38 using CellTiter Glo. CRISPR-Cas9 and plasmid-based over-expression methods were used to KO or over-express (OE) SLFN11 in ES, DSRCT and OST cell lines. Microarray studies were performed in SLFN11 wild-type (wt), KO and OE cell lines. Levels of SLFN11 and modulators of apoptosis were quantified using Western blot. DNA damage was quantified via Western blot and immunofluorescence microscopy using □-H2AX. *In vivo* efficacy to combination therapy including irinotecan (IRN), TAL and temozolomide (TMZ) was assessed using orthotopic xenograft models. SLFN11 protein expression was profiled by immunohistochemistry (IHC) in tumor samples of patients enrolled in clinical trials for the treatment of pediatric solid tumors and retrospective chart review was performed to correlate SLFN11 expression with event free (EFS) and overall survival (OS).

Results: SLFN11 is correlated with sensitivity to TAL and SN-38 in 14 diverse pediatric sarcoma cell lines. This correlation was confirmed *in vivo* in an ES, DSRCT, OST and clear cell sarcoma model. Subsequent analysis identified four ES cell lines expressing high levels of SLFN11 that were resistant to TAL, SN-38 and other DDA, with 1 cell line showing a SLFN11 truncation. We identified a SLFN11 wt positive patient-derived xenograft model that was resistant to TAL + IRN + TMZ *in vivo*. Resistant models showed a high amount of DNA damage when treated with IRN however showed a significant decrease in the expression of BAK and/or BID. Expression analysis revealed SLFN11 KO results in an increase in arginine succinate synthase 1 expression and activation of the interferon-alpha and gamma pathways consistent with increased antigen presentation through class 1 MHC. IHC studies in 335 different samples from 220 unique patients revealed 57% of the samples were negative for SLFN11, though 89.3, 86.7 and 62.8% of ES, DSRCT and OST samples were positive respectively. SLFN11 level, as measured by H-score, only correlated with binary survival outcomes for OS or EFS in DSRCT but not ES or OST (Figure 1).

Conclusion: SLFN11 is variably expressed in pediatric sarcomas, most pronounced in ES, DSRCT and OS. Protein levels only correlated with the binary survival event in DSRCT but not ES or OST. These findings, coupled with the identification and characterization of resistant tumor models, indicate SLFN11 expression alone is not sufficient to render tumor cells sensitive to DDA, and implicate defects in the apoptotic pathway as a mechanism of resistance. Further, we found SLFN11 may play important roles in tumorigenesis and evasion of the immune response, revealing new potential drug targets that operate independent of DNA damage.

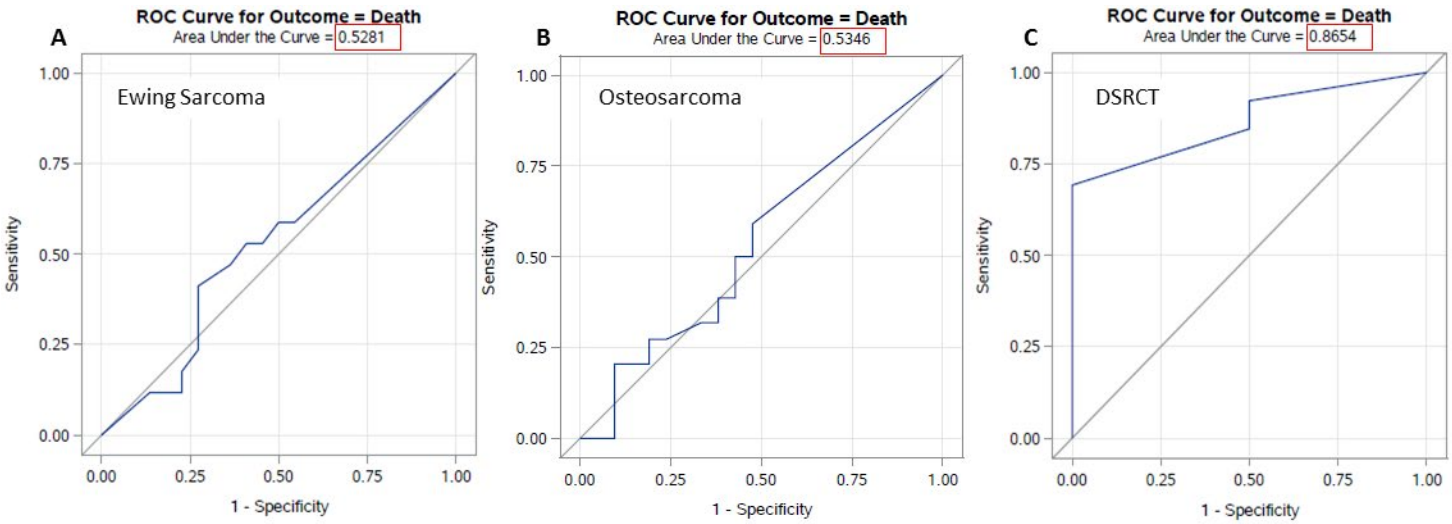


Figure 1. ROC analysis of SLFN11 as a predictor of binary overall survival in (A) ES, (B) osteosarcoma and (C) DSRCT

Paper #65 3255481

SURVEY OF ACTIONABLE GENOMIC ALTERATIONS IN A COHORT OF SOFT TISSUE AND BONE SARCOMAS

Maya Kansara[1]*; Subotheni Thavaneswaran*[1]*; John Grady*[1]*; Mandy Ballinger*[1]*; Lucille Sebastian*[2]*; Audrey Silvestri*[1]*; Christine Napier*[1]*; Katrin Sjoquist*[2]*; Wendy Hague*[2]*; Anthony Joshua*[1]*; John Simes*[2]*; David Thomas*[1]
[1]Garvan Institute, Sydney, New South Wales, Australia; [2]Sydney Medical School, NHMRC Clinical Trials Centre, Sydney, New South Wales, Australia

Objective: Patients (pts) with advanced sarcomas have a median overall survival of less than 18 months. The Molecular Screening and Therapeutics (MoST) program enables pts with pathologically confirmed, advanced or metastatic rare cancers to access precision medicine trials. To date we have screened over 1300 pts with panel testing and have identified 269 pts with soft tissue sarcomas (STS) and bone sarcomas. Here we investigate actionable genetic lesions, tumor mutation burden (TMB) and oncogenic pathway analysis to identify potential therapeutic strategies in pts with sarcomas.

Methods: Panel testing using the Illumina TST170 Illumina platform and next generation sequencing was used to assess genomic lesions and TMB in 269 pts with STS and bone sarcomas, including 219 adult tumors and 50 pediatric-type tumors. We investigated the presence of known driver mutations that are potentially druggable identified in OncoKB (http:/oncokb.org/actionableGenes)(Level 1 FDA approved, Level 2 Standard care, Level 3 Clinical evidence and Level 4 Biological evidence. We defined the pattern of somatic alterations in 11 oncogenic signalling pathways (P53, RTK/RAS, Cell cycle, PI3K, Notch, Hedgehog, Wnt, Myc, Hippo, TGF and NF2[1]) as well as Death, Epigenetic and DNA Damage Repair and /Microsatellite Instability (DDR/MSI) pathway genes. This approach was applied to cBioportal TCGA Pan Cancer atlas data, comprising an additional 253 STS's.

Results: In total, 522 pts with 32 histologies were evaluated; liposarcomas, leiomyosarcomas and sarcomas MFH/UPS were the most prevalent tumor subtypes. In the MoST cohort we identified 476 genetic lesions in total distributed across different pathways (Fig 1) with 5% involved in epigenetic regulation and 3.5% in the death pathway. In this cohort we found 102 actionable lesions in 66 of the 219 adult sarcomas (30%) and 18 actionable lesions in 14/50 of pediatric-type sarcomas (28%). The most affected signaling pathways that have available drugs include the P53, Cell cycle, PI3K and DDR/MSI pathways (Fig 2). Consistent with these findings investigation of 253 Pts in the TCGA Pan Cancer dataset, revealed 64 pts (25%) had actionable lesions in similar pathways. In addition, TMB was evaluated for 240 pts within the MoST cohort. The median TMB was 6.8 mutations/Mb (M/MB) in adult STS and 6.2 in pediatric-type tumors (Fig 3). Of the 240 pts, 14 (6%) had a TMB over 20M/Mb. Pts with a high TMB, as well as those with defects in DDR/MSI signalling, may be more amenable to immune checkpoint blockade.

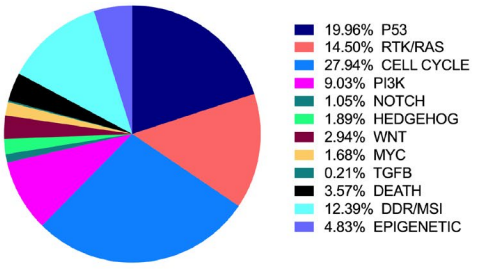


Fig 1. Pathway alteration frequencies in 269 sarcomas in the MoST cohort. We identified 476 lesions associated with defined oncogenic pathways.

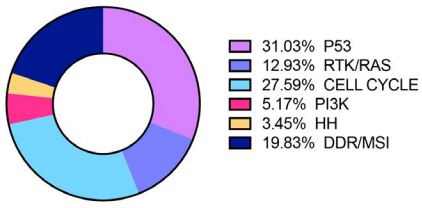


Fig 2. The most common actionable pathways identified in the MoST cohort (116 Pts)

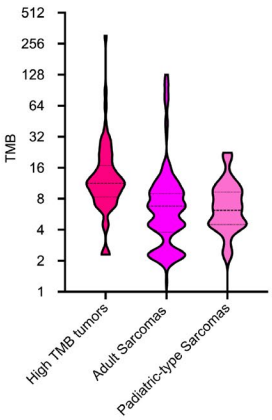


Fig 3. TMB analysis. High TMB tumors (median 11.3; n=73) include Merkel cell carcinoma, malignant melanoma, colorectal cancer and renal cell cancer, adult sarcomas (median 6.8; n=219) and pediatric-type sarcomas (median 6.2; n=50).

1. Sanchez-Vega, F. *et al.* Oncogenic Signaling Pathways in The Cancer Genome Atlas. *Cell* **173**, 321-337 e310, doi:10.1016/j.cell.2018.03.035 (2018).

Conclusion: Panel testing can identify novel therapeutic targets to address the limited options and poor prognosis of pts with STS's and bone sarcomas. As many as 30% of pts with sarcoma may harbor actionable genetic alterations identified in OncoKB. Pathway analysis has revealed gene targets involved in DDR/MSI, death and epigenetic regulation. As more effective drugs targeting these pathways become available e.g. drugs targeting MCL1 or epigenetic regulators, more beneficial options will become available for patients with sarcomas.

4:00 pm - 5:00 pm

– SESSION 14 –

Sarcomas: Novel Therapy

Paper #66 3254636

EFFECTIVE TREATMENT OF ALVEOLAR SOFT PART SARCOMA WITH SINGLE AGENT ATEZOLIZUMAB

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Objective: There are no currently approved therapies for alveolar soft part sarcoma (ASPS), which frequently presents in the adolescent and young adult (AYA, age 15-39) population. Emerging clinical data have shown responses in adult ASPS patients using anti-VEGF and checkpoint inhibitor combination therapy, though with substantial rates of dose interruption (48%) and dose reduction (58%) (Wilky el al. Lancet, 2019). We are currently evaluating the clinical activity of single-agent atezolizumab (Tecentriq, Genentech), a human monoclonal antibody directed against programmed death-ligand 1 (PD-L1), in both adult and pediatric patients (pts) with advanced ASPS (NCT03141684). Here we present the updated results for this trial previously reported at CTOS 2018 (O'Sullivan, 2018) on behalf of the Experimental Therapeutics Clinical Trials Network.

Methods: This is an open label, phase II study, with an overall target response rate (RR) of 25%. Pts ≥2 years of age are eligible, with no restriction on prior lines of treatment. Pts with untreated, asymptomatic, parenchymal brain metastases are eligible. HIV+ pts are considered. Atezolizumab is administered at a fixed dose of 1200 mg in adults or 15 mg/kg (1200 mg max) in pediatric pts age ≥2 once every 21 days. Primary objective: determine the objective response rate of atezolizumab using RECIST v 1.1. Secondary objectives include correlation of response with expression of immune biomarkers (including PD-1/PD-L1 levels, markers of T cell activation/inhibition and apoptosis biomarkers) in both blood and tumor specimens, and comparison of RECIST v 1.1 to immune RECIST (iRECIST). Tumor biopsies are collected at baseline, prior to cycle 3 day 1, or at any point where there is evidence of clinical response.

Results: Twenty-four pts have been enrolled as of April 1st, 2019. Median age on study is 33 years (range 13-53); seventeen pts are of AYA age. Eight pts (8/24, 33%) did not receive prior systemic therapy, with 6 of these pts undergoing surgery only. Sixteen pts (16/24, 67%) received prior systemic therapy (median 3 lines, range 1-7), including tyrosine kinase inhibitors, chemotherapy and interferon. Six pts (6/24, 25%) had CNS metastasis, with 2 of these pts treated with resection only. One pt experienced a complete response (CR) and 10 pts experienced a partial response (PR), with nine of these responses confirmed; overall RR of 37.5% (9/24 pts) to date. One pt with PR underwent resection of the primary following resolution of distal disease and remains without evidence of disease. Additionally, one pt with parenchymal CNS disease had resolution on repeat scan. Eleven (11/24) pts had stable disease (SD). Median time to confirmed response: 4.4 months, with a variable range (1-16 months). Median duration of confirmed response: 10.9 months (range, 1-21+ months). Twelve pts remain on study (range 1-23 months), and no pts with CR/PR have progressed. Age and prior lines/types of therapy did not predict response. Median time on study 8.9 months (range 1-25+ months). Drug-related adverse events during study

include grade 3 extremity pain, myalgia, rash and fracture (n=1 each). Grade 2 events occurring in ≥2 pts include: fatigue (3), fever (2), lymphocyte count decrease (2), and allergic rhinitis (2). No grade 4 or 5 events have been reported. No dose reductions are permitted on this study, and no patient has been taken off treatment due to toxicity.

Conclusion: Atezolizumab is very well tolerated, with single-agent activity resulting in durable responses. Additional patients are being accrued to better define the activity and pharmacodynamic biomarkers. Correlation of responses with immune biomarker analysis in both blood and tumor specimens will be forthcoming. Given the durable responses noted to date, evaluation of the long term effects of immunotherapy may be feasible in this trial, which will be important given the young patient demographic of this disease.

Funded by NCI Contract No HHSN261200800001E.

Paper #67 3212975

THE SYNOVIAL SARCOMA SUBSET ANALYSIS OF THE MULTI-HISTOLOGY PHASE I TRIAL OF ADP-A2M4 (MAGE-A4)

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Objective: This study (NCT03132922) evaluates safety, tolerability, and antitumor activity of ADP-A2M4, genetically engineered autologous specific peptide enhanced affinity receptor (SPEAR) T-cells directed towards a MAGE-A4 peptide expressed in the context of HLA-A*02. Here, we report on a subset of patients with synovial sarcoma (SS).

Methods: This is a first-in-human T-cell dose-escalation study; patients are HLA-A*02^{+} (excluding *02:05, *02:07), have inoperable or metastatic MAGE-A4^{+} disease, and meet eligibility criteria for treatment. Following apheresis, T-cells are isolated, transduced with MAGE-A4^{c1032}TCR, and expanded. The lymphodepletion chemotherapy doses varied, with maximum dose of 30 mg/m^2/day fludarabine x 4 days and 1800 mg/m^2/day cyclophosphamide x 2 days. During dose escalation, 3 patients with various tumor types received 0.1 x 10^9 (±20%), 1 x 10^9 (range: 0.5 – 1.2 × 10^9), or 5 x 10^9 (range: 1.2 – 6 × 10^9) transduced cells and were monitored for dose-limiting toxicities (DLTs). During the ongoing expansion phase, 30 patients (with SS, non-small cell lung cancer, melanoma, myxoid/round cell liposarcoma, squamous cell head and neck, ovarian, urothelial, gastric or esophageal tumors) are being treated with 1.2 – 10 x 10^9 transduced cells. Disease is assessed per RECIST v1.1 by CT/MRI at weeks 6, 12, 18, and 24, and every 3 months for 2 years, then every 6 months or until disease progression. Correlative studies investigate transduced cell persistence, phenotype, and function, and serum and tumor microenvironment factors.

Results: No DLTs were reported during the dose escalation phase. Ten patients with SS have been treated in cohort 3 and the expansion phase (data cut-off 16May19). Six patients are male, and 4 are female. The median age is 51 (range: 31 - 76). Median T-cell dose was 9.7 x 10^9 (range: 4.49 - 9.98 x 10^9). Median peak cell expansion was 226,368.3 vector copies/mg DNA (range: 19,385.7 – 324,728.9). The most frequent AEs (occurring in ≥40% of patients) were leukopenia, neutropenia, cytokine release syndrome (CRS), lymphopenia, pyrexia, fatigue, nausea, diarrhea, sinus tachycardia/tachycardia, anemia, dyspnea, rash, and thrombocytopenia. The AEs ≥ grade 3 assessed by investigators as related to T-cells include CRS, febrile neutropenia, hypophosphatemia, influenza-like illness, pancytopenia, rash, sepsis, and thrombocytopenia; each occurred in one patient. Serious AEs that were reported as T-cell-related include CRS (4 patients), pancytopenia (1), pyrexia (1), sepsis (1), and thrombocytopenia (1). Other reported SAEs include dyspnea (1), neutropenia (1), pustular rash (1), and supraventricular tachycardia (1). To date there have been 4 partial responses (-86%, -54%, -45%, -31%) in ADP-A2M4-treated patients with SS. Best overall response (BOR) was stable disease in 5 patients (-27%, -21%, -18%, -15%, +12%), and 4 of these patients continue on study. BOR was progressive disease in 1 patient. Progression-free survival will be reported at the time of presentation. *Ex vivo* analysis from one patient's transduced cells from peripheral blood and tumor showed cells were cytolytic and activated in an antigen-specific manner.

Conclusion: ADP-A2M4 induced clinical responses in pts with SS. Transduced T-cells expand upon exposure to antigen and are functional. Updated data from this ongoing study will be presented.

Paper #68 3255157

IMMUNOSARC: A COLLABORATIVE SPANISH (GEIS) AND ITALIAN (ISG) SARCOMA GROUPS PHASE I/II TRIAL OF SUNITINIB PLUS NIVOLUMAB IN ADVANCED SOFT TISSUE AND BONE SARCOMAS: RESULTS OF THE PHASE II SOFT TISSUE SARCOMA COHORT

*Javier Martin-Broto[1]; **Nadia Hindi**[1]; Giovanni Grignani[2]; Javier Martinez-Trufero[3]; Andres Redondo[4]; Claudia Valverde[5]; Antonio López Pousa[6]; Silvia Stacchiotti[7]; Emanuela Palmerini[8]; Enrique de Alava[9]; David d. Moura[10]; Herminia Perez-Vega[11]; Paola Collini[7]; Irene Otero[12]; Patricio Ledesma[13]; Emanuela Marchesi[14]; Lorenzo D'Ambrosio[2]; Jose A Lopez-Martin[12]*

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Objective: Disruption of angiogenesis could enhance the efficacy of immune-based cancer therapies. The combination of sunitinib (SU) and nivolumab (NI) showed to be safe in the phase I part of IMMUNOSARC study. Here we report the results of the phase II part of the combination of SU-NI in the advanced soft-tissue sarcoma (STS) cohort.

Methods: Pretreated progressing patients (pts), ECOG 0-1 and diagnosed with undifferentiated pleomorphic sarcoma (UPS), synovial sarcoma (SS), clear cell sarcoma (CCS), angiosarcoma (AS), epithelioid hemangioendothelioma (EH), solitary fibrous tumor (SFT), epithelioid sarcoma (ES), extraskeletal myxoid chondrosarcoma (ECM), or alveolar soft part sarcoma (ASPS) were eligible. SU was given as induction at 37.5 mg/d for the first 14 days and then reduced to 25mg/d continuously. NI was administered at 3 mg/Kg every 2 weeks from week 3. SU-NI were maintained up to progression or intolerance. Primary efficacy end-point was progression-free survival rate (PFSR) at 6 months (mos) based on RECIST 1.1. The trial would be considered positive if 6m-PFSR> 15%. Secondary end-points included overall survival (OS), objective response rate (ORR) by RECIST 1.1 and CHOI, and toxicity.

Results: From Nov 2017 to Dec 2018, 50 eligible pts were included in 8 centers:(M/F 30/20), median age 45y (19-77). Diagnosis was: SS in 9 (18%), CCS in 7 (14%), SFT in 7 (14%), UPS in 6 (12%), ES in 6 (12%), AS in 5 (10%), ECM in 4 (8%), ASPS in 3 (6%) and other in 3 (6%). With a median FU of 6.1 m (0.1+-13), 23 pts (46%) had a RECIST progression and 9 pts (18%) have died. Median PFS was 5.9 mos (95% IC 2.7-9.1) and median OS has not been reached. Based on local evaluation, PFSR at 3 and 6 m were 69% and 50%, respectively and OS at 3 and 6 m were 86% and 77%. Based on central radiological review, there were 1 CR (2%), 4 PR (9%), 28 SD (61%, 11 of them showing shrinkage) and 13 PD (28%) according to RECIST (46 evaluable pts). RECIST responses were seen in AS (2), ECM, SS and ASPS (1 each). By CHOI (37 evaluable pts), there were 24 PR (64.8%), 9 SD (24.3%) and 4 PD (10.8%). 8/46 evaluable pts had previously received antiangiogenics. Most relevant G3/4 toxicities were: AST increase 6 (11.8%), ALT increase 5 (9.8%), neutropenia 5 (9.8%), fatigue 3 (5,9%), thrombocytopenia, diarrhea, renal function impairment 2 (3.9%) patients each. There were no toxic deaths.

Conclusion: The trial met its primary endpoint.SU-NI is an active combination for the treatment of advanced selected STS patients, with 50% of patients free from progression at 6m. Further exploration of immunomodulatory strategies are warranted in selected sarcomas subtypes.

Paper #69 3255439

MOLECULAR ANALYSIS OF ARCHIVAL INFLAMMATORY MYOFIBROBLASTIC TUMOR TISSUE SAMPLES FROM EORTC 90101 "CREATE" AND CORRELATION WITH RESPONSE TO CRIZOTINIB

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Objective: Approximately 50% of inflammatory myofibroblastic tumors (IMFT) harbor rearrangements of anaplastic lymphoma kinase *(ALK)*, the most common driver in this rare tumor type. A number of other genetic alterations have been described in individual patients (Antonescu et al. Am J Surg Pathol. 2015(7):957-967). EORTC 90101 "CREATE" is the only prospective, disease-specific Phase 2 clinical trial performed in IMFT so far (Schöffski et al. Lancet Respir Med. 2018(6):431-41). High anti-tumor activity was seen with the ALK-inhibitor crizotinib in *ALK*-rearranged IMFTs, but the trial results suggested that other molecular events may correlate with sensitivity to this agent. We performed an in-depth molecular analysis of archival tumor material from patients included in CREATE with the aim to identify other genetic alterations.

Methods: DNA was isolated from archival IMFT tissue (primary tumor, local relapse or metastatic lesion). Samples were sequenced using Illumina HiSeq 4000. Shallow sequencing and GISTIC (genomic identification of significant targets in cancer) were performed to identify regions of the genome that are significantly amplified or deleted. Whole-exome sequencing was performed to assess the mutational landscape. Mutations affecting Cancer Consensus Genes (CCGs) were analyzed further. Survival analysis with Kaplan-Meier estimates and comparison with log-rank test were used to assess the correlation between molecular findings and clinical outcome of patients. Statistical analysis was performed using GraphPad Prism v7 and p values <0.05 were considered significant.

Results: In 24 IMFTs analyzed, the most common whole arm copy number losses were: 22q (58% of cases), 16p (33%), 16q (29%), 13q (29%), 19q (29%), 19p (25%), 6p (25%), 6q (21%) and 18q (21%). Loss of chromosome 19 was found to be associated with shorter progression-free survival in patients receiving crizotinib ($p = 0.008$). Moreover, 2p21 (including *EPAS1, SIX2, EML4* from the CCG set*)* was frequently amplified (in 54% of cases), while recurrent losses were observed at 22q12.3 (71%, *ISX*), 7q36.3 (54%, *MNX1*), 1p36.32 (50%, *RPL22, SKI, TNFRSF14, CAMTA1, PRDM16*), 8p23.3 (50%, *ARHGEF10*), 10q26.3 (54%, *MGMT, DUX4*), 12q24.33 (46%, *POLE*), and 11q13.4 (33%, *CCND1*). No significant correlations were found between focal copy number alterations and response to crizotinib. A complex pattern of genetic rearrangements involving chromosome 2 was identified in two *ALK*-rearranged cases. This is likely consistent with chromothripsis, a form of genomic instability which promotes cancer development and affects therapy. Whole exome sequencing was done in 22 cases with an average of 392 (range 212-766) alterations per sample. When considering non-synonymous mutations in CCG, a total of 178 mutations were identified, affecting 143 genes with the average of 7 (range 7-35) per case. In one ALK-negative case a substitution in *ALK* was identified (p.N571K), previously described in a single esophageal squamous cell carcinoma (COSMIC v.89). This mutation is considered as damaging by PolyPhen v.2 (http://genetics.bwh.harvard.edu/pph2). Mutations in 31 CCGs were identified in ≥ 2 samples and were mainly related to DNA damage and repair mechanisms, Wnt and RB-p53 signaling, and RTK-RAS-PI3K.

Conclusion: We identified multiple molecular alterations in archival tumor material from IMFT and provide further insight in the molecular profile of this ultra-rare malignancy, which may potentially lead to the identification of novel targets for treatment.

5:00 pm - 6:00 pm

– SESSION 15 –

Challenges in MPNST and NF1

Paper #70 3327498

CHALLENGES IN THE DIAGNOSIS OF NF1-MPNSTS: PATHOLOGY PERSPECTIVE

Alexander J. Lazar
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The diagnosis of malignant peripheral nerve sheath tumor (MPNST) is challenging, particularly in patients who do not have neurofibromatosis type 1 (NF1). New immunohistochemical tools (H3K27me3) and additional genomic features (NF1, CDKN2A, TP53, and PRC2 complex status) are assisting to better define pathogenesis and can be diagnostically informative within the appropriate context. In NF1 patients, there is an array of neoplasms that exist in the diagnostic space between a simple deep / plexiform neurofibroma and MPNST—these exceed the diagnostic criteria of the former, but fall short of those of the latter. The proposed nomenclature, diagnostic criteria and clinical significance of these will be discussed from a recent consensus paper produced with the involvement of both soft tissue pathologists and neuropathologists. By attending this session, you will gain an understanding of our current state of knowledge in the diagnosis of MPNST and related peripheral nerve sheath tumors seen in NF1 patients.

Paper #71 3253627

GENOMICS OF MPNST (GEM) CONSORTIUM: IN-DEPTH GENOMIC CHARACTERIZATION OF NF1-ASSOCIATED AND SPORADIC MPNSTS

Angela Hirbe, MD, PhD[1]*; Isidro Ciriano-Cortes*[2]*; Nischalan Pillay*[3]*; Matija Snuderl*[4]*; Alyaa Al-Ibraheemi*[5]*; Marilyn Bui*[6]*; Brendan Dickson*[7]*; James Gusella*[8]*; Jesse Hart*[9]*; Kevin B. Jones*[10]*; Justin Jordan*[8]*; Raymond Kim*[7]*; Daniel Lindsay*[3]*; Yoshihiro Nishida*[11]*; Katherine Piculell*[5]*; Diane Shao*[5]*; Nicole J. Ullrich*[5]*; Xia Wang*[6]*; Peter Park*[12]*; Adrienne Flanagan*[3]*; David T. Miller*[5]

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Background: Malignant Peripheral Nerve Sheath Tumors (MPNSTs) are aggressive sarcomas affecting 8-13% of individuals with Neurofibromatosis Type 1 (NF1) with no effective treatment. We hypothesize that high-depth multi-omic characterization of a large tumor set correlated with annotated clinical data, will identify clinically useful distinct tumor subsets.

Methods: We established an international consortium and collected 85 fresh frozen (FF) MPNSTs (~70% NF1-related). Whole-genome sequencing (WGS; FF tumor at 80x and matched germline DNA at 30x), RNAseq matched to normal peripheral nerve tissue, and MethylationEPIC 850k microarray data will be processed by uniform protocols.

Results: We anticipate a high degree of genomic complexity based on pilot data allowing MPNST classification into subgroups based on recurrent alterations. Our high-depth comprehensive profiling, adds to prior efforts by providing increased power to detect subclonal alterations. Tumor subset analysis will also be performed on RNAseq and epigenetic datasets.

Conclusions: This Consortium-based MPNST study provides the most comprehensive assessment of this genomically complex tumor type at the genomic, epigenomic and transcriptomic levels. Our ongoing efforts include highly detailed pathology characterization through tissue microarray with incorporation of histologic, genomic, and clinical data to improve clinical diagnosis, prognostication, and development of effective medical treatments. Summary data will be made available through a publicly accessible instance of cBioPortal.

Support: Anonymous gift to the NF Research Initiative at Boston Children's Hospital
Abstract submitted on behalf of the Genomics of MPNST (GeM) Consortium (www.nfresearch-childrens.org)

Paper #72 3316611

CLINICAL TRIALS FOR MPNST: LESSONS LEARNED

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MMPNST are aggressive soft tissue sarcoma associated with dismal clinical outcomes. The risk of MPNST is increased dramatically in individuals with Neurofibromatosis Type 1. Based on limited treatment options and high mortality, there is clearly a need for more effective medical treatments for patients with MPNST. While the clinical outcome or effective therapies have not changed substantially over the past two decades, knowledge of the biological pathways at work in MPNST have greatly expanded. These insights along with advances in preclinical models and increasing pipeline of agents for cancer therapy have shaped the development of clinical trials for this rare malignancy. Past clinical trials of investigational agents in MPNST have failed to demonstrate efficacy, but many lessons have been learned. Clinical trials in this rare disease are feasible with rapid accrual and execution through clinical trials consortia efforts. These trials give insight into future design and development of new therapeutic and preventative approaches for MPNST both at the bench and clinics.

Paper #73 3317570

CURRENT STATUS OF MANAGEMENT FOR NF1-MPNST IN JAPAN

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Background: Malignant peripheral nerve sheath tumors (MPNST) is commonly a high-grade sarcoma, and half of MPNST arises in neurofibromatosis type-1 (NF1) patients, particularly in pre-existing plexiform neurofibroma. MPNST 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 the size of tumor becomes too large. In order to detect tumors early, and perform early surgery, it is necessary to construct an efficient medical care system for NF1 patients. For MPNST, one of the very rare malignant neoplasms, no effective anticancer drug has been developed yet. Recently, various molecular targeted drugs have been developed. The aim of this presentation is to introduce the established multidisciplinary system to care NF-1 patients in Japan, particularly focused on the early detection of MPNST or precursors of MPNST. In addition, we introduced the ongoing phase II study of pazopanib for patients with advanced MPNST.

Methods: In 2009, The Japanese Society of Recklinghausen Disease was established for the purpose of multidisciplinary medical care and research for NF1. Academic activities have been promoting for the purpose of improving the quality of medical care and research for medical professionals involved in NF1, particularly MPNST medical care. In Nagoya University, in-hospital NF1 clinical care network was established, and a multidisciplinary care started from January, 2014. From the perspective of musculoskeletal oncologists, whole body MRI has been performed on all NF1 cases in order to comprehensively investigate deep neurofibroma, and MPNST precursor lesions, which is now being called as atypical neurofibromatous neoplasms of uncertain biologic potential (ANNUBP). Regarding the phase II clinical trial of pazopanib for MPNST, 11 institutions participated in this trial. Primary endpoint was set as clinical benefit (non-PD) rate at 12-week.

Results: Annual meeting of The Japan Society of Recklinghausen Disease has already been held 10 times. In the annual meeting, the contents of the international MPNST consensus meeting, which was held at the NIH in 2016, were introduced, so that the state-of-the-art contents of MPNST medical care are made known to physicians. A total of 152 patients were enrolled in-hospital clinical network for NF1 in Nagoya University Hospital until March 2018. whole-body MRI revealed not only plexiform neurofibroma, also distinct nodular lesion, which is a possible precursor lesion (ANNUBP) of MPNST. Prospectively, these lesions are now being actively removed. In total, ten patients of advanced MPNST were included in Phase II clinical trial of pazopanib, and the primary endpoint is now being analyzed.

Discussion and Conclusions: The construction of an effective medical care system will lead to early detection and early treatment of MPNST, particularly focusing on the precursor lesions, ANNUBP. Multicenter prospective clinical trials are essential for this rare cancer, MPNST. International collaboration for medical care and research is required to provide better medical care to patients with NF1, particularly MPNST.

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Poster Presentations Listing

Poster #001 3241719

COMPARISON OF CACHECTIC AND NON-CACHECTIC SARCOMA PATIENTS REVEALS AN IMPORTANT ROLE OF NOTCH SIGNALING IN METASTASIS AND MYOGENESIS

Feiqi Lu[2]*; David Osei*[2]*; Jonathan Mandell*[1]*; Alejandro Morales*[1]*; Margaret L. Hankins*[1]*; Jared Crasto*[1]*; Ruichen Ma*[2]*; Vu Dinh*[2]*; Rebecca Watters*[1]*; Kurt R. Weiss*[1]

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Poster #002 3243870

METABOLIC REPROGRAMMING IN HIGH-GRADE SARCOMAS, REPURPOSING ANTI-CHOLESTEROL AGENTS AS A NOVEL THERAPEUTIC STRATEGY

Jennifer Dorsey, Master's Candidate[1]*; Yael Babichev*[2]*; Rosemarie Venier*[2]*; Richard Marcellus*[3]*; Rima Al-awar*[3]*; Linda Z. Penn*[4]*; Albiruni Razak*[5]*; Brendan Dickson*[6]*; Eric Chen*[5]*; Jay Wunder*[7]*; Rebecca Gladdy*[2]

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Poster #003 3249741

DUAL INHIBITION OF DISTINCT METABOLIC FEATURES TARGETS OSTEOSARCOM STEM-LIKE CELLS BY PHYTOCHEMICAL PTEROSTILBENE AND C-MYC INHIBITORS

Shingo Kishi[2]*; Kanya Honoki*[1]*; Hiromasa Fujii*[3]*; Shinji Tsukamoto*[4]*; Yumiko Kondo*[3]*; Hiroki Kuniyasu*[2]*; Yasuhito Tanaka*[3]

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Poster #004 3256372

IMPROVING ONCOLYTIC VIROTHERAPY USING VANADIUM-BASED COMPOUNDS IN SARCOMAS

Anabel Bergeron, MSc[1]*; Nouf Alluqmani*[1]*; Mohammed Selman*[1]*; Andrew Chen*[1]*; Fanny Tzelepis*[1]*; Rozanne Arulanandam*[1]*; Hesham Abdelbary*[2]*; Joel Werier*[2]*; Debbie Crans*[3]*; Jean-Simon Diallo*[1]

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Poster #005 3256542

INHIBITORY EFFECTS OF INDOMETHACIN ON HUMAN OSTEOSARCOMA TUMOR CELLS

Saied Mirshahidi[2]*; Rosalia de Necochea Campion*[2]*; Anne Moretta*[2]*;* ***Nadine L. Williams***[1]*; Mark Reeves*[3]*; Salman Otoukesh*[4]*; Hamid Mirshahidi*[4]*; Penelope Duerksen-Hughes*[2]*; Lee M. Zuckerman*[1]

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Poster #006 3243435

HUMAN BONE MARROW-DERIVED STEM CELLS INDUCE EPITHELILAL-MESENCHYMAL TRANSITION AND ENHANCE STEMNESS FEATURES IN LOW-INVASIVENESS LUNG CANCER CELLS

Wei-Hsin E. Lin, MD[1]*; Jia-Lin Lee*[2]*; Jui-Sheng Sun*[1]*; Chia-Che Lee*[1]*; Hsiang-Chieh Hsieh*[3]*; Rong-Sen Yang*[1]

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Poster #007 3220620

XANTHOHUMOL INDUCE APOPTOSIS THROUGH P38 MAPK SIGNALING PATHWAY IN HUMAN NASOPHARYNGEAL CANCER CELLS

Yu-Sheng Lo[2]*; Mu-Kuan Chen*[1]
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Poster #008 3232396

OSTEONECROSIS OF JAW AFTER USE OF DENOSUMAB IN PATIENTS WITH GIANT CELL TUMOR OF BONE

Hiroshi Urakawa[3]*; Eisuke Arai*[1]*; Kunihiro Ikuta*[1]*; Tomohisa Sakai*[1]*; Hiroshi Koike*[1]*; Naoki Ishiguro*[1]*; Yoshihiro Nishida*[2]
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Poster #009 3249808

TREATMENT OF OSTEOFIBROUS DYSPLASIA IN A 13-MONTH OLD CHILD WITH CURETTAGE AND PLACEMENT OF ALLOGRAFT BONE

Brendon Bauer; ***Nadine L. Williams****; Stephen Morris; Alex Mierke; Omar Ramos; Lee M. Zuckerman*
Orthopaedic Surgery, Loma Linda University Medical Center, Loma Linda, CA, USA

Poster #010 3250654

DESMOID TUMOR VOLUMETRIC ANALYSIS FOR DISEASE RESPONSE POST ABLATION WITH MAGNETIC RESONANCE GUIDED HIGH INTENSITY FOCUSED ULTRASOUND (MR-HIFU)

Caitlin Tydings[1]*; Pavel Yarmolenko*[1]*; James I. Geller*[2]*; Joseph G. Pressey*[2]*; John M. Racadio*[2]*; Haydar Celik*[1]*; Avinash Eranki*[1]*; Matthew Lanier*[2]*; Karun V. Sharma*[1]*; AeRang Kim*[1]
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Poster #011 3253315

CLINICAL FEATURES OF CHONDROBLASTOMA: A REVIEW OF 19 CASES

Toru Hirozane[1]*; Naofumi Asano*[1]*; Kazutaka Kikuta*[2]*; Michiro Susa*[3]*; Itsuo Watanabe*[4]*; Takeshi Morii*[5]*; Masaya Nakamura*[1]*; Morio Matsumoto*[1]*; Robert Nakayama*[1]
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Poster #012 3254301

TARGETABLE DRIVER MUTATIONS IN MULTICENTRIC RETICULOHISTIOCYTOSIS

Tomohisa Sakai[1]*; Norihiro Murakami*[2]*; Eisuke Arai*[1]*; Hideaki Muramatsu*[2]*; Daisuke Ichikawa*[2]*; Shuji Asai*[1]*; Yoshie Shimoyama*[3]*; Naoki Ishiguro*[1]*; Yoshiyuki Takahashi*[2]*; Yusuke Okuno*[4]*; Yoshihiro Nishida*[5]
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Poster #013 3254342

TWO WEEKS INTERVAL OF METHOTREXATE AND VINBLASTION CHEMOTHERAPY SHOWS THE SIMILAR EFFECT AS WEEKLY ADMINISTRATION

Yoshihiro Nishida, MD, PhD[1]*; Tomohisa Sakai*[2]*; Hiroshi Koike*[2]*; Hiroshi Urakawa*[2]*; Eisuke Arai*[2]*; Kunihiro Ikuta*[2]*; Yuichi Ando*[3]*; Koki Shimizu*[4]*; Naoki Ishiguro*[2]
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Poster #014 3254507

PRIMARY BONE ROSAI-DRFMAN DISEASE ARISING IN INFANTILE ILEUM

Yuya Izubuchi*; Akihiko Matsumine*
Orthopaedics, University of Fukui, Yoshida-gun, Fukui, Japan

Poster #015 3255103

NANOSTRING ANALYSES OF TYROSINE KINASE FUSION GENES IN INFLAMMATORY MYOFIBROBLASTIC TUMOR/ INFLAMMATORY PSEUDOTUMOR

Taisei Kurihara*; Yoshiyuki Suehara; Kei Sano; Keisuke Akaike; Takuo Hayashi; Nobuhiko Hasegawa; Tatsuya Takagi; Taketo Okubo; Takashi Yao; Kazuo Kaneko; Tsuyoshi Saito*
Juntendo University, Tokyo, Japan

Poster #016 3255260

FACTOR ANALYSIS ASSOCIATED WITH LOCAL RECURRENCE AND LIMB FUNCTION OF 105 PATIENTS WITH DIFFUSE-TYPE TENOSYNOVIAL GIANT CELL TUMOR: A MULTINATIONAL STUDY OF AN ASIAN POPULATION

Akihiko Takeuchi, MD, PhD[1]*; Norio Yamamoto*[1]*; Xiaohui Niu*[2]*; Wei M. Chen*[3]*; Tomoki Nakamura*[4]*; Saminathan S. Nathan*[6]*; Takafumi Ueda*[5]*; Shintaro Iwata*[7]*; Akira Kawai*[8]*; Yong K. Kang*[9]*; Apichat Asavamongkolkul*[10]*; Edward H. Wang*[11]*; Vivek A. Singh*[12]*; Toshiharu Shirai*[13]*; Yang G. Chung*[14]*; Hiroyuki Tsuchiya*[1]
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Poster #017 3255673

SIMPLE BONE CYSTS TREATED BY INJECTION OF AUTOGENOUS BONE MARROW

Munehisa Kito[1]*; Masanori Okamoto*[1]*; Shuichiro Suzuki*[1]*; Atsushi Tanaka*[1]*; Kaoru Aoki*[1]*; Akira Takazawa*[2]*; Yasuo Yoshimura*[2]
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Poster #018 3255781

DEVELOPMENT OF MULTIFOCAL EXTRA-ABDOMINAL DESMOID FIBROMATOSIS AFTER SURGICAL RESECTION

Brendon Bauer; ***Nadine L. Williams****; Stephen Morris; Alex Mierke; Omar Ramos; Lee M. Zuckerman*
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Poster Presentations Listing

Poster #019 3255783

MASSIVE LOCALIZED LYMPHEDEMA (MLL) ASSOCIATED WITH MORBID OBESITY: A RARE, BENIGN CLINICAL ENTITY RESEMBLING A GLUTEAL LIPOSARCOMA

Mark Gimbel, MD
Banner MD Anderson Cancer Center, Phoenix, AZ, USA

Poster #020 3255921

NOVEL TREATMENT OF ZALTOPROFEN FOR DIFFUSE-TYPE TENOSYNOVIAL GIANT CELL TUMOR: A PILOT STUDY

***Akihiko Takeuchi, MD, PhD**; Norio Yamamoto; Katsuhiro Hayashi; Shinji Miwa; Kentaro Igarashi; Yuta Taniguchi; Hirotaka Yonezawa; Yoshihiro Araki; Sei Morinaga; Hiroyuki Tsuchiya*
Orthopaedic Surgery, Kanazawa University Graduate School of Medical Sciences, Kanazawa, Japan

Poster #021 3256403

COMBINATION DRUG THERAPY AND AGGRESSIVE FIBROMATOSIS

***Puviindran Nadesan, BSc**[1]; Raymond Poon[2]; Vijitha Puviindran[1]; Mushriq Al-Jazrawe[4]; Sean Ryan[1]; Alessandro Datti[6]; Robert Maki[5]; Alexander Lazar[3]; Benjamin Alman[1]*
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Poster #022 3256572

CRYOABLATION FOR DESMOID TUMORS: THE FRENCH NATIONWIDE CRYODESMO-01, CURRENT PRACTICE AND PERSPECTIVES

***Jen Wmmanuel Kurtz, MD, PhD**[9]; Xavier Buy[1]; Erik Sauleau[8]; Maud Toulmonde[2]; Frédéric Deschamps[3]; Charles Honoré[4]; Amine Bouhamama[5]; Jean-Yves Blay[6]; Afshin Gangi[7]*
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Poster #023 3257659

CAN WAIT AND SEE BE THE STANDARD OF CARE FOR INITIAL APPROACH TO PRIMARY SPORADIC DESMOID TUMORS? PRELIMINARY DATA FROM MULTICENTER EUROPEAN PROSPECTIVE STUDIES

***Chiara Colombo**[1]; Milea Timbergen[4]; Paola Boccone[2]; Dirk Grunhagen[4]; Erica Palesandro[2]; Marco Fiore[1]; Alba Bianco[1]; Federica Perrone[1]; Elena Palassini[1]; Lorenzo D'Ambrosio[2]; Silvia Stacchiotti[1]; Paola Collini[1]; Angelo Paolo Dei Tos[3]; Paolo Casali[1]; Giovanni Grignani[2]; Alessandro Gronchi[1]; Cornelis Verhoef[4]*
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Poster #024 3232140

ANLOTINIB, VINCRISTINE AND IRINOTECAN(AVI) FOR ADVANCED EWING SARCOMA AFTER FAILURE OF STANDARD MULTIMODAL THERAPY: A MULTICENTER, TWO - COHORT, PHASE IB/II TRIAL (NCT03416517)

***Jie Xu**[1]; Wei Guo[1]; Lu Xie[1]; Xin Sun[1]; Kuisheng Liu[1]; Bingxin Zheng[1]; Tingting Ren[1]; Yi Huang[1]; Taiqiang Yan[1]; Xiaodong Tang[1]; Rongli Yang[1]; Jin Gu[2]*
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Poster #025 3256530

TWO YEARS IN, WHAT HAVE WE LEARNED ABOUT *ATRX* MUTATION IN OSTEOSARCOMA? THEY INCREASE AGGRESSIVENESS THROUGH MULTIPLE MECHANISMS

William C. Eward, MD, DVM; *Suzanne Bartholf DeWitt; So Young Kim; Vidya Seshadri; Sarah M. Hoskinson; Brian Brigman; Jason Somarelli; Benjamin Alman*
Duke University Medical Center, Durham, NC, USA

Poster #026 3254140

MONOCLONAL ANTIBODY BLOCKADE OF SEMA4-PLXNB2 AXONAL GUIDANCE SIGNALING REDUCES TUMOR PROGRESSION AND METASTASIS IN ANIMAL MODELS OF OSTEOSARCOMA

Branden Smeester[1]; *Kelsie Becklin*[1]; *Garrett Draper*[1]; *Emily Pomeroy*[1]; *Nicholas Slipek*[1]; *Joseph Peterson*[1]; *Eric Rahrmann*[2]; *Margaret Crosby*[1]; *Branden Moriarity*[1]
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Poster #027 3220213

PRECLINICAL TESTING OF A NOVEL TARGETED TRAIL THERAPEUTIC FOR DEDIFFERENTIATED CHONDROSARCOMA

Zakareya Gamie[1]; *Martin Siegemund*[2]; *Craig Gerrand*[4]; *Anja Krippner-Heidenreich*[3]; *Roland Kontermann*[2]; *Kenneth Rankin*[1]
[1]*Northern Institute for Cancer Research, Newcastle University, Newcastle upon Tyne, United Kingdom;* [2]*University of Stuttgart, Stuttgard, Germany;* [3]*Prinses Máxima Center for Pediatric Oncology, Utrecht, Netherlands;* [4]*The Royal National Orthopaedic Hospital, Stanmore, United Kingdom*

Poster #028 3224408

PEMBROLIZUMAB IN ADVANCED OSTEOSARCOMA: RESULTS OF A SINGLE-ARM, OPEN-LABEL PHASE 2 TRIAL

Boye Kjetil, MD, PhD[1]; *Alessandra Longhi*[2]; *Tormod Guren*[1]; *Stine Næss*[1]; *Michela Pierini*[2]; *Ingeborg Taksdal*[3]; *Ingvild Lobmaier*[4]; *Marilena Cesari*[2]; *Anna Paioli*[2]; *Elisabetta Setola*[2]; *Ivar Hompland*[1]; *Kirsten Sundby Hall*[1]; *Emanuela Palmerini*[2]
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Poster #029 3241057

PHASE I COMBINATION DOSE-FINDING/PHASE 2 EXPANSION COHORTS OF LENVATINIB + ETOPOSIDE + IFOSFAMIDE IN PATIENTS AGED 2 TO ≤25 YEARS WITH RELAPSED/REFRACTORY OSTEOSARCOMA

Nathalie Gaspar[1]; *Francisco J. Bautista Sirvent*[2]; *Rajkumar Venkatramani*[3]; *Alessandra Longhi*[4]; *Cyril Lervat*[5]; *Michaela Casanova*[6]; *Isabelle Aerts*[7]; *Stefan Bielack*[8]; *Natacha Entz-Werle*[9]; *Sandra J. Strauss*[10]; *Cixin He*[11]; *Estelle Thebaud*[12]; *Franco Locatelli*[13]; *Bruce Morland*[14]; *Soledad Gallego Melcon*[15]; *Adela Cañete Nieto*[16]; *Perrine Marec-Berard*[17]; *Marion Gambart*[18]; *Claudia Rossig*[19]; *Quentin Campbell-Hewson*[20]
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Poster #030 3241713

IDENTIFICATION OF NOVEL THERAPEUTIC TARGETS FOR METASTATIC OSTEOSARCOMA

Margaret L. Hankins, MD[1]*; Ivy John*[2]*; David Boone*[3]*; Sarangarajan Ranganathan*[2]*; Rita Alaggio*[2]*; Vaidehi Patel*[4]*; Benjamin Martin*[5]*; Kurt R. Weiss*[1]*; Rebecca Watters*[1]
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Poster #031 3245110

CLINICAL UTILITY OF BRCANESS TESTING OF PEDIATRIC OSTEOSARCOMA PATIENTS AT DIFFERENT STAGES OF THE DISEASE

Michal Kovac[1]*; Baptiste Ameline*[1]*; Maxim Barenboim*[2]*; Andreas Krieg*[3]*; Michaela Nathrath*[2]*; Daniel Baumhoer*[1]
[1]*University Hospital Basel, Basel, Switzerland;* [2]*Technical University Munich, Munich, Germany;* [3]*University Children's Hospital Basel, Basel, Switzerland*

Poster #032 3253025

ABCA6 AND ABCA7 ARE NOVEL BIOMARKERS OF PROGNOSIS IN EWING SARCOMA: ROLE OF INTRACELLULAR LEVELS OF CHOLESTEROL

Katia Scotlandi, PhD[1]*; Michela Pasello*[1]*; Anna Maria Giudice*[1]*; Alberto Righi*[2]*; Davide Donati*[3]
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Poster #033 3253251

UPFRONT SURGERY FOLLOWED BY ADJUVANT CHEMOTHERAPY MAY IMPROVE METASTASIS-FREE SURVIVAL OF PATIENTS WITH STAGE IIB OSTEOSARCOMA OF EXTREMITY

Yong Sung Kim*; Wan Hyeong Cho; Hwan Seong Park; Kyunghoon Kim; Dae-Geun Jeon*
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Poster #034 3254188

SINGLE-CELL TRANSCRIPTOMIC ANALYSES OF MUTANT IDH1 GROWTH PLATE CHONDROCYTES REVEAL DISTINCT CELL POPULATIONS

Vijitha Puviindran, BS[2]*; Ga Ban*[2]*; Yu Xiang*[1]*; Yarui Diao*[1]*; Jianhong Ou*[1]*; Hongyuan Zhang*[2]*; Benjamin Alman*[2]
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Poster #035 3254196

IMPACT OF LIMB SALVAGE VERSUS AMPUTATION ON OVERALL SURVIVAL IN PATIENTS WITH OSTEOSARCOMA OF THE EXTREMITIES

Daniel Evans; ***Alexander L. Lazarides, MD****; Julia Visgauss; Brian Brigman; William Eward*
Department of Orthopaedic Surgery, Duke University Medical Center, Durham, NC, USA

Poster #036 3254674

FEASABILITY AND PREDICTIVE VALUE OF FUNCTIONAL PRECISION MEDICINE APPROACH FOR BONE SARCOMAS

Christina M. Linder Stragliotto, MD, PhD*; Antroula Papakonstantinou; Panagiotis Tsagkosis; S. Potdar; J. Wilson; Asle Hesla; Henrik Bauer; Otto Brosjö; Berta Brodin*
Karolinska Institute, oncology pathology, Stockholm, Spånga, Sweden

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Poster #037 3256261

PHASE II TRIAL OF GEMCITABINE AND NAB-PACLITAXEL IN PATIENTS WITH RECURRENT EWING SARCOMA: A REPORT FROM THE NATIONAL PEDIATRIC CANCER FOUNDAITON

Javier Oesterheld[2]; Damon Reed[3]; Bhuvana Setty[4]; Michael Isakoff[5]; Joanne Lagmay[6]; Masanori Hayashi[7]; David Loeb[8]; Tiffany Smith[3]; Rikesh Makanji[3]; Hong Yin[9]; Brooke Fridley[3]; ***Lars Wagner, MD****[1]*
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Poster #038 3256472

REDUCED BARD1 EXPRESSION ENHANCES PARP INHIBITOR-MEDIATED INCREASES IN PD-L1 EXPRESSION IN EWING SARCOMA

Lisa Maurer[1]; Rose Venier[2]; Claire Julian[1]; ***Kelly M. Bailey, MD, PhD****[1]*
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Poster #039 3254462

AOST1321, A PHASE 2 TRIAL OF RANKL ANTIBODY, DENOSUMAB, IN 2 COHORTS OF PATIENTS WITH RECURRENT OR REFRACTORY OSTEOSARCOMA: A REPORT FROM THE CHILDREN'S ONCOLOGY GROUP

Katherine A. Janeway, MD*[1]; Alexander J. Chou[2]; Pooja Hingorani[3]; Michael Isakoff[4]; Lisa Kopp[7]; Allen Buxton[5]; Laura Hall[8]; Timothy M. Fan[16]; Dinesh Rakheja[11]; Heike Daldrup-Link[12]; Damon Reed[13]; John Doski[14]; Lor Randall[15]; Tony Wagner[6]; Steven DuBois[1]; Mark Krailo[9]; Holcombe E. Grier[1]; Richard Gorlick[10]*
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Poster #040 3242742

EWS-FLI1 MODULATED ALTERNATIVE SPLICING OF ARID1A REVEALS NOVEL ONCOGENIC FUNCTION THROUGH THE BAF COMPLEX

Jeffrey Toretsky*; Saravana Selvanathan; Garrett Graham; Aykut Uren*
Georgetown University, Washington, USA

Poster #041 3253291

THE ROLE OF R0 RESECTION IN INTERMEDIATE AND HIGH-GRADE OSTEOSARCOMA OF THE PELVIS

Cierra S. Hong*[1]; Alexander L. Lazarides[2]; David Kerr[2]; Jason Somarelli[3]; Julia Visgauss[2]; Brian Brigman[2]; William Eward[2]*
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Poster #042 3254086

INTRACELLULAR CHOLESTEROL BIOSYNTHESIS IN ENCHONDROMA AND CHONDROSARCOMA

Hongyuan Zhang*[1]; Qingxia Wei[2]; Hidetoshi Tsushima[3]; Vijitha Puviindran[1]; Yuning Tang[1]; Sinthu Pathmanapan[2]; Jay Wunder[4]; Benjamin Alman[1]*
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Poster Presentations Listing

Poster #043 3254151

GROWTH PATTERN HETEROGENEITY IN EWING SARCOMA PATIENT-DERIVED CELLS REVEALS DIFFERENTIAL SENSITIVITY TO ANTICANCER AGENTS

Antroula Papakonstantinou, Consultant[1]*; Christina M. Linder Stragliotto*[1]*; Carolina Brodin*[2]*; Bertha Brodin*[2]

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Poster #044 3254873

DIFFERENTIAL REGULATION OF GLYCOGEN METABOLISM IN MUTANT IDH CHONDROSARCOMAS AND CHONDROCYTES

Sinthu Pathmanapan, PhD[1]*; Raymond Poon*[1]*; Aakriti Pasricha*[1]*; Vijitha Puviindran*[2]*; Hongyuan Zhang*[2]*; Chistopher Newgard*[4]*; Jay Wunder*[3]*; Benjamin Alman*[2]

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Poster #045 3255255

METASTATIC BONE DISEASE AT DIAGNOSIS IN EXTREMITY SOFT-TISSUE SARCOMAS: RISK FACTORS AND SURVIVAL ANALYSIS USING THE SEER REGISTRY

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Poster #046 3255261

TEMPORAL HETEROGENEITY OF *IDH1* AND *IDH2* MOLECULAR STATUS IN CONVENTIONAL CHONDROSARCOMA

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Poster #047 3255308

MITOCHONDRIAL OXIDATIVE PHOSPHORYLATION MARKERS IN CHONDROSARCOMA: EVIDENCE OF HIGH METABOLIC ACTIVITY

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Poster #048 3255665

DNA DAMAGE RESPONSE DEFICIENCY IN OSTEOSARCOMA

Wei-Lien Wang, MD[1]*; Alexander Lazar*[1]*; Chia-Chu Wu*[2]*; Hannah Beird*[2]*; Davis Ingram*[3]*; Samia Khan*[3]*; Khalida Wani*[3]*; Najat C. Daw*[4]*; Andrew Futreal*[2]*; J. Andrew Livingston*[5]

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Poster #049 3256060

COMBINATION THERAPY OF MTOR INHIBITOR AND VEGFR INHIBITOR REGRESS A DOXORUBICIN-RESISTANT OSTEOSARCOMA IN A PATIENT-DERIVED ORTHOTOPIC XENOGRAFT MODEL AND IN VIVO ANGIOGENESIS ASSAY MODEL

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Poster Presentations Listing

Poster #050 3256334

LOCAL CONTROL WITH INTRALESIONAL CURETTAGE AND ADJUVANT CRYOPABLATION IN EWING'S SARCOMA OF THE APPENDICULAR SKELETON

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Poster #051 3256389

THE TEMPORAL DEREGULATION OF THE BALANCE BETWEEN THE ACTION OF MACROPHAGES AND OSTEOCLASTS IS ESSENTIAL FOR THE EFFECTIVENESS OF TREATMENT IN OSTEOSARCOMAS

Anne G. Brouchet[1]*; Regis Brion*[3]*; Julia Gilhodes*[2]*; B. Ouvrard*[3]*; Corinne Bouvier*[4]*; Nathalie Gaspar*[5]*; Laurence Brugieres*[5]*; Sophie Piperno-Neumann*[6]*; Françoise Redini*[3]

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Poster #052 3256509

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

Jade Wulff, MD[1]*; Gargi Ghosal*[2]*; Ha Ram Kim*[1]*; Ryan Shuck*[1]*; Lyazat Kurenbekova*[1]*; Jason Yustein*[1]

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Poster #053 3256519

SAFETY OF DISCHARGE AT HIGHER SERUM METHOTREXATE LEVELS IN PEDIATRIC OSTEOSARCOMA PATIENTS

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Poster #054 3229328

ATR EXPRESSION AS A PROGNOSTIC BIOMARKER AND POTENTIAL THERAPEUTIC TARGET IN OSTEOSARCOMA

Xiaoyang Li[1]*; Dylan Dean*[1]*; Gregory Cote*[2]*; Francis Hornicek*[1]*;* ***Zhenfeng Duan***[1]

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Poster #055 3240352

TARGETING SPINDLE ASSEMBLY CHECKPOINT AS A NOVEL THERAPEUTIC STRATEGY IN EWING SARCOMA

Shunya Ohmura[1]*; Martin Orth*[1]*; Aruna Marchetto*[1]*; Stein Stefanie*[1]*; Julia Gerke*[1]*; Julian Musa*[1]*; Maximilian Knott*[1]*; Fabienne Wehweck*[4]*; Tanja Paul*[4]*; Tilman Hölting*[1]*; Laura Romero-Pérez*[1]*; Florencia Cidre-Aranaz*[1]*; Merve Kasan*[1]*; Wolfgang Hartmann*[2]*; Uta Dirksen*[3]*; Thomas Kirchner*[5]*; Thomas Grünewald*[6]

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Poster Presentations Listing

Poster #056 3253293

A CROSS SPECIES PERSONALIZED MEDICINE PIPELINE IDENTIFIES THE CRM1 EXPORT PATHWAY AS A POTENTIALLY NOVEL TREATMENT FOR OSTEOSARCOMA

Alexander L. Lazarides, MD[1]; *Jason Somarelli*[1]; *Erdem Altunel*[1]; *Sneha Rao*[1]; *Sarah M. Hoskinson*[1]; *Maya O. Sheth*[1]; *Serene Cheng*[1]; *So Young Kim*[1]; *Kathryn Ware*[1]; *Laura Selmic*[2]; *Cindy Eward*[1]; *David Hsu*[1]; *William Eward*[1]
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Poster #057 3253294

THE ROLE OF SURGICAL RESECTIONS FOR INTERMEDIATE AND HIGH-GRADE PELVIC CHONDROSARCOMA

Cierra S. Hong[1]; *Alexander L. Lazarides*[2]; *David Kerr*[2]; *Jason Somarelli*[3]; *Julia Visgauss*[2]; *Brian Brigman*[2]; *William Eward*[2]
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Poster #058 3253859

PRIMARY SOLITARY FIBROUS TUMORS OF BONE: A MONOCENTRIC RETROSPECTIVE ANALYSIS OF 22 PATIENTS

Giuseppe Bianchi*; Andrea Sambri; Marco Gambarotti; Davide Donati*
Istituto Ortopedico Rizzoli, Bologna, Italy

Poster #059 3254498

TARGETING BIG3-PHB2 PROTEIN INTERACTION TO SUPRESS OSTEOSARCOMA PROGRESSION

Shunichi Toki[1]; *Tetsuro Yoshimaru*[1]; *Hitoshi Aibara*[1]; *Yosuke Matsushita*[1]; *Koichi Sairyo*[2]; *Toyomasa Katagiri*[1]
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Poster #060 3254783

SIGNALING CROSS-TALK BETWEEN HUMAN OSTEOSARCOMA AND MESENCHYMAL STEM CELLS VIA INTERLEUKIN-8 IN THE TUMOR MICROENVIRONMENT

Masanori Kawano*; Kazuhiro Tanaka; Ichiro Itonaga; Tatsuya Iwasaki; Shogo Matsuda; Hiroshi Tsumura*
Orthopaedic Surgery, Oita University, Yufu, Oita, Japan

Poster #061 3255251

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

Christiane Schaefer, Dr. Rer. Nat.[1]; *Yassmine El Gourari El Gourari*[2]; *Birgit Lechtape*[1]; *Thomas Grünewald*[3]; *Wolfgang Hartmann*[4]; *Jenny Potratz*[2]; *Uta Dirksen*[1]
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Poster #062 3255313

COPPER LEVELS AND ALDH1A1 EXPRESSION VARIES BETWEEN LOW AND HIGHLY METASTATIC OSTEOSARCOMA CELL LINES AND HUMAN SAMPLES

Jonathan Mandell*; Nerone Douglas; Jan Beumer; Rebecca Watters; Kurt R. Weiss*
University of Pittsburgh, Pittsburgh, PA, USA

Poster Presentations Listing

Poster #063 3255608

EPIGENETIC MODULATING DRUGS ON CARTILAGE AND CHONDROSARCOMA DIFFERENTIATION AND VIABILITY

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Poster #064 3255652

DIABETES-ASSOCIATED ADVANCED GLYCATION END-PRODUCTS Nε-CARBOXYMETHYLLYSINE AND PENTOSIDINE EXERT MALIGNANCY ON BONE TUMORS VIA THE ACTIVATION OF SKELETAL CANCER STEMNESS

Rong-Sen Yang[1]*; Tsung-Han Yang*[2]*; Shing-Hwa Liu*[1]

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Poster #065 3255959

ARE INTRA-ARTICULAR RESECTIONS FOR PROXIMAL FEMUR SARCOMAS WITH INTRA-ARTICULAR DISEASE SAFE?

Prakash R. Nayak, MD[1]*; Srinath Gupta*[1]*; Akshay Patil*[2]*; Ashish Gulia*[1]*; Ajay Puri*[1]

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Poster #066 3256013

BASED ON THE POTENTIAL IMMUNOGENIC EFFECT OF TREATED TUMOR TISSUE REIMPLANTATION DOES EXTRA CORPOREAL RADIATION AND RE-IMPLANTATION (ECRT) FOR INTERCALARY OSTEOSARCOMA RESECTION PROVIDE OUTCOME BENEFITS?

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Poster #067 3256546

IMPACT OF LOCAL TREATMENT STRATEGY FOR PRIMARY SITE ON OUTCOMES OF EWING SARCOMA

Yen-Lin Chen, MD[1]*; Saveli I. Goldberg*[1]*; Ruoyu Miao*[1]*; Edwin Choy*[2]*; Gregory Cote*[2]*; Kevin Raskin*[3]*; Santiago Lozano-Calderon*[3]*; Joseph Schwab*[3]*; Thomas DeLaney*[1]

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Poster #068 3222958

GENOMIC ANALYSIS DOES NOT SUPPORT 'MALIGNANT TRANSFORMATION' OF OSTEOBLASTOMA TO OSTEOSARCOMA

David Geller[1]*; Nicole L. Levine*[2]*; Bang Hoang*[1]*; Rui Yang*[1]*; Daniel Weiser*[3]*; Jonathan Morris*[4]*; Richard Gorlick*[5]*; Jonathan B. Gill*[5]*; Michael Roth*[5]*; Janet Tingling*[1]*; Andrew S. Brohl*[6]

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Poster Presentations Listing

Poster #069 3231545

GENETIC TRANSPOSITION OF *TP53* REGULATORY ELEMENTS ELICITS ONCOGENE EXPRESSION IN OSTEOSARCOMA

Karim Saba[1]*; Louise Cornmark*[1]*; Michal Kovac*[2]*; Hilda van den Bos*[3]*; Linda Magnusson*[1]*; Jenny Nilsson*[1]*; Jakob Hofvander*[1]*; Diana C. Spierings*[3]*; Mahtab Bidgoli*[1]*; Tord Jonson*[1]*; Sumathi Vaiyapuri*[4]*; Otte Brosjö*[5]*; Johan Staaf*[1]*; Emelie Styring*[6]*; Floris Foijer*[3]*; Michaela Nathrath*[7]*; Daniel Baumhoer*[2]*; Karolin Hansén Nord*[1]

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Poster #070 3253039

SURVIVAL IN PATIENTS WITH CARCINOMAS PRESENTING WITH BONE METASTASIS AT DIAGNOSIS: A SEER POPULATION-BASED COHORT STUDY

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Poster #071 3253213

PERCUTANEOUS CORE NEEDLE BIOPSY VERSUS OPEN BIOPSY OF MALIGNANT BONE TUMOR IN DIAGNOSTIC ACCURACY, COMPLICATIONS, AND COST-EFFECTIVENESS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Poster #072 3254536

CLINICAL PROGNOSTIC FACTORS AND TREATMENT OUTCOMES IN ADULT PATIENTS TREATED WITH EWING SARCOMA

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Poster #073 3254945

MICRORNA-451A-CMTM6 NETWORK IS A POTENTIAL METASTASIS REGULATOR OF EWING SARCOMA CELLS

Naofumi Asano, MD, PhD[1]*; Yuko Nishiyama*[2]*; Eisuke Kobayashi*[3]*; Robert Nakayama*[1]*; Masaya Nakamura*[1]*; Morio Matsumoto*[1]*; Akira Kawai*[3]*; Tadashi Kondo*[4]*; Naoto Tsuchiya*[2]

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Poster #074 3255070

IDENTIFICATION OF FSTL1 AS A POSSIBLE THERAPEUTIC TARGET FOR OSTEOSARCOMA

Fumihiko Nakatani*; Makoto Nakagawa; Takeshi Hirose; Akira Kawai; Chie Kudo; Yamato Ogiwara*

National Cancer Center Hospital, Tokyo, Japan

Poster #075 3255111

EFFICACY OF IRE1α-XBP1 INHIBITORS IN OSTEOSARCOMAS

Taisei Kurihara*; Yoshiyuki Suehara; Takuo Hayashi; Tatsuya Takagi; Keisuke Akaike; Kei Sano; Kazuo Kaneko; Tsuyoshi Saito*

Juntendo University, Tokyo, Japan

Poster #076 3256081

DETECTION OF PULMONARY METASTASIS USING GFP TRANSFECTED PATIENT-DERIVED OSTEOSARCOMA CELLS IN A PATIENT-DERIVED ORTHOTOPIC XENOGRAFT (PDOX) MODEL

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Poster #077 3256400

MIRNA COMPONENTS OF MRNA TRANSCRIPTIONAL PATTERNS DISCOVERED USING DIMENSIONAL REDUCTION ANALYSES OF OSTEOSARCOMA TUMOR RNA-SEQ DATA

Aaron L. Sarver, PhD; *Subbaya Subramanian; Logan Spector; Jaime Modiano; David A. Largaespada; Anne Sarver*
Masonic Cancer Center, University of Minnesota, Minneapolis, MN, USA

Poster #078 3256446

UNUSUAL SITES OF OSTEOSARCOMA ISOLATED RELAPSE TO THE HEAD AND NECK REGION: PHARYNGEAL TONSIL AND THYROID

Janay McKnight; *Anna Tamulonis; Paul Kent*
Rush University, Chicago, IL, USA

Poster #079 3256479

CHANGES IN BODY MASS INDEX AMONG BONE SARCOMA SURVIVORS DURING LONG-TERM FOLLOW-UPS

Ruoyu Miao, MD[1]; *Gregory Cote*[2]; *Edwin Choy*[2]; *Kevin Raskin*[3]; *Joseph Schwab*[3]; *Thomas DeLaney*[1]; *Yen-Lin Chen*[1]
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Poster #080 3257333

OSTEONECROSIS OF THE JAW (ONJ) WITH DENOSUMAB (D'MAB) FOR GIANT-CELL TUMOR OF BONE (GCTB)

Noemi Simeone, Medicine[1]; *Anna Maria Frezza*[1]; *Elena Palassini*[1]; *Giacomo G. Baldi*[1]; *Alessandra Raimondi*[1]; *Rocio Lesta Mellid*[1]; *Carlo Morosi*[2]; *Gabriella Greco*[2]; *Massimo Maniezzo*[3]; *Marco Guzzo*[4]; *Paolo Casali*[1]; *Silvia Stacchiotti*[1]
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Poster #081 3240850

MUSCULOSKELETAL AND TRANSLATIONAL RESEARCH BIOBANK (MTRB): ESTABLISHMENT, MAINTENANCE AND CHARACTERIZATION OF PATIENT-DERIVED OSTEOSARCOMA CELLS

Pimpisa Teeyakasem[1]; *Dumnoensun Pruksakorn*[1]; *Jongkolnee Settakorn*[2]; *Areerak Phanphaisarn*[1]; *Piyaporn Budprom*[1]; *Nutnicha Sirikaew*[1]; *Viraporn Thepbundit*[1]; *Jeerawan Klangjorhor*[1]; *Parunya Chaiyawat*[1]
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Poster #082 3241715

DEVELOPING A NOVEL SPHEROID MODEL FOR CHONDROSARCOMA RESEARCH AND DRUG SCREENING

Ruichen Ma; *Feiqi Lu; Jonathan Mandell; Margaret L. Hankins; Anette Duensing; Rebecca Watters; Kurt R. Weiss*
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Poster #083 3252962

THREE-DIMENSIONAL CULTURE MODEL OF CHONDROSARCOMA FOR CHEMO/ RADIOTHERAPEUTIC TREATMENT PREDICTION

Ieva Palubeckaite, PhD; *Sanne Venneker; Brendy van den Akker; Inge Briaire - de Bruijn; Judith Bovee*
Pathology, Leiden University Medical Centre, Leiden, Netherlands

Poster #084 3252983

A RARE CASE OF MALIGNANT PERIVASCULAR EPITHELIOID TUMOR (PECOMA) IN THE LUMBAR SPINE

Yoshikazu Tanzawa, PhD
Orthopaedic Surgery, Tokai University, Isehara, Kanagawa, Japan

Poster #085 3253046

NEUROTOXICITY IN OSTEOSARCOMA PATIENTS FOLLOWING TREATMENT WITH HIGH DOSE METHOTREXATE

Yair Peled
Pediatric Hematology and Oncology, Tel Aviv Medical Center Israel, Tel Aviv, Israel

Poster #086 3255697

APPROACHES IN IMMUNOTHERAPY CHECKPOINT INHIBITORS FOR CHILDREN WITH REFRACTORY BONE SARCOMAS

Janay McKnight; *Anna Tamulonis; Paul Kent*
Rush University, Chicago, IL, USA

Poster #087 3256406

PROLONGED SURVIVAL AFTER SECOND RELAPSE OF OSTEOSARCOMA FOLLOWING REPEATED DOSES OF IMMUNOTHERAPY AND SAMARIUM

Connor Murphy; *Caleb Oh; Anna L. Tamulonis; Paul Kent*
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Poster #088 3239467

COMPREHENSIVE GENOMIC PROFILING (CGP) OF DESMOPLASTIC SMALL ROUND CELL TUMORS (DSRCT) IDENTIFIES PREDICTED NEOANTIGENIC GENE FUSIONS

Dexter X. Jin, PhD[1]; *Natalie Danziger*[4]; *Meagan Montesion*[1]; *Dean C. Pavlick*[1]; *Ethan S. Sokol*[1]; *Jonathan K. Killian*[4]; *Justin Newberg*[1]; *Sherri Millis*[2]; *Warren Chow*[5]; *Jeff S. Ross*[4]; *Vince A. Miller*[3]; *Mrinal M. Gounder*[6]; *Garrett Frampton*[1]; *Siraj Ali*[3]; *Sally Trabucco*[1]
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Poster #089 3245715

OUTCOME OF PALLIATIVE CHEMOTHERAPY IN ADULT DESMOPLASTIC SMALL ROUND CELL TUMOR PATIENTS: A SINGLE CENTER EXPERIENCE

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Poster #090 3249075

COMPREHENSIVE GENOMIC AND IMMUNE-PROFILING OF HYPERPROGRESSIVE DESMOPLASTIC SMALL ROUND CELL TUMORS TREATED WITH IMMUNE CHECKPOINT INHIBITORS

Roman Groisberg, MD[1]; *Jason Roszik*[2]; *Behrang Amini*[2]; *Vivek Subbiah*[2]
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Poster Presentations Listing

Poster #091 3253564

LANDSCAPE OF GENOMIC ABERRATIONS IN DESMOPLASTIC SMALL ROUND CELL TUMORS AND EWING'S SARCOMAS REVEALS DIVERSE BIOLOGY: CLINICAL IMPLICATIONS

Jason Roszik[1]*; Joseph A. Ludwig*[1]*; Anthony Conley*[1]*; J. Andrew Livingston*[1]*; Aung Naing*[1]*; Roman Groisberg*[2]*; Alexander Y. Andreev-Drakhlin*[1]*; Roberto Carmagnani Pestana*[1]*; Vivek Subbiah*[1]
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Poster #092 3255247

***EWS-WT1* FUSION TRANSCRIPT STRUCTURE IS NOT PREDICTIVE OF PROGNOSIS IN DESMOPLASTIC SMALL ROUND CELL TUMOR**

Emily Slotkin, MD[1]*; Neerav Shukla*[1]*; Paul Meyers*[1]*; Leonard Wexler*[1]*; Anita S. Bowman*[2]*; Ahmet Zehir*[2]*; Jessie Hillsberg*[1]*; Ryma Benayed*[2]*; Meera Hameed*[2]*; Narasimham Agaram*[2]*; Marc Ladanyi*[2]*; William D. Tap*[3]*; Cristina Antonescu*[2]*; Todd Heaton*[1]*; Michael P. LaQuaglia*[1]*; Shakeel Modak*[1]
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Poster #093 3255470

UPDATED RESULTS OF A PILOT TRIAL OF IRINOTECAN, TEMOZOLOMIDE AND BEVACIZUMAB FOR TREATMENT OF NEWLY DIAGNOSED DESMOPLASTIC SMALL ROUND CELL TUMOR

Emily Slotkin, MD*; Heather Magnan; Leonard Wexler; Shakeel Modak; Anita Price; Audrey Mauguen; Jessie Hillsberg; Kelly Swanson; Justin T. Gerstle; Todd Heaton; Michael P. LaQuaglia; Paul Meyers
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Poster #094 3255482

IMPROVING THE EFFICACY OF ANDROGEN RECEPTOR-BASED ANTI-SENSE THERAPY BY TARGETING EWSR1 OR TAZ FOR THE TREATMENT OF DESMOPLASTIC SMALL ROUND CELL TUMOR

Salah-Eddine Lamhamedi Cherradi, PhD[1]*; Brian A. Menegaz*[1]*; Branko Cuglievan*[2]*; Pamela Pamela*[2]*; Alejandra R. Velasco*[1]*; Standhya Krishnan*[1]*; Amelia Vetter*[1]*; Youngsoo Kim*[3]*; Robert MacLeod*[4]*; Andrea Hayes-Jordan*[5]*; Joseph A. Ludwig*[1]
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Poster #095 3255856

RESULTS OF DESMOPLASTIC SMALL ROUND CELL TUMOR TREATMENT – SINGLE INSTITUTION EXPERIENCE

Pawel Teterycz; Hanna Kosela-Paterczyk; Katarzyna Kozak; Tomasz Switaj; Anna Klimczak;
Piotr Rutkowski, MD
Department of Soft Tissue/Bone Sarcoma and Melanoma , Maria Sklodowska-Curie Institute - Oncology Center; Department of Soft Tissue/Bone Sarcoma and Melanoma, Warsaw, Poland

Poster #096 3255901

ADVANCED DESMOPLASTIC SMALL ROUND CELL TUMOR SUCCESSFULLY TREATED IN A 21 YEAR OLD WOMAN, A CASE REPORT

Dorota Goplen, MD, PhD[1]*; Hans Kristian Haugland*[2]*; Kjell Kåre Øvrebø*[3]
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Poster Presentations Listing

Poster #097 3256316

INTRAPERITONEAL RADIOIMMUNOTHERAPY FOR DESMOPLASTIC SMALL ROUND CELL TUMOR: FINAL RESULTS OF A PHASE I STUDY (CLINICALTRIALS.GOV IDENTIFIER NCT01099644)

Shakeel Modak, MD[1]; *Pat Zanzonico*[2]; *Emily Slotkin*[1]; *Todd Heaton*[1]; *Nai-Kong Cheung*[1]; *Michael P. LaQuaglia*[1]; *Neeta Pandit-Taskar*[3]

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Poster #098 3256475

MSK-IMPACT GENOMIC PROFILING OF DESMOPLASTIC SMALL ROUND CELL SARCOMA REVEALS RECURRENT COPY NUMBER ALTERATIONS

Anita S. Bowman, MS[1]; *Ahmet Zehir*[1]; *Emily Slotkin*[2]; *Leonard Wexler*[2]; *William D. Tap*[3]; *Todd Heaton*[4]; *J. T. Gerstle*[4]; *Michael Berger*[1]; *Michael P. LaQuaglia*[4]; *Shakeel Modak*[2]; *Marc Ladanyi*[1]; *Neerav Shukla*[2]

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Poster #099 3256523

COMPUTATIONAL SEARCH FOR GENE ABNORMALITIES IN DSRCT AND ASSOCIATED POSSIBLE THERAPEUTIC AGENTS

Michael P. LaQuaglia, MD[1]; *Emily Slotkin*[2]; *Neerav Shukla*[2]; *Shakeel Modak*[2]

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Poster #100 3256525

GENERATION OF PATIENT DERIVED XENOGRAFT MODELS OF DESMOPLASTIC SMALL ROUND CELL TUMOR

Emily Slotkin, MD; *Sagarika Pachhal; Paul Meyers; Kristina Guillan; Andoyo Ndengu; Jessie Hillsberg; Kelly Swanson; Shakeel Modak; Justin T. Gerstle; Todd Heaton; Michael P. LaQuaglia; Daoqi You; Andrew Kung; Filemon Dela Cruz*

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Poster #101 3256529

COMPASSIONATE USE OF BIVALENT ANTI-GD2/GD3 VACCINE WITH IMMUNOLOGICAL ADJUVANT OPT-821 IN COMBINATION WITH ORAL BETA-GLUCAN FOR THE TREATMENT OF RELAPSED GD2+ DESMOPLASTIC SMALL ROUND CELL TUMOR

Jessie Hillsberg; ***Emily Slotkin, MD****; Shakeel Modak; Brian Kushner*

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Poster #102 3256531

CHK1 KINASE INHIBITION IN DESMOPLASTIC SMALL ROUND CELL TUMOR

Emily Slotkin, MD[1]; *Sagarika Pachhal*[1]; *Peilin Ma*[1]; *Filemon Dela Cruz*[1]; *Alex Kentsis*[1]; *William D. Tap*[2]; *Andrew Kung*[1]

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Poster #103 3256819

THERAPEUTIC POTENTIAL OF NTRK3 IN DESMOPLASTIC SMALL ROUND CELL TUMOR

Koichi Ogura, MD, PhD[1]; *Julija Hmeljak*[1]; *Romel Somwar*[1]; *Heather Magnan*[2]; *Marina Asher*[1]; *Achim Jungbluth*[1]; *Amir Momeni*[1]; *Ryma Benayed*[1]; *Alifiani B. Hartono*[3]; *Sean Bong Lee*[3]; *Lee Spraggon*[1]; *Marc Ladanyi*[1]

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Poster Presentations Listing

Poster #104 3256561

ULTRA-HIGH FIELD MRI (7 TESLA): ARE WE HEADING TO THE FUTURE OF TUMOURS MUSCULOSKELETAL IMAGING?

Jean-Camille Mattei, MD, PhD
AP-HM, Aix-Marseille University, Marseille, France

Poster #105 3257777

COMPUTED-TOMOGRAPHY (CT) SCAN IN RETROPERITONEAL SARCOMAS (RPS): A RADIOMIC ANALYSIS OF THE SARCOMICS STUDY

*Raffaella Vigorito[1]; **Sandro Pasquali**[1]; Marco Bologna[2]; Raffaella Greco[1]; Rosalba Miceli[1]; Francesco Barretta[1]; Valentina Corino[2]; Paola Collini[1]; Nicolo Rampello[1]; Lorella Rusi[1]; Luca Mainardi[2]; Dario Callegaro[1]; Carlo Morosi[1]; Alessandro Gronchi[1]*
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Poster #106 3257781

MAGNETIC RESONANCE IMAGING (MRI) SCAN IN EXTREMITY SOFT TISSUE SARCOMAS (ESTS): A RADIOMIC ANALYSIS OF THE SARCOMICS STUDY

***Sandro Pasquali**[1]; Antonella Messina[1]; Marco Bologna[2]; Alessandra Casale[1]; Rosalba Miceli[1]; Francesco Barretta[1]; Valentina Corino[2]; Paola Collini[1]; Nicolo Rampello[1]; Lorella Rusi[1]; Luca Mainardi[2]; Dario Callegaro[1]; Alessandro Gronchi[1]*
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Poster #107 3232369

APPLYING RADIOMICS IN PREDICTING OUTCOMES IN PATIENTS WITH RETROPERITONEAL SARCOMA TREATED WITH PREOPERATIVE RADIOTHERAPY

***Jeremy Lewin**[1]; David Gyorki[1]; Katrina Ingley[1]; Krystel Tran[1]; Shona Hendry[2]; Catherine Mitchell[1]; Michael Henderson[1]; Price Jackson[1]; Sam Ngan[1]; Sarat Chander[1]; Alan Herschtal[1]; Nicholas Hardcastle[1]*
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Poster #108 3241854

DIMENSIONAL AND NON-DIMENSIONAL CHANGES WITH LOW-DOSE CHEMOTHERAPY IN SPORADIC DESMOID TUMORS (DT)

***Edoardo Zanchetta**[1]; Chiara M. Ciniselli[2]; Chiara Colombo[3]; Silvia Stacchiotti[4]; Giacomo Baldi[4]; Salvatore Provenzano[4]; Rossella Bertulli[4]; Noemi Simeone[6]; Alessandra Casale[5]; Francesca G. Greco[5]; Paolo Verderio[2]; Marco Fiore[3]; Alessandro Gronchi[3]; Paolo Casali[4]; Carlo Morosi[5]; Elena Palassini[4]*
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Poster #109 3253768

LINEAR MIXED EFFECTS MODELS FOR ESTIMATION OF PULMONARY METASTASIS GROWTH RATE: IMPLICATIONS FOR CHEST CT SCREENING IN PATIENTS WITH SARCOMA

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Poster Presentations Listing

Poster #110 3254463

DISTINCTION BETWEEN BENIGN AND MALIGNANT SOFT TISSUE TUMORS BASED ON AN ULTRASONOGRAPHIC EVALUATION OF VASCULARITY AND ELASTICITY

Shusa Ohshika; *Tetsuya Ogawa; Yasuyuki Ishibashi*
Department of Orthopaedic Surgery, Hirosaki University Graduate School of Medicine, Hirosaki, Aomori, Japan

Poster #111 3255153

DIAGNOSTIC EFFICACY OF POSITRON EMISSION TOMOGRAPHY IN ADIPOCYTIC TUMORS

Yasunori Tome, MD, PhD; *Hiromichi Oshiro; Takashi Toma; Hiroki Maehara; Kotaro Nishida*
Department of Orthopedic Surgery, University of the Ryukyus, Nishihara, Okinawa, Japan

Poster #112 3253128

GEMCITABINE PLUS PACLITAXEL THERAPY AGAINST ADVANCED BONE AND SOFT TISSUE SARCOMA

Hiroyuki Kawashima[1]; *Akira Ogose*[1]; *Takashi Ariizumi*[1]; *Naoki Oike*[1]; *Yasuo Saijo*[2]; *Yuki Sakai*[3]; *Naoto Endo*[1]
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Poster #113 3225830

THE ANALYSIS OF EPIDEMIOLOGICAL CHARACTERISTICS OF 1624 SOFT TISSUE SARCOMA CASES IN 2006-2016 IN HENAN PROVINCE CANCER HOSPITAL, CHINA

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Poster #114 3219647

REFERRAL PATTERN OF RETROPERITONEAL SARCOMAS TO A SURGICAL ONCOLOGY SERVICE WITH SARCOMA INTEREST IN A DEVELOPING COUNTRY

Raza H. Sayyed, MBBS, FRCSEd, EBSQ Surgical Oncology[1]; *Nasir Uddin*[2]; *Bilal M. Qureshi*[3]; *Fahd Haroon*[4]; *Adeel Ahmed*[7]; *Fawad Qureshi*[5]; *Samiullah K. Niazi*[6]; *Marco Fiore*[8]; *Alessandro Gronchi*[8]
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Poster #115 3252957

TUMOUR NECROSIS IS AN INDEPENDENT PROGNOSTIC FACTOR FOR OVERALL SURVIVAL AFTER CURATIVE RESECTION OF GIST

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Poster #116 3255281

QUANTITATIVE MASS SPECTROMETRY IMAGING IN SECONDARY RESISTANT GIST LIVER METASTASIS DEMONSTRATES LACK OF IMATINIB DISTRIBUTION

Denis Abu-Sammour[2]; *Peter Hohenberger*[1]; *Christian Marsching*[2]; *Jan-Hinrich Rabe*[2]; *Alexander Marx*[3]; *Alexander Geisel*[2]; *Katrin Erich*[2]; *Sandra Schulz*[2]; *Peter Findeisen*[4]; *Carsten Hopf*[2]
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Poster #117 3256201

EXON 9 MUTATED GIST AND ADJUVANT IMATINIB: A MULTICENTRIC RETROSPECTIVE STUDY

Bruno Vincenzi[1]*; Marianna Silletta*[1]*; Andrea Napolitano*[1]*; Alessandro Mazzocca*[1]*; Alessandro Minelli*[1]*; Giovanni Grignani*[2]*; Antonella Brunello*[3]*; Giacomo G. Baldi*[4]*; Javier Martin-Broto*[5]*; Nadia Hindi*[5]*; Elena Fumagalli*[6]*; Robin L. Jones*[7]*; Spyridon Gennatas*[7]*; Piotr Rutkowski*[8]*; Bernd Kasper*[13]*; Margherita Nannini*[10]*; Peter Hohenberger*[13]*; Silvia Gasperoni*[11]*; Giuseppe Badalamenti*[12]*; Tommaso De Pas*[14]*; Alessandro Gronchi*[6]*; Angelo Paolo Dei Tos*[9]*; Maria Abbondanza Pantaleo*[10]
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Poster #118 3253758

MUTATIONAL PROFILING IS COST-EFFECTIVE FOR TAILORING FIRST-LINE TREATMENT IN PATIENTS WITH METASTATIC GASTROINTESTINAL STROMAL TUMOR: RESULTS OF A MARKOV MODEL ANALYSIS

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Poster #119 3254407

PATTERNS OF MULTIDISCIPLINARY CARE AND OUTCOMES OF PATIENTS WITH METASTATIC GIST IN A REAL-LIFE SETTING: THE METAGIST OBSERVATIONAL STUDY FROM 3 COORDINATING CENTERS OF THE GSF-GETO

Maud Toulmonde[1]*; Mehdi Brahmi*[2]*; Axel Le Cesne*[3]*; Derek Dinart*[1]*; Armelle Dufresne*[2]*; Olivier Mir*[3]*; Pierre Meeus*[2]*; Eberhard Stoeckle*[1]*; Amine Bouhamama*[2]*; Xavier Buy*[1]*; Marie Karanian*[2]*; Julien Domont*[3]*; Carine Bellera*[1]*; Antoine Italiano*[1]*; Jean-Yves Blay*[2]*; Philippe Terrier*[3]*; Francois Le Loarer*[1]*; Charles Honoré*[3]
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Poster #120 3255128

PRECLINICAL ACTIVITY OF AXITINIB IN GIST CELL MODELS WITH CLINICALLY REPRESENTATIVE KIT PRIMARY AND SECONDARY MUTATIONS

Alfonso García-Valverde; Daniel Pilco-Janeta; Marina Polo; Jesse K. Fletcher; Claudia Valverde; Joan Carles; Joaquín Arribas; ***César Serrano, MD, PhD***
Medical Department, Vall d'Hebron Institute of Oncology, Barcelona, Barcelona, Spain

Poster #121 3255526

ROLE OF PAZOPANIB IN METASTATIC GASTROINTESTINAL STROMAL TUMOR (GIST), PROGRESSING AFTER STANDARD OF CARE THERAPY

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Poster #122 3255898

PRESERVATION OF ORGAN FUNCTION BY MINIMIZING SURGICAL RESECTION BY NEOADJUVANT IMATINIB THERAPY IN GASTROINTESTINAL STROMAL TUMORS (GIST)

Nikos Vassos[1]*; Jens Jakob*[2]*; Peter Reichardt*[6]*; Daniel Pink*[3]*; Alexander Marx*[5]*; Eva Wardelmann*[4]*; Peter Hohenberger*[1]

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Poster #123 3256451

CIRCULATING MIRNAS AS BIOMARKERS OF IMATINIB RESISTANCE IN GIST-LIQUID BIOPSIES AND FUNCTIONAL VALIDATION

Giovanni Grignani[1]*; Maria Laura Centomo*[1]*; Alessandra Merlini*[1]*; Valentina Martin*[1]*; Giulia Chiabotto*[2]*; Enrico Berrino*[2]*; Tiziana Venesio*[3]*; Anna Sapino*[3]*; Massimo Aglietta*[1]*; Lorenzo D'Ambrosio*[1]*;* ***Ymera Pignochino***[1]

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Poster #124 3258000

AVAPRITINIB FOR THE TREATMENT OF GIST: ANALYSIS OF EFFICACY, SAFETY, AND PATIENT MANAGEMENT STRATEGIES AT THE RECOMMENDED PHASE 2 DOSE

Cissimol Joseph[1]*; Sarah Abaricia*[2]*; Michelle Angelis*[3]*; Suzanne George*[4]*; Robin L. Jones*[5]*; Yoon-Koo Kang*[6]*; Richard F. Riedel*[7]*; Patrick Schöffski*[8]*; César Serrano*[9]*; Jonathan C. Trent*[10]*; Tuan Dong Si*[11]*; Teresa Zhou*[11]*; Ashley Doyle*[11]*; Maria Roche*[11]*; Tracy Havnaer*[12]

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Poster #125 3231084

A DANISH PROSPECTIVE STUDY INCLUDING LIQUID BIOPSIES, PLASMA CONCENTRATION OF TYROSINE KINASE INHIBITORS (TKIS) AND QUALITY OF LIFE IN PATIENTS WITH GASTROINTESTINAL STROMAL TUMOR (GIST)

Charlotte M. Brinch[1]*; Ninna Aggerholm-Pedersen*[5]*; Pieter de Heer*[4]*; Malene Møller Jørgensen*[3]*; Adile Orhan*[1]*; Estrid Høgdall*[2]*; Anders Krarup-Hansen*[1]

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Poster #126 3253856

PROTEIN EXPRESSION ANALYSIS BY REGULATING C-KIT AND KCTD12 EXPRESSION IN GASTROINTESTINAL STROMAL TUMOR

Keita Sasa[1]*; Yoshiyuki Suehara*[1]*; Taketo Okubo*[1]*; Takuo Hayashi*[2]*; Kei Sano*[1]*; Taisei Kurihara*[1]*; Keisuke Akaike*[1]*; Midori Ishii*[1]*; Youngji Kim*[1]*; Kazuo Kaneko*[1]*; Tsuyoshi Saito*[2]
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Poster #127 3246597

TYK2 PROMOTES MALIGNANT PERIPHERAL NERVE SHEATH TUMOR PROGRESSION THROUGH INHIBITION OF CELL DEATH

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Poster #128 3253528

GENOME ENGINEERING OF DISEASE SPECIFIC CELL TYPES REVEALS HIDDEN VULNERABILITIES AND NEW THERAPEUTIC APPROACHES FOR TREATMENT OF NEUROFIBROMATOSIS TYPE-1 RELATED CANCER

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Poster #129 3256376

ROLE OF FDG PET-CT IN MALIGNANT PERIPHERAL NERVE SHEET TUMOR (MPNST)

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Poster #130 3257924

ACTIVITY OF NEO-ADJUVANT CHEMOTHERAPY ALONE OR COMBINED WITH RADIATION-THERAPY IN SPORADIC VERSUS NF1-RELATED MPNST IN THE CONTEXT OF TWO INTERNATIONAL, PHASE III, RANDOMIZED CLINICAL TRIALS IN LOCALIZED HIGH-RISK SOFT TISSUE SARCOMA

Elena Palassini[1]*; Sara Pizzamiglio*[1]*; Emanuela Palmerini*[2]*; Vittorio Quagliuolo*[3]*; Javier Martin-Broto*[4]*; Antonio Lopez-Pousa*[5]*; Giovanni Grignani*[6]*; Antonella Brunello*[7]*; Jean-Yves Blay*[8]*; Roberto D. Beveridge*[9]*; Virginia Ferraresi*[10]*; Iwona Lugowska*[11]*; Angela Buonadonna*[12]*; Alessandro Comandone*[13]*; Giuseppe Bianchi*[2]*; Paolo Verderio*[1]*; Domenico Merlo*[14]*; Valeria Fontana*[15]*; Emanuela Marchesi*[2]*; Silvia Stacchiotti*[1]*; Angelo Paolo Dei Tos*[16]*; Piero Picci*[2]*; Paolo Bruzzi*[15]*; Paolo Casali*[1]*; Alessandro Gronchi*[1]
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Poster #131 3253329

EVALUATION OF CANCER-TESTIS ANTIGENS IN OSTEOSARCOMA AND DEDIFFERENTIATED LIPOSARCOMA AS TARGETS FOR IMMUNOTHERAPY

Ashley Flaman, MD[1]*; Anna Jirovec*[1]*; Bibianna Purgina*[4]*; Fanny Tzelepis*[2]*; Joel Werier*[3]*; Jean-Simon Diallo*[2]

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Poster #132 3223596

PROGNOSTIC SIGNIFICANCE OF PD-L1 EXPRESSION AND MICROSATELLITE INSTABILITY IN PATIENTS WITH RETROPERITONEAL LEIOMYOSARCOMAS

Vladislav Bugaev[1]*; Maxim Nikulin*[1]*; Natalia Pospehova*[2]*; Safronova Vera*[2]*; Kokosadze Natalia*[3]*; Yana Bozhchenko*[3]*; Sergey Nered*[1]*; Ludmila Lyubchenko*[2]*; Ivan Stilidi*[1]

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Poster #133 3252978

CTNNB1 MUTATIONS AND AGGRESSIVE BEHAVIOR IN NEUROMUSCULAR CHORISTOMA-ASSOCIATED FIBROMATOSIS

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Poster #134 3256176

MALIGNANT TRANSFORMATION OF LIPOSCLEROSING MYXOFIBROUS TUMOR: A CASE REPORT

Yoshihiro Araki[1]*; Norio Yamamoto*[1]*; Katsuhiro Hayashi*[1]*; Akihiko Takeuchi*[1]*; Shinji Miwa*[1]*; Kentaro Igarashi*[1]*; Yuta Taniguchi*[1]*; Hirotaka Yonezawa*[1]*; Sei Morinaga*[1]*; Takayuki Nojima*[2]*; Hiroyuki Tsuchiya*[1]

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Poster #135 3239164

AN ANALYSIS OF THE STAGE AT PRESENTATION AND OUTCOMES OF PEDIATRIC PATIENTS WITH OSTEOSARCOMA IN CANADA

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Poster #136 3253373

A RETROSPECTIVE STUDY OF GEMCITABINE AND DOCETAXEL FOR RELAPSED OR REFRACTORY PEDIATRIC OSTEOSARCOMA AND SOFT TISSUE SARCOMAS

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Poster #137 3255166

EVALUATION OF THE ANTIBODY-DRUG CONJUGATE ABBV-085 TARGETING LRRC15 IN THE PEDIATRIC PRECLINICAL TESTING CONSORTIUM OSTEOSARCOMA IN VIVO MODELS

Jonathan B. Gill[2]*; Michael Roth*[2]*; Douglas Harrison*[2]*; Wendong Zhang*[2]*; Beverly Teicher*[1]*; Stephen Erickson*[3]*; Malcolm Smith*[1]*; Edward A. Kolb*[2]*; Richard Gorlick*[2]
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Poster #138 3255557

SALVAGE CHEMOTHERAPY USING IRINOTECAN AND TEMOZOLOMIDE IN PAEDIATRIC, AYA AND ADULT POPULATIONS WITH RELAPSED EWING SARCOMA

Jeremy Lewin[1]*; Taleb Ismaeel*[2]*; Yat Hang To*[1]*; Omar Khzouz*[2]*; Iyad Sultan*[2]*; Sameer Yaser*[2]*; Anoud Zaid Alnsour*[2]*; Ramiz Abuhijleh*[2]*; Omar Shahin*[2]*; Rasha Aldouri*[2]*; Samer Salah*[2]
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Poster #139 3255563

HIGH ENGRAFTMENT RATE OF PEDIATRIC AND YOUNG ADULT BONE AND SOFT-TISSUE SARCOMA PATIENT-DERIVED XENOGRAFTS

Joseph G. Pressey, MD[1]*; David Milewski*[2]*; Brian Turpin*[1]*; Rajaram Nagarajan*[1]*; Neil Johnson*[3]*; Roshni Dasgupta*[6]*; Joel Sorger*[4]*; John Donovan*[2]*; Sara Szabo*[5]*; Tanya Kalin*[2]
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Poster #140 3254269

PRESERVING THE PHYSIS IN VERY YOUNG PEDIATRIC PATIENTS WITH LOWER EXTREMITY EWING SARCOMA

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Poster #141 3256327

ENUMERATION OF CELL SURFACE VIMENTIN POSITIVE CELLS AS A METHOD OF DETECTING TUMOR CELLS IN PEDIATRIC PATIENTS WITH SARCOMA

Long Dao, PhD*; Jessica Foglesong; Izhar Batth; Wafik Zaky; Jonathan B. Gill; Diane Liu; Aisha Albert; Nancy Gordon; Winston Huh; Douglas Harrison; Cynthia Herzog; Eugenie Kleinerman; Richard Gorlick; Najat C. Daw; Shulin Li*
Pediatrics, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Poster #142 3227605

IDENTIFYING A NEED AND KNOWLEDGE GAP OF OSTEOPATHIC MEDICINE FOR PEDIATRIC SARCOMA PATIENTS

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Poster #143 3253042

OFFERING GNRH AGONISTS FOR FERTILITY PRESERVATION IN FEMALE ADOLESCENT & YOUNG ADULT SARCOMA PATIENTS: A NEW STANDARD OF CARE?

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Poster #144 3256229

EVALUATION OF THE TPO-RECEPTOR AGONIST ELTROMBOPAG IN THE PEDIATRIC PRECLINICAL TESTING CONSORTIUM OSTEOSARCOMA IN VIVO MODELS

*Michael Roth[1]; Grace Nevil[4]; **Jonathan B. Gill**[1]; Wendong Zhang[1]; Beverly Teicher[2]; Stephen Erickson[3]; Malcolm Smith[2]; Edward A. Kolb[1]; Richard Gorlick[1]*
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Poster #145 3229100

CLINICAL FEATURES AND OUTCOMES OF PRIMARY BONE AND SOFT TISSUE SARCOMAS IN ADOLESCENTS AND YOUNG ADULTS

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Poster #146 3254677

FACTORS INFLUENCING SARCOMA ACT EFFICACY

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Poster #147 3255443

DISCOVERY OF TARGETED EXPRESSION DATA FOR NOVEL ANTIBODY-BASED AND CHIMERIC ANTIGEN RECEPTOR- BASED THERAPEUTICS IN SOFT TISSUE SARCOMAS USING RNA-SEQ: CLINICAL IMPLICATIONS

***Roberto Carmagnani Pestana**[1]; Jason Roszik[1]; David McCall[1]; Roman Groisberg[3]; Shiraj Sen[2]; Anthony Conley[1]; Vivek Subbiah[1]*
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Poster #148 3255480

EVALUATING THE POTENTIAL OF TUMOUR INFILTRATING LYMPHOCYTES FOR THE TREATMENT OF ADULT SARCOMA

***Alice Ko**[1]; Minji Lee[2]; Victoria Coward[4]; Kayley Xu[5]; Nalan Gokgoz[2]; Brendan Dickson[3]; Jay Wunder[3]; Irene L. Andrulis[2]*
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Poster #149 3256028

PREVALENCE OF GERMLINE VARIANTS AS DETERMINED BY EXPANDED MULTIGENE PANELS IN PATIENTS WITH SOFT TISSUE SARCOMA

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GSTP1 EXPRESSION IS PREDICTIVE OF SARCOMA RESPONSE TO DOXORUBICIN BASED CHEMOTHERAPY

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IN SITU CRYO-ABLATION OF DESMOID TUMORS ASSISTED BY 3D MODELLING AND NAVIGATION BY O ARM

Ortal Segal; *Ido Druckmann; Yehuda Kollander; Solomon Dadia; Amir Sternheim; Yair Gortzak*
The National Unit for Orthopedic Oncology, Tel Aviv Medical Center, Tel Aviv, Israel

Poster #152 3228336

THERAPEUTIC IMPLICATION OF GENOIC LANDSCAPE OF ADULT METASTATIC SARCOMA

Xiaolan Feng, MD, PhD[6]; *Erin Pleasance*[1]; *Eric Zhao*[1]; *Tony Ng*[2]; *Jasleen Grewal*[1]; *Mohammad Nissreen*[2]; *Sara K. Taylor*[4]; *Christine Simmons*[5]; *Srikanthan Amirrtha*[5]; *Rod Rassekh*[3]; *Rebecca Deyell*[3]; *Yaoqing Shen*[1]; *Emma Titmuss*[1]; *Lim Howard*[5]; *Daniel Renouf*[5]; *Karen Gelmon*[5]; *Stephen Yip*[2]; *Steven Jones*[1]; *Marco Marra*[1]; *Janessa Laskin*[5]
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Poster #153 3245758

EXPLORATORY ANALYSIS OF HYBRID-CAPTURE BASED NEXT-GENERATION SEQUENCING CONFIRMS SUCCINATE DEHYDROGENASE DEFICIENCY AS THE SOLITARY GENOMIC DRIVER IN PARAGANGLIOMA, PHEOCHROMOCYTOMA, AND GIST

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Poster #154 3254176

USING A CROSS-SPECIES PRECISION MEDICINE PIPELINE TO IDENTIFY PROMISING NEW THERAPIES FOR OSTEOSARCOMAS

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Poster #155 3255682

EWS-FUSION PARTNERS IN SARCOMA AS REVEALED BY "REAL WORLD" GENOMIC SEQUENCING: CLINICAL IMPLICATIONS

David McCall, Doctorate of Medicine[2]; *Jason Roszik*[1]; *Branko Cuglievan*[2]; *Joseph A. Ludwig*[3]; *Maria A. Zarzour*[3]; *Jonathan B. Gill*[2]; *J. Andrew Livingston*[3]; *Vivek Subbiah*[4]
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Poster #156 3229444

SAFETY AND FEASIBILITY OF CIVO PHASE 0 PLATFORM FOR SIMULTANEOUS EVALUATION OF MULTIPLE DRUGS AND DRUG COMBINATIONS IN THE TUMOR MICROENVIRONMENT OF SOFT TISSUE SARCOMA PATIENTS

Kenneth R. Gundle, MD[1]; *Gary Deutsch*[4]; *Seth Pollack*[5]; *Matthew Thompson*[6]; *Jessica Davis*[2]; *Mee-young Lee*[4]; *Daniel Ramirez*[4]; *William Kerwin*[3]; *Jessica Bertout*[3]; *Marc Grenley*[3]; *Kimberly Sottero*[3]; *Emily Beirne*[3]; *Richard Klinghoffer*[3]; *Robert G. Maki*[4]
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Poster #157 3230261

DIFFERENCES IN RESPONSE WITH PEMBROLIZUMAB IN UNDIFFERENTIATED PLEOMORPHIC SARCOMA BASED ON PROSPECTIVE KNOWLEDGE OF PDL-1 EXPRESSION

Benjamin Powers, MD[1]*; Elizabeth Friedman*[4]*; Kyle Sweeney*[2]*; Howard Rosenthal*[2]*; Vickie Massey*[3]*; Laure Dubois*[5]
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Poster #158 3253907

MOLECULAR THERAPY FOR SOFT TISSUE SARCOMA

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Poster #159 3256526

CELL CYCLE CHECKPOINT INHIBITION SYNERGIZES WITH MITOTIC SPINDLE INHIBITION IN LEIOMYOSARCOMA

Eddie Passen[2]*;* ***Nathan D. Seligson, PharmD***[1]*; Colin Stets*[2]*; Bryce Demoret*[2]*; Achal Awasthi*[2]*; John Hays*[2]*; James L. Chen*[2]
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Poster #160 3258092

HIGH-THROUGHPUT DRUG SCREENING OF PATIENT-DERIVED TUMOR ORGANOIDS FROM OSTEOSARCOMA PULMONARY METASTASES

Jane Yanagawa, MD[1]*; Noah C. Federman*[2]*; Scott D. Nelson*[3]*; Sarah M. Dry*[3]*; Benjamin J. DiPardo*[1]*; Huyen Nguyen-Thi-Lam*[4]*; Francis J. Hornicek*[4]*; Arun Singh*[4]*; Chmielowski Bartosz*[4]*; Fritz C. Eilber*[1]*; Anusha Kalbasi*[5]*; Nicholas M. Bernthal*[4]*; Alice Soragni*[4]
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Poster #161 3256197

DEVELOPMENT OF AN *IN VITRO* DRUG PROFILING PLATFORM TO TAILOR PATIENT-SPECIFIC SARCOMA TREATMENTS

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Poster #162 3254985

PATIENT-CENTERED CARE AT THE NEW KAROLINSKA UNIVERSITY HOSPITAL SARCOMA CENTER IMPROVED CONTINUITY AND THE ROLE OF THE CONTACT NURSE

Helen Lernedal
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Poster #163 3256277

A CROSS-SPECIES PERSONALIZED MEDICINE APPROACH TO TREAT LEIOMYOSARCOMA

Sarah M. Hoskinson[1]*; Sneha Rao*[1]*; Erdem Altunel*[1]*; Wayne Glover*[1]*; Laura Selmic*[1]*; Cindy Eward*[2]*; David Hsu*[1]*; William Eward*[1]*; Jason Somarelli*[1]
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Poster #164 3256378

QUANTIFICATION OF SERUM LEVEL OF CIRCULATING DNA AND DNASE I IN LOCALLY ADVANCED AND METASTATIC SYNOVIAL SARCOMA, PILOT STUDY. CORRELATION WITH RESPONSE TO TREATMENT

Jorge L. Martínez Tlahuel, MsC[1]*; Catalina Trejo*[2]*; Enrique Perez*[2]*; Eder Arango*[1]
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Poster #165 3241353

PATIENT BURDEN AND MEDICAL CARE OF SARCOMA IN GERMANY: NATIONWIDE COHORT STUDY FOCUSING ON MODIFIABLE DETERMINANTS OF PATIENT-REPORTED OUTCOME MEASURES IN SARCOMA PATIENTS (PROSA) - BASELINE DESCRIPTION

Bernd Kasper, MD, PhD[1]*; Peter Hohenberger*[1]*; Martin Eichler*[2]*; Stephan Richter*[2]*; Andreou Dimosthenis*[3]*; Daniel Pink*[4]*; Henriette Golcher*[5]*; Stephen Fung*[6]*; Eva Wardelmann*[7]*; Karin Arndt*[8]*; Leopold Hentschel*[9]*; Maria Eberlein-Gonska*[10]*; Martin Bornhäuser*[9]*; Jochen Schmitt*[12]*; Markus Schuler*[11]
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Poster #166 3253141

DEVELOPING HOLISTIC PERSONALISED MODELS OF REHABILITATION TO OPTIMISE SURVIVORSHIP OUTCOMES AFTER TREATMENT FOR LOWER EXTREMITY SARCOMA – A FEASIBILITY STUDY

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Poster #167 3253147

CAN HOLISTIC PERSONALISED MODELS OF REHABILITATION IMPROVE SURVIVORSHIP OUTCOMES AFTER TREATMENT FOR LOWER EXTREMITY SARCOMAS? A PRELIMINARY EFFICACY STUDY

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Poster #168 3253216

INCORPORATING THE PATIENT VOICE IN SARCOMA RESEARCH: HOW CAN WE ASSESS HEALTH-RELATED QUALITY OF LIFE IN THIS HETEROGENEOUS GROUP OF PATIENTS?

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Poster #169 3255137

KNOWLEDGE OF PATIENTS WITH SARCOMA FOR THEIR ILLNESS IN AN INDIAN SETTING (KNOWSARC STUDY)

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Poster #170 3255976

MOBILE APPLICATION FOR SARCOMA PATIENTS AND THEIR RELATIVES

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Poster #171 3256393

PREVALENCE, TEMPORALITY AND ASSOCIATION WITH MORTALITY OF SYMPTOM CLUSTERS AMONG SARCOMA PATIENTS ON SYSTEMIC TREATMENT

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Poster #172 3256444

HEALTH-RELATED QUALITY OF LIFE IN TENOSYNOVIHEALTH-RELATED QUALITY OF LIFE IN TENOSYNOVIAL GIANT CELL TUMORS (TGCT) PATIENTS IN EUROPE AND US: AN OBSERVATIONAL DISEASE REGISTRY

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Poster #173 3258041

HOW BENEFICIAL IS VIDEO SEMINAR FOR SARCOMA PATIENTS?

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Poster #174 3239614

FEMORAL FRACTURE IN PRIMARY SOFT-TISSUE SARCOMA OF THE THIGH AND GROIN TREATED WITH INTENSITY-MODULATED RADIATION THERAPY WITH AND WITHOUT DOSE CONSTRAINTS

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Poster #175 3241461

GENOMIC CHARACTERIZATION OF RADIATION-INDUCED SARCOMA USING WHOLE GENOME SEQUENCING

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Poster #176 3256155

MODELING GENOMIC ADJUSTED RADIATION DOSE (GARD) IN SOFT TISSUE SARCOMA

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Poster #177 3235168

EARLY OUTCOMES OF PREOPERATIVE 5-FRACTION RADIATION THERAPY FOR SOFT TISSUE SARCOMA WITH IMMEDIATE RESECTION

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Poster #178 3239332

EFFICACY OF AN ESOPHAGEAL SPACER FOR HIGH-DOSE SINGLE-FRACTION RADIOSURGERY FOR DE NOVO SPINE CHORDOMA- FIRST EXPERIENCE

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Poster #179 3256255

CLINICAL OUTCOME OF NEOADJUVANT ALTERNATING CHEMORADIOTHERAPY FOR SOFT TISSUE SARCOMAS

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Poster #180 3244842

ADJUVANT INTENSITY MODULATED RADIATION THERAPY IN PRIMARY SOFT TISSUE SARCOMA OF THE SUPERFICIAL TRUNK

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Poster #181 3246554

KAPOSI'S SARCOMA: EXPERIENCE OF A RADIOTHERAPY DEPARTMENT

André Figueiredo; Andre D. Florindo; Diogo Delgado; Helena Pais; Raquel Brás; ***Isabel Fernandes****; Virgínia Mareco; André Abrunhosa-Branquinho; Vera Mendonça; Maria F. de Pina*
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Poster #182 3255340

RETROPERITONEAL SARCOMA PATIENTS TREATED WITH RADIOTHERAPY AFTER R1 SURGERY – A SINGLE CENTER RETROSPECTIVE STUDY

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Poster #183 3223161

THERAPEUTIC VALUES OF RADIOTHERAPY IN THE TREATMENT OF DESMOID TUMORS

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Poster #184 3239881

TARGETING PAX3-FOXO1 ONCOPROTEIN: AN INVESTIGATION OF SMALL MOLECULE INHIBITORS FOR RHABDOMYOSARCOMA

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Poster #185 3256164

EPIGENETIC CHEMICAL SCREENS TO IDENTIFY NOVEL THERAPEUTIC STRATEGIES FOR RHABDOMYOSARCOMA (RMS)

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Poster #186 3256678

CLONAL EVOLUTION OF CHEMOTHERAPY RESISTANT RHABDOMYOSARCOMA VIA MULTIFOCAL GENOMIC ANALYSIS OF PRE-TREATMENT AND TREATMENT-RESISTANT AUTOPSY SPECIMENS

Michael Kinnaman, MD[1]; *Alvin Makohon-Moore*[2]; *Nancy Bouvier*[2]; *Dominik Glodzik*[2]; *Max Levine*[2]; *Ellie Papaemmanuil*[3]; *Filemon Dela Cruz*[1]; *Leonard Wexler*[1]; *Andrew Kung*[1]; *Christine Iacobuzio-Donahue*[4]
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Poster #187 3256484

INTERIM RESULTS FROM A PHASE I/II TRIAL OF GANITUMAB PLUS DASATINIB IN PATIENTS WITH RELAPSED RHABDOMYOSARCOMA (RMS)

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Poster #188 3255404

CELL-CELL INTERACTION IN UNDIFFERENTIATED PLEOMORPHIC SARCOMA

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Poster #189 3256145

E-CADHERIN REPRESSES ANCHORAGE-INDEPENDENT GROWTH IN SARCOMAS THROUGH BOTH SIGNALING AND MECHANICAL MECHANISMS

Suzanne Bartholf DeWitt, DVM[3]; *Mohit Kumar Jolly*[2]; *Kathryn Ware*[3]; *Alexander L. Lazarides*[1]; *David Kerr*[1]; *William Eward*[1]; *Herbert Levine*[2]; *Jason Somarelli*[3]
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Poster #190 3258044

REVIEW OF GENETIC ALTERATIONS IN SARCOMA PATIENTS OF HISPANIC ETHNICITY: ANALYSIS OF 167 PATIENTS, A SINGLE INSTITUTION EXPERIENCE

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Poster #191 3258096

MUTATIONAL AND BIOMARKER CORRELATIVE ANALYSIS OF MTOR PATHWAY ABERRATIONS IN PATIENTS WITH ADVANCED MALIGNANT PERIVASCULAR EPITHELIOID CELL TUMORS (PECOMA) TREATED WITH *NAB*-SIROLIMUS: RESULTS FROM AMPECT, AN OPEN-LABEL PHASE 2 REGISTRATION TRIAL

Andrew Wagner[2]; *Mark Dickson*[3]; *Vinod Ravi*[4]; *Richard F. Riedel*[5]; *Kristen Ganjoo*[6]; *Brian A. Van Tine*[7]; *Rashmi Chugh*[8]; *Lee Cranmer*[9]; *Erlinda Gordon*[10]; *Jason Hornick*[11]; *Heng Du*[11]; *Berta Grigorian*[1]; *Anita N. Schmid*[1]; *Shihe Hou*[1]; *Katherine Harris*[1]; *Neil Desai*[1]; *David Kwiatkowski*[11]
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Poster Presentations Listing

Poster #192 3255343

THE SAINT: RESULTS OF A PHASE 1/2 STUDY OF SAFETY/EFFICACY USING SAFE AMOUNTS OF IPILIMUMAB, NIVOLUMAB AND TRABECTEDIN AS FIRST LINE TREATMENT OF ADVANCED SOFT TISSUE SARCOMA *(NCT 03138161)*

Erlinda M. Gordon, MD; *Victoria Chua-Alcala; Katherine M. Kim; Nicole Angel; Rekha Baby; Ania Moradkhani; Doris M. Quon; Steven Wong; Sant P Chawla M. Inc*
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Poster #193 3255504

INITIAL RESULTS OF A PHASE 1/2 INVESTIGATION OF SAFETY/EFFICACY OF NIVOLUMAB AND ABI-009 (NAB-RAPAMYCIN) IN ADVANCED UNDIFFERENTIATED PLEOMORPHIC SARCOMA (UPS), LIPOSARCOMA (LPS), CHONDROSARCOMA (CS), OSTEOSARCOMA (OS), AND EWING'S SARCOMA (NCT 03190174)

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Poster #194 3256430

RESPONDER ANALYSIS OF PATIENT-REPORTED OUTCOMES MEASUREMENT INFORMATION SYSTEM (PROMIS) PHYSICAL FUNCTION (PF) AND WORST STIFFNESS AMONG PATIENTS WITH TENOSYNOVIAL GIANT CELL TUMORS (TGCT) IN THE ENLIVEN STUDY

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Poster #195 3255349

DEVELOPMENT OF RAPID AND COST-EFFECTIVE ASSAY TO DETECT AMPLIFICATION OF CHROMOSOME 12Q13-15 IN WELL DIFFERENTIATED AND DE-DIFFERENTIATED LIPOSARCOMA

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Poster #196 3255331

CLINICAL OUTCOMES IN THE SETTING OF MULTIMODALITY TREATMENT OF PRIMARY ANGIOSARCOMA AND RADIATION-INDUCED ANGIOSARCOMA OF THE BREAST

Emily L. Ryon, MD, MPH[1]*; Sina Yadegarynia[1]; Florou Vaia[2]; Susan Kesmodal[1]; Raphael Yechieli[2]; Jonathan Trent[2]; Neha Goel[1]*
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Poster #197 3255375

DETECTION OF TRANSLOCATION ASSOCIATED SARCOMAS BY EXON EXPRESSION IMBALANCE AND GENE OVER-EXPRESSION

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Poster Presentations Listing

Poster #198 3255558

RETROSPECTIVE ANALYSIS OF CT VERSUS XR SURVEILLANCE FOR METASTASIS AFTER SURGICAL RESECTION OF LOCALIZED SOFT TISSUE SARCOMA

Hilary Dietz; *Cara Cipriano; Douglas McDonald; Brian A. Van Tine; Peter Oppelt; Angela Hirbe*
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Poster #199 3255785

THE PROGNOSTIC INFLUENCE OF HYALURONIC ACID EXPRESSION IN RESECTED SOFT TISSUE SARCOMA

Dersheng Sun; *Jihyun Yang; Seorhee Kim*
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Poster #200 3256055

EVALUATION OF DISTROFIN EXPRESSION BY INMUNOHISTOCHEMISTRY AS A PROGNOSTIC FACTOR IN LEIOMYOSARCOMAS

Raul Teres[1]; Ruth Orellana[2]; Eduard Gallardo[3]; Isidro Gracia[4]; Ana Peiro[4]; Jose González[5]; Alberto Gallardo[2]; Sandra Valverde[6]; Jaume Llauger[6]; Diana Hernández[6]; Manuel Fernández[7]; Antonio Lopez-Pousa[1]; ***Ana Sebio, MD, PhD***[1]
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Poster #201 3256112

CLINICAL AND MOLECULAR CHARACTERISTICS AND OUTCOMES OF 59 PATIENTS WITH EXTRASKELETAL MYXOID CHONDROSARCOMA TREATED AT TWO INSTITUTIONS

Benedetta Chiusole[7]*; Axel Le Cesne[1]; Antonella Brunello[7]; Marco Rastrelli[3]; Marco Maruzzo[7]; Martina Lorenzi[7]; Rocco Cappellesso[2]; Paolo Del Fiore[3]; Marta Sbaraglia[4]; Philippe Terrier[6]; Pietro Ruggieri[5]; Angelo Paolo Dei Tos[4]; Carlo Riccardo Rossi[3]; Vittorina Zagonel[7]*
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Poster #202 3256175

NY-ESO-1 TCR T (GSK3377794)– CASE STUDIES – SARCOMA AND MRCLS – CORRELATES OF PREDICTABLE RESPONSE CHARACTERISTICS

Brian A. Van Tine[1]; ***Sandra P. D'Angelo***[2]*; Alex Gyurdieva[3]; Laura A. Johnson[3]; David C. Turner[3]; Jenna Tress[3]; M. Philip DeYoung[3]; Yuehui Wu[3]; Aisha N. Hasan[3]; Dejka Araujo[4]*
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Poster #203 3256364

PHASE 1 TRIAL OF NY-ESO-1-SPECIFIC ADOPTIVE T-CELL THERAPY WITH GSK3377794 IN PATIENTS WITH ADVANCED SYNOVIAL SARCOMA

Sandra P. D'Angelo, MD[8]*; George D. Demetri[1]; Brian A. Van Tine[2]; Mihaela Druta[3]; John Glod[4]; Warren Chow[5]; Jenna Tress[6]; M. Philip DeYoung[6]; Aisha N. Hasan[6]; Yuehui Wu[6]; David C. Turner[6]; Dan Schramek[6]; Ran Ji[6]; Alex Gyurdieva[6]; Dejka Araujo[7]*
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Poster #204 3256543

OUTCOME AFTER SURGICAL TREATMENT OF DERMATOFIBROSARCOMA PROTUBERANCE (DFSP): DOES IT REQUIRE ALL THIS FOLLOW-UP? WHAT IS AN ADEQUATE RESECTION MARGIN?

Ibrahim S. Alshaygy; *Jean-Camille Mattei; Georges Basile; Anthony Griffin; Rebecca Gladdy; Carol J. Swallow; Brendan Dickson; Peter Ferguson; Jay Wunder*
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Poster #205 3257861

THE ROLE OF NEOADJUVANT CHEMOTHERAPY IN THE MANAGEMENT OF ANGIOSARCOMA

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Poster #206 3257892

ITALIAN SARCOMA GROUP (ISG) - SPANISH SARCOMA GROUP (GEIS) - FRENCH SARCOMA GROUP (FSG) - POLISH SARCOMA GROUP (PSG) CLINICAL TRIAL ON NEO-ADJUVANT CHEMOTHERAPY IN HIGH-RISK SOFT TISSUE SARCOMAS (STS): RESULTS OF NON-RANDOMIZED GROUP OF PATIENTS

Elena Palassini[1]; *Emanuela Palmerini*[14]; *Vittorio Quagliuolo*[2]; *Javier Martin-Broto*[3]; *Antonio Lopez-Pousa*[4]; *Giovanni Grignani*[5]; *Antonella Brunello*[6]; *Jean-Yves Blay*[7]; *Roberto D. Beveridge*[8]; *Virginia Ferraresi*[9]; *Iwona Lugowska*[10]; *Domenico Merlo*[11]; *Luca Braglia*[11]; *Valeria Fontana*[12]; *Davide M. Donati*[14]; *Andrea Marrari*[2]; *Carlo Morosi*[1]; *Silvia Stacchiotti*[1]; *Silvia Baguè*[16]; *Jean M. Coindre*[15]; *Angelo Paolo Dei Tos*[13]; *Piero Picci*[14]; *Paolo Bruzzi*[12]; *Paolo Casali*[1]; *Alessandro Gronchi*[1]
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Poster #207 3245645

GENETIC ANALYSIS OF SOFT TISSUE SARCOMAS REVEALS HISTOTYPE-SPECIFIC PATHWAY ALTERATIONS AND POTENTIAL PREDICTORS OF IMMUNOTHERAPY RESPONSE

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Poster #208 3253973

THE ASSOCIATION OF CHEMOTHERAPY AND SURVIVAL IN PATIENTS WITH PRIMARY, LOCALIZED, HIGH-GRADE, EXTREMITY AND TRUNK SOFT TISSUE SARCOMA

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Poster #209 3254426

SAFETY AND EFFICACY OF TAZEMETOSTAT, A FIRST-IN-CLASS EZH2 INHIBITOR, IN PATIENTS WITH EPITHELIOID SARCOMA (ES) (NCT02601950)

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Poster #210 3220904

PLOCABULIN, A NOVEL TUBULIN INHIBITOR, HAS ANTITUMOR ACTIVITY IN A PATIENT-DERIVED XENOGRAFT (PDX) MODEL OF *CIC*-REARRANGED SARCOMA

Yannick Wang[1]; *Agnieszka Wozniak*[1]; *María José Guillén*[2]; *Pablo M. Avilés*[2]; *Maria Debiec-Rychter*[3]; *Raf Sciot*[4]; *Patrick Schöffski*[5]

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Poster #211 3232641

INDIVIDUALIZATION OF FOLLOW-UP IN PATIENTS WITH HIGH-GRADE SOFT TISSUE SARCOMA

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Poster #212 3241036

A PHASE II STUDY OF PAZOPANIB AS FRONT-LINE THERAPY IN PATIENTS WITH NON-RESECTABLE OR METASTATIC SOFT TISSUE SARCOMAS WHO ARE NOT CANDIDATES FOR CHEMOTHERAPY

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Poster #213 3242737

CONCURRENT PACLITAXEL AND RADIATION THERAPY FOR THE TREATMENT OF CUTANEOUS ANGIOSARCOMA

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Poster #214 3245787

GLO1 AS NOVEL POTENTIAL TARGET TO OVERCOME TRABECTEDIN RESISTANCE IN SOFT TISSUE SARCOMAS

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Poster #215 3247828

CIRCULATING TUMOR DNA LEVELS PREDICT PARTIAL RESPONSE IN A COHORT OF RELAPSED LEIOMYOSARCOMA PATIENTS

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Poster #216 3249535

THE PROGNOSTIC IMPACT OF PULMONARY METASTASECTOMY IN SOFT TISSUE SARCOMA PATIENTS

Teruya Kawamoto[1]; *Toshihiro Akisue*[2]; *Masayuki Morishita*[3]; *Hitomi Hara*[1]; *Naomasa Fukase*[1]; *Yohei Kawakami*[1]; *Ikuo Fujita*[3]; *Takuya Fujimoto*[3]; *Toshiyuki Takemori*[1]; *Shuichi Fujiwara*[1]; *Kazumichi Kitayama*[1]; *Shunsuke Yahiro*[1]; *Ryosuke Kuroda*[1]
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Poster #217 3253397

A PHASE IB STUDY OF THE SAFETY AND PRELIMINARY EFFICACY OF LENVATINIB (LENV) PLUS ERIBULIN (ERI) IN ADVANCED ADIPOCYTIC SARCOM (LPS) AND LEIOMYOSARCOM (LMS) (NCT03526679)

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Poster #218 3253883

SYNERGISTIC ACTIVITIES OF THE HISTONE DEACETYLASE INHIBITORS WITH CONVENTIONAL CYTOTOXIC CHEMOTHERAPIES IN ANGIOSARCOMAS

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Poster #219 3254568

XENOSARC: PATIENT-DERIVED XENOGRAFT MODELS OF SOFT TISSUE SARCOMA – AN UPDATE ON A PRECLINICAL PLATFORM FOR EARLY DRUG TESTING

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Poster #220 3254669

INVESTIGATING THE CIRCULATING TUMOR DNA AS A BIOMARKER OF CANCER PROGRESSION AND RECURRENCE IN SARCOMA

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Poster #221 3254681

DURABLE RESPONSES TO COMBINATION ANTI-CTLA-4 AND ANTI-PD-1 THERAPY AMONG PATIENTS WITH CHEMOTHERAPY/TYROSINE KINASE INHIBITOR RESISTANT SOFT TISSUE AND BONE SARCOMAS

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Poster #222 3254823

LOW-DOSE PREOPERATIVE RADIATION THERAPY, RESECTION, AND REDUCED-FIELD POST-OPERATIVE RADIATION THERAPY FOR SOFT TISSUE SARCOMA

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Poster #223 3254961

HIGH-THROUGHPUT ANALYSIS OF TRANSCRIPTIONAL STARTING POINT AND IDENTIFICATION OF PROMOTER

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Poster #224 3255113

TRABECTEDIN WITH CONCURRENT LOW-DOSE OF RADIATION THERAPY FOR METASTATIC SOFT TISSUE SARCOMAS (TRASTS): A MULTICENTER EUROPEAN, SINGLE ARM PHASE II TRIAL OF SPANISH, FRENCH AND ITALIAN SARCOMA GROUPS

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Poster #225 3255195

ACTIVITY OF CHEMOTHERAPY IN INFLAMMATORY MYOFIBROBLASTIC TUMOUR (IMT): RETROSPECTIVE ANALYSIS WITHIN EUROPEAN REFERENCE CENTRES

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Poster #226 3255203

IMPROVEMENT IN PATIENT-REPORTED PAIN IN A PHASE III TRIAL OF PEXIDARTINIB (PLX3397) AMONG PATIENTS WITH TENOSYNOVIAL GIANT CELL TUMOR (TGCT)

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Poster #227 3255213

LONG NON-CODING RNA NEAT1 PROMOTES SARCOMA METASTASIS BY REGULATING RNA SPLICING PATHWAYS

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Poster Presentations Listing

Poster #228 3255242

ARE THERE PATIENTS WITH SOFT TISSUE SARCOMA OF TRUNK OR LIMBS WHO MAY NOT BENEFIT FROM RADIATION THERAPY?
A LARGE RETROSPECTIVE STUDY OF THE FRENCH SARCOMA GROUP

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Poster #219 3255266

PRIMARY CUTANEOUS SARCOMAS - A RETROSPECTIVE ANALYSIS OF A 10-YEAR PERIOD AT A TERTIARY TEACHING HOSPITAL

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Poster #230 3255287

EFFICACY AND SAFETY OF ANLOTINIB IN REFRACTORY METASTATIC SOFT-TISSUE SARCOMA: A RETROSPECTIVE STUDY IN CHINA

Wei Xiao; Bushu Xu; Xizhi Wen; Jingjing Zhao; Qiuzhong Pan; ***Xing Zhang***
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Poster #231 3255311

EFFICACY AND SAFETY OF BEVACIZUMAB COMBINED WITH CHEMOTHERAPY IN REFRACTORY METASTATIC SOFT-TISSUE SARCOMA: A RETROSPECTIVE STUDY IN CHINA

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Poster #232 3255449

PERIVASCULAR EPITHELIOID CELL TUMOR (PECOMA) TREATMENT: 20 YEARS OF EXPERIENCE IN ONE REFERENCE SARCOMA CENTER

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Poster #233 3255705

SURGICAL RESULTS AND INFLUENTIAL FACTORS FOR COMPLICATIONS AND LIMB FUNCTION IN PATIENTS WITH SOFT TISSUE SARCOMA OF THE THIGH

Sei Morinaga*; Norio Yamamoto; Katsuhiro Hayashi; Akihiko Takeuchi; Shinji Miwa; Kentaro Igarashi; Yuta Taniguchi; Hirotaka Yonezawa; Yoshihiro Araki; Hiroyuki Tsuchiya*
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Poster #234 3256118

POOR TREATMENT OUTCOMES WITH SECOND-LINE CHEMOTHERAPY IN ADULT ADVANCED AND METASTATIC SYNOVIAL SARCOMA

Yuki Kojima, MD, PhD[1]; *Kan Yonemori*[1]; *Takuji Seo*[1]; *Shu Yazaki*[1]; *Toshihiro Okuya*[1]; *Yohei Ohtake*[1]; *Tadaaki Nishikawa*[1]; *Kazuki Sudo*[1]; *Maki Tanioka*[1]; *Akihiko Shimomura*[1]; *Emi Noguchi*[1]; *Tatsunori Shimoi*[1]; *Akihiko Yoshida*[2]; *Akira Kawai*[3]; *Yasuhiro Fujiwara*[1]; *Kenji Tamura*[1]
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Poster #235 3256204

A CLINICAL RANDOMIZED CONTROLLED TRIAL OF TOTAL (IPSILATERAL) RETROPERITONEAL LIPECTOMY WITH HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY FOR RETROPERITONEAL LIPOSARCOMA

Cheng Li Miao[1]; ***Shahbaz Hanif, MD***[2]; *Xiao Bing Chen*[1]; *Mei Huang*[1]; *Cheng Hua Luo*[1]
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Poster #236 3256260

DOES RADIOTHERAPY BENEFIT PATIENTS WITH SUPERFICIAL SOFT TISSUE SARCOMAS?

Tomohiro Fujiwara; *Yusuke Tsuda; Louis-Romee Le Nail; Scott Evans; Jonathan Stevenson; Michael Parry; Jonathan Gregory; Roger Tillman; Lee Jeys; Adesegun Abudu*
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Poster #237 3256278

PROGNOSTIC ROLE OF INITIAL ELEVATED NEUTROPHIL-LYMPHOCYTE RATIO AND POOR PERFORMANCE STATUS IN SOFT TISSUE SARCOMA

Tatsunori Shimoi; *Kan Yonemori; Yuki Kojima; Kazuki Sudo; Tadaaki Nishikawa; Maki Tanioka; Akihiko Shimomura; Emi Noguchi; Yasuhiro Fujiwara; Kenji Tamura*
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Poster #238 3256317

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

Jonathan Trent, MD, PhD[1]; *Neeta Somaiah*[2]; *Silvia Stacchiotti*[3]; *Peter Reichardt*[4]; *Hector Soto Parra*[5]; *Rainer Hamacher*[6]; *Donna E. Levy*[8]; *Gary Mo*[7]; *Ashwin Shahir*[7]; *Jennifer Wright*[7]; *Sebastian Bauer*[6]
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Poster #239 3256398

CLINICOPATHOLOGIC PROFILE OF EXTREMITY SOFT TISSUE SARCOMAS TREATED AT NATIONAL CANCER INSTITUTE (MEXICO) FROM 1990-2017

Dorian Yarih Garcia Ortega, MD[1]; *Alethia Alvarez-Cano*[2]; *Claudia Haydee Sarai Caro-Sanchez*[3]; *Miguel Angel Clara-Altamirano*[1]
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Poster Presentations Listing

Poster #240 3256405

IVCSARC STUDY: INFERIOR VENA CAVA SARCOMA EXPERIENCE AT A TERTIARY CARE CENTER IN SOUTH INDIA

Beulah R. Samuel, MS[1]; *Coelho Victor*[1]; *Titus DK*[1]; *Abinaya Nadarajan*[1]; *Suchita Chase*[1]; *Sukria Nayak*[1]; *Vimalin Samuel*[2]; *Philip Joseph*[3]; *Sitaram V*[3]; *Anne J. Prabhu*[4]; *Patricia Solomon*[5]; *Ashish Singh*[6]
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Poster #241 3256503

PHASE 2 STUDY OF ALODOXORUBICIN WITH IFOSFAMIDE/MESNA IN TREATMENT SUBJECTS WITH METASTATIC, LOCALLY ADVANCED, OR UNRESECTABLE SOFT TISSUE SARCOMA

Sant Chawla, MD[1]; *Victoria Chua-Alcala*[1]; *Doris V. Quon*[1]; *Steven G. Wong*[1]; *Neal Chawla*[1]; *Ania Moradkhani*[1]; *John Lee*[2]; *Katherine M. Kim*[1]; *Rekha Baby*[1]; *Erlinda Gordon*[1]
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Poster #242 3256549

WHAT CAN YOU EXPECT FROM LYMPH NODE METASTASES IN SOFT TISSUE SARCOMAS?

Georges Basile; *Jean-Camille Mattei; Ibrahim S. Alshaygy; Anthony Griffin; Peter Ferguson; Jay Wunder*
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Poster #243 3257932

PRELIMINARY DATA ON A PHASE 2 STUDY ON TRABECTEDIN (T) IN ADVANCED RETROPERITONEAL LEIOMYOSARCOMA AND WELL DIFFERENTIATED/DEDIFFERENTIATED LIPOSARCOMA (TRAVELL)

Roberta Sanfilippo, MD[1]; *Giovanni Grignani*[2]; *Bruno Vincenzi*[3]; *Tommaso De Pas*[4]; *Toni Ibrahim*[5]; *Maria Abbondanza Pantaleo*[6]; *Antonella Brunello*[7]; *Giacomo G. Baldi*[8]; *Alessandro Comandone*[9]; *Sonia Fatigoni*[10]; *Andrea Marrari*[11]; *Alfredo Berruti*[12]; *Monica Giordano*[13]; *Michele Guida*[14]; *Giuseppe Badalamenti*[15]; *Angela Buonadonna*[16]; *Marcella Occelli*[17]; *Elena Fumagalli*[1]; *Matilde De Luca*[18]; *Luciano Carlucci*[18]; *Piero Picci*[19]; *Emanuela Marchesi*[21]; *Angelo Paolo Dei Tos*[20]; *Paolo Casali*[1]
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Poster #244 3206529

DOXORUBICIN VS DOXORUBICIN+IFOSFAMIDE VS OBSERVATION FOR THE ADJUVANT TREATMENT OF PATIENTS WITH SOFT-TISSUE SARCOMA: AN UPDATED META-ANALYSIS

Lisa M. Hess, PhD; *Alan J. Brnabic; Zbigniew Kadziola; Patrick Peterson; Volker Wacheck*
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Poster #245 3208650

PEXIDARTINIB FOR LOCALLY ADVANCED TENOSYNOVIAL GIANT CELL TUMOR (TGCT): OVERALL LONG-TERM POOLED EFFICACY AND SAFETY WITH CHARACTERIZATION OF HEPATIC ADVERSE REACTIONS FROM ENLIVEN AND OTHER STUDIES

John H. Healey[1]; *Hans Gelderblom*[2]; *Andrew Wagner*[3]; *Silvia Stacchiotti*[4]; *William D. Tap*[1]; *Nicholas M. Bernthal*[5]; *Sebastian Bauer*[6]; *Chia-Chi Lin*[7]; *Laurie D. DeLeve*[8]; *Emanuela Palmerini*[9]; *Jayesh Desai*[10]; *Antonio López Pousa*[11]; *Arun Singh*[5]; *Mihaela Druta*[12]; *Henry H. Hsu*[13]; *Dale E. Shuster*[14]; *Joseph McGill*[14]; *Qiang Wang*[14]; *James H. Lewis*[15]; *Michiel van de Sande*[2]
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Poster #246 3217271

LONG-TERM OUTCOMES FOR EXTRASKELETAL MYXOID CHONDROSARCOMA (EMC): A POPULATION-BASED ANALYSIS

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Poster #247 3222026

LUNG SURVEILLANCE STRATEGY FOR HIGH-GRADE SOFT TISSUE SARCOMAS: CT SCAN OR CHEST X-RAY?

Adriana C. Gamboa, MD[1]; *Cecilia G. Ethun*[1]; *Mohammad Y. Zaidi*[1]; *Thuy B. Tran*[2]; *George A. Poultsides*[2]; *Valerie Grignol*[3]; *John H. Howard*[4]; *Meena Bedi*[5]; *T. C. Gamblin*[6]; *Kevin K. Roggin*[7]; *Konstantinos Chouliaras*[8]; *Konstantinos Votanopoulos*[8]; *Darren Cullinan*[9]; *Ryan C. Fields*[9]; *Shervin Oskouei*[10]; *David K. Monson*[10]; *Nickolas B. Reimer*[10]; *Shishir K. Maithel*[1]; *Keith A. Delman*[1]; *Kenneth Cardona*[1]
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Poster #248 3229069

DISEASE RESPONSE WITH PD-1 IMMUNE CHECKPOINT INHIBITOR PEMBROLIZUMAB IN ADVANCED SARCOMA

Steven Bialick, DO; *Lee Hartner; Laetitia Simeral*
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Poster #249 3239155

CHARACTERISING THE IMMUNE MICROENVIRONMENT IN LIPOSARCOMA, ITS IMPACT ON PROGNOSIS AND THE EFFECT OF RADIOTHERAPY

Hayden Snow[1]*; Shona Hendry*[2]*; Catherine Mitchell*[1]*; Madeleine McKinley*[1]*; Sam Ngan*[1]*; Sarat Chander*[1]*; Julie Chu*[1]*; Susie Bae*[1]*; Jayesh Desai*[1]*; Peter Choong*[1]*; Michael Henderson*[1]*; David Gyorki*[1]
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Poster #250 3239422

SOFT TISSUE SARCOMA SURVIVAL RATES CORRELATE TO T-CELL RECEPTOR AND MUTANT AMINO ACID CHEMICAL COMPLEMENTARITIES

Michelle Yeagley*; Boris Chobrutskiy; George Blanck*
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Poster #251 3240770

COMBINATION THERAPY WITH TETRAHYDROPYRANYL-ADRYAMICIN (PIRARUBICIN) + IFOSFAMIDE + ETOPOSIDE FOR ADVANCED SOFT TISSUE SARCOMA

Hisaki Aiba[1]*; Satoshi Yamada*[1]*; Katsuhiro Hayashi*[2]*; Hiroaki Kimura*[2]*; Shinji Miwa*[2]*; Hideki Murakami*[1]
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Poster #252 3241734

PHASE 1 STUDY OF DCC-3014 TO ASSESS THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND PHARMACODYNAMICS IN PATIENTS WITH MALIGNANT SOLID AND DIFFUSE-TYPE TENOSYNOVIAL GIANT CELL TUMOR

Breelyn Wilky, MD[1]*; Matthew Taylor*[2]*; Todd Bauer*[3]*; Steven Leong*[1]*; Ying Su*[4]*; Cynthia Leary*[5]*; Xiaoyan Li*[4]*; Keisuke Kuida*[4]*; Rodrigo Ruiz Soto*[4]*; Lara E. Davis*[6]
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Poster #253 3253165

EXPANSION COHORT OF ADVANCED SARCOMA PATIENTS IN THE PHASE I TRIAL OF PEMBROLIZUMAB COMBINED WITH ZIV-AFLIBERCEPT

Geraldine O'Sullivan Coyne[1]*; Jennifer Zlott*[1]*; Lamin Juwara*[2]*; Anita Gobbie-Hurder*[3]*; Sabrina Khan*[1]*; Albiruni Razak*[4]*; Andrew S. Brohl*[5]*; Daniel Renouf*[6]*; Naoko Takebe*[1]*; Arjun Mittra*[1]*; Elad Sharon*[1]*; James Doroshow*[1]*; Stephen Hodi*[3]*;* ***Alice Chen***[1]
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Poster #254 3253225

RARE MULTINUCLEATED GIANT CELLS IN HUMAN ANGIOSARCOMA CONFER WORSE CLINICAL OUTCOMES

Grace Fangmin Tan[1]*; Timothy Kwang Yong Tay*[2]*; Sathiyamoorthy Selvarajan*[2]*; Mikio Masuzawa*[3]*; Eileen Yi Ling Poon*[5]*; Nagavalli Somasundaram*[5]*; Mohamad Farid*[5]*;* ***Cedric Chuan-Young NG***[4]*; Bin Tean Teh*[4]*; Jason Yong Sheng Chan*[5]
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Poster Presentations Listing

Poster #255 3253280

MULTIDISCIPLINARY INTERVENTION IN RADIATION-ASSOCIATED ANGIOSARCOMA OF THE BREAST: PATTERNS OF RECURRENCE AND RESPONSE TO TREATMENT

Sheena Guram, MBBS[1]*; Andrea Covelli*[1]*; Anne O'Neill*[2]*; David Shultz*[4]*; Elizabeth Demicco*[5]*; Abha Gupta*[3]*; Rebecca Gladdy*[1]

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Poster #256 3254044

POST-NEPHRECTOMY OUTCOMES FOLLOWING EN BLOC RESECTION OF PRIMARY RETROPERITONEAL SARCOMA: A MULTICENTER ANALYSIS

Mark Fairweather, MD[1]*; Heather Lyu*[1]*; Lorenzo Conti*[2]*; Dario Callegaro*[2]*; Stefano Radaelli*[2]*; Marco Fiore*[2]*; Deanna Ng*[3]*; Carol J. Swallow*[3]*; Alessandro Gronchi*[2]*; Chan Raut*[1]

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Poster #257 3220630

IMPACT OF SMOKING ON LUNG METASTASIS-FREE SURVIVAL IN SOFT TISSUE SARCOMA PATIENTS

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Poster #258 3225003

EFFICACY AND SAFETY OF TRABECTEDIN FOR PATIENTS WITH UNRESECTABLE AND RELAPSED SOFT TISSUE SARCOMA IN JAPAN: A JAPANESE MUSCULOSKELETAL ONCOLOGY GROUP (JMOG) STUDY

Hiroshi Kobayashi[1]*; Shintaro Iwata*[2]*; Toru Wakamatsu*[3]*; Keiko Hayakawa*[4]*; Jyunji Wasa*[5]*; Shigeki Kakunaka*[6]*; Michiyuki Hakozaki*[7]*; Takashi Yanagawa*[8]*; Satoshi Tsukushi*[9]*; Tsukasa Yonemoto*[10]*; Sakae Tanaka*[1]*; Takafumi Ueda*[6]

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Poster #259 3229371

DETECTION OF *CSF1* REARRANGEMENTS DELETING THE 3' UTR IN TENOSYNOVIAL GIANT CELL TUMOURS

Julie Ho[1]*; Brendan Dickson*[2]*; Thomas Peters*[3]*; David Swanson*[2]*; Anita Fernandez*[3]*; Marie-Anne Valentin*[3]*; Ursula Schramm*[3]*; Marc Sultan*[3]*; Torsten O. Nielsen*[1]*; **Elizabeth Demicco***[2]

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Poster #260 3230868

COMPETING RISKS ANALYSIS OF THE INFERIORITY OF PATIENTS AGED 80 YEARS OR OLDER WITH SOFT TISSUE SARCOMAS

Jungo Imanishi[2]; *Lester Chan*[2]; *Peter Choong*[1]
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Poster #261 3232627

ABDOMINAL METASTASES OF SOFT TISSUE SARCOMA. INCIDENCE AND OUTCOME IN 769 PATIENTS

Joanna Szkandera[2]; *Maria A. Smolle*[1]; *Angelika J. Schaffler*[3]; *Andreas Leithner*[1]; *Veroniek van Praag*[4]; *Marko Bergovec*[1]; *Bernadette Liegl-Atzwanger*[5]; *Maya Niethard*[6]; *Per-Ulf Tunn*[6]; *Michiel van de Sande*[4]; *Dimosthenis Andreou*[7]
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Poster #262 3236442

PRIMARY RETROPERITONEAL ILIOCAVAL LEIOMYOSARCOMAS: OUTCOME FOLLOWING SURGICAL RESECTION AND THE CALL FOR NOVEL THERAPEUTICS

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Poster #263 3239268

SOFT TISSUE SARCOMAS OF THE TRUNK: CLINICAL OUTCOME AND FACTORS AFFECTING LOCAL RECURRENCE

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Poster #264 3240025

OUTCOMES OF ELDERLY PATIENTS WITH SOFT TISSUE SARCOMA OF THE EXTREMITIES

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Poster #265 3240767

TYPES OF PNEUMOTHORAX DURING TRATMENT WITH PAZOPANIB FOR SOFT-TISSUE TUMOR

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Poster #266 3241937

SOFT TISSUE LEIOMYOSARCOMA: RECURRENCE RATE BASED ON TUMOR DEPTH

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Poster #267 3245414

ERIBULIN SUPPRESSES CLEAR CELL SARCOMA GROWTH BY INHIBITING CELL PROLIFERATION AND INDUCING MELANOCYTIC DIFFERENTIATION BOTH DIRECTLY AND VIA TUMOR VASCULAR REMODELING

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Poster #268 3250619

RADIOGUIDED CORE NEEDLE BIOPSIES ARE ACCURATE FOR THE DIAGNOSIS OF DEEP ATYPICAL LIPOMATOUS TUMORS OF THE LIMBS: A RETROSPECTIVE STUDY OF 110 CASES FROM A CENTER OF THE FRENCH SARCOMA NETWORK NETSARC

Corinne Bouvier[1]*;* ***Alexandra Assolen***[1]*; Nicolas Macagno*[1]*; Christophe Chagnaud*[2]*; Alexandre Rochwerger*[3]*; Xavier Muracciole*[5]*; Florence Duffaud*[4]*; Sébastien Salas*[4]
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SAFETY AND EFFICACY OF IMMUNE CHECKPOINT INHIBITORS IN PATIENTS WITH ANGIOSARCOMA

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Poster #270 3252942

OUTCOMES OF ELDERLY PATIENTS WITH SOFT TISSUE SARCOMA IN AN ASIAN TERTIARY CANCER CENTRE

Jiancheng Hong[1]*; Wei Lin Goh*[1]*; Grace Fangmin Tan*[5]*; Timothy Kwang Yong Tay*[2]*; Sathiyamoorthy Selvarajan*[2]*; Kesavan Sittampalam*[2]*; Chin-Ann J. Ong*[3]*; Grace Hwei Ching Tan*[3]*; Claramae Shulyn Chia*[3]*; Melissa Ching Ching Teo*[3]*; Richard Quek*[4]*; Eileen Yi Ling Poon*[1]*; Nagavalli Somasundaram*[1]*; Jason Yong Sheng Chan*[1]*; Mohamad Farid*[1]
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Poster #271 3253088

OVERALL SURVIVAL OF PATIENTS WITH SOFT TISSUE SARCOMAS NOT INFLUENCED BY SOCIO-ECONOMIC FACTORS WHEN PATIENTS TREATED AT A LARGE RESEARCH INSTITUTION

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Poster Presentations Listing

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IMMUNOTHERAPY AND HYPERPROGRESSION IN SOFT TISSUE SARCOMA: A TWO INSTITUTION EXPERIENCE

Anna Chalmers; *Shelly Hummert; Vaia Florou*
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Poster #273 3253322

DEMOGRAPHICS, DISEASE CHARACTERISTICS, TREATMENT PATTERNS, RESOURCE UTILIZATION, AND SURVIVAL OF PATIENTS WITH ADVANCED SOFT-TISSUE SARCOMA IN TAIWAN USING THE NATIONAL HEALTH INSURANCE DATABASE

Narayan Rajan[1]; *Diego Novick*[2]; *Wesley Furnback*[3]; *Jenny Chang*[4]; *Rebecca Cheng*[4]; *Chou Tse-Chih*[5]; *Chee-Jen Chang*[5]; *Chueh-Chuan Yen*[6]; *Bruce Wang*[3]
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Poster #274 3253673

THE OUTCOMES OF INTENSIVE COMBINED THERAPY OF ADULT PATIENTS WITH HIGH RISK STAGE III PRIMARY LOCALIZED SYNOVIAL SARCOMA

Katarzyna Kozak; Pawel Teterycz; Hanna Kosela-Paterczyk; Tomasz Switaj; Iwona Lugowska; Tomasz Goryn; Wirginiusz Dziewirski; Tadeusz Morysinski; Slawomir Falkowski; ***Piotr Rutkowski, MD***
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Poster #275 3253904

REAL-WORLD OUTCOMES OF PATIENTS WITH LOCALLY ADVANCED OR METASTATIC EPITHELIOID SARCOMA

Mrinal M. Gounder[1]; *Priscilla Merriam*[2]; *Ravin Ratan*[3]; *Shreyaskumar Patel*[3]; *Rashmi Chugh*[4]; *Victor Villalobos*[5]; *Mark Thornton*[6]; *Brian A. Van Tine*[7]; *Amr Abdelhamid*[2]; *Preeti Joshi*[8]; *Jennifer Whalen*[8]; *Jay Yang*[8]; *Anand Rajarethinam*[8]; *Mei Sheng Duh*[9]; *Priyanka J. Bobbili*[9]; *Cristi L. Cavanaugh*[9]; *Lynn Huynh*[9]; *Todor Totev*[9]; *George D. Demetri*[10]
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Poster #276 3254053

PALLIATIVE RESECTION FOR RETROPERITONEAL SARCOMA: EVALUATION OF POSTOPERATIVE SYMPTOMS AND SURVIVAL

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Poster #277 3254467

CLINICAL PRESENTATION, NATURAL HISTORY, THERAPEUTIC APPROACH AND TREATMENT OUTCOME IN PATIENTS WITH SOLITARY FIBROUS TUMOR

Patrick Schöffski[6]; *Iris Timmermans*[6]; *Daphne Hompes*[2]; *Marguerite Stas*[2]; *Veerle Boecxstaens*[2]; *Paul De Leyn*[4]; *Willy Coosemans*[7]; *Dirk Van Raemdonck*[7]; *Esther Hauben*[5]; *Raf Sciot*[3]; *Paul M. Clement*[1]; *Oliver Bechter*[6]; *Benoit Beuselinck*[6]; *Feng J. Woei-A-Jin*[6]; *Herlinde Dumez*[6]; *Tim Wessels*[6]
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Poster #278 3251890

NEOADJUVANT RADIATION AND DUAL CHECK POINT BLOCKADE IN RESECTABLE SOFT TISSUE SARCOMA: INITIAL OUTCOMES IN FIRST 5 PATIENTS ON STUDY

Adrienne Victor, MD[1]; *Louis Constine*[3]; *Susan McDowell*[2]; *Peter Prieto*[4]; *Deepak Sahasrabudhe*[1]
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Poster #279 3254560

CLINICAL OUTCOMES OF SOLITARY FIBROUS TUMOR: A SINGLE INSTITUTION EXPERIENCE OF 54 CASES

Yongjune Lee; *Jeong Eun Kim; Jin-hee Ahn*
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Poster #280 3254837

POTENTIAL PREDICTORS OF TUMOR RESPONSE TO NEOADJUVANT SYSTEMIC THERAPY IN PATIENTS WITH RETROPERITONEAL SARCOMA – A MULTI-INSTITUTIONAL TARPSWG STUDY

William W. Tseng, MD[1]; *Francesco Barretta*[2]; *Lorenzo Conti*[3]; *Markus Albertsmeier*[4]; *Martin Angele*[4]; *Chan Raut*[5]; *Mark Fairweather*[5]; *Antonino De Paoli*[6]; *Frederico Navarria*[6]; *Piotr Rutkowski*[7]; *Jacek Skoczylas*[7]; *Alessandro Gronchi*[3]
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Poster #281 3254980

AN EVALUATION OF A MULTI-DISCIPLINARY PRECEPTORSHIP (MDTP) FOR ONCOLOGY TRAINEES IN NATIONAL CANCER CENTRE SINGAPORE (NCCS)

Wei Lin Goh[1]; *Jiancheng Hong*[1]; *Nagavalli Somasundaram*[1]; *Jason Yong Sheng Chan*[1]; *Mohamad Farid*[1]; *Tom Wei-Wu Chen*[4]; *Herbert H. Loong*[5]; *Richard Quek*[2]; *Eileen Yi Ling Poon*[1]; ***Gracieux Y. Fernando***[3]
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Poster #282 3254984

COMORBIDITIES IN CASES WITH SOFT TISSUE SARCOMA-IMPACT ON THE COMPLETION OF STANDARD THERAPY AND ONCOLOGICAL OUTCOME

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Poster #283 3255122

LONG-TERM OUTCOMES EFFICACY OF MULTIDISCIPLINARY TREATMENT OF EPITHELIOID SARCOMA

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Poster #284 3255194

EVALUATION OF LATERAL EXTENT OF THE TUMOR INFILTRATION AREA AROUND SUBCUTANEOUS MYXOFIBROSARCOMA BY ULTRASONOGRAPHY

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Poster #285 3255214

DERMATOFIBROSARCOMA PROTUBERANS - A UNICENTRIC RETROSPECTIVE ANALYSIS OF A 10-YEAR PERIOD AT A TERTIARY TEACHING HOSPITAL

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Poster #286 3255873

FIRST INTERIM RESULTS FROM A GERMAN RETROSPECTIVE STUDY OF SARCOMA PATIENTS TREATED WITH TRABECTEDIN (RETRASARC)

Bernd Kasper, MD, PhD[2]*; Peter Reichardt*[3]*; Stephan Richter*[4]*; Anne Floercken*[5]*; Christoph K.W Deinzer*[6]*; Gerlinde Egerer*[7]*; Philipp Ivanyi*[8]*; Armin Tuchscherer*[9]*; Torsten Kessler*[10]*; Markus Schuler*[11]*; Christian A. Schmidt*[12]*; Jeannette Bahr*[12]*; Till Ittermann*[13]*; Adrian Richter*[13]*; Daniel Pink*[1]
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DETECTION OF APO10 AND TKTL1 FOR FOLLOW AND POST TREATMENT SCREENING IN SARCOMA PATIENTS

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Poster #288 3258032

CHEMOTHERAPY IN ADVANCED MALIGNANT PHYLLODES TUMOR (PT) OF THE BREAST: A MULTI-INSTITUTIONAL EUROPEAN RETROSPECTIVE CASE-SERIES ANALYSIS

Elena Palassini[1]*; Olivier Mir*[2]*; Giovanni Grignani*[6]*; Bruno Vincenzi*[3]*; Hans Gelderblom*[4]*; Ana Sebio Garcia*[5]*; Giacomo G. Baldi*[1]*; Antonella Brunello*[7]*; Giovanni Cardellino*[8]*; Andrea Marrari*[9]*; Gaetano Apice*[10]*; Giuseppe Badalamenti*[11]*; Javier Martin-Broto*[12]*; Virginia Ferraresi*[13]*; Paola Poletti*[14]*; Anita Rimanti*[15]*; Salvatore Turano*[16]*; Ithar Gataa*[2]*; Paola Collini*[17]*; Angelo Paolo Dei Tos*[18]*; Massimiliano Gennaro*[19]*; Salvatore Provenzano*[1]*; Axel Le Cesne*[2]*; Paolo Casali*[1]

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Poster #289 3231289

GENERATING SOFT TISSUE SARCOMA PATIENT-DERIVED XENOGRAFT (PDX) MODELS FROM CORE-NEEDLE BIOPSY: A PROSPECTIVE CLINICAL TRIAL

Danielle S. Graham[1]*; Mark A. Eckardt*[2]*; Bianca Carapia*[9]*; Jonathan Nakashima*[3]*; Benjamin D. Levine*[4]*; Scott Nelson*[5]*; Arun Singh*[6]*; Nicholas M. Bernthal*[7]*; Fritz C. Eilber*[8]

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Poster #290 3240354

ESTABLISHMENT OF A NOVEL HUMAN CIC-DUX4 SARCOMA CELL LINE, KITRA-SRS, WITH AUTOCRINE IGF-1R ACTIVATION AND METASTATIC POTENTIAL TO THE LUNGS

Sho Nakai[3]*; Shutaro Yamada*[1]*; Hidetatsu Outani*[3]*; Takaaki Nakai*[2]*; Naohiro Yasuda*[3]*; Hirokazu Mae*[3]*; **Yoshinori Imura***[4]*; Toru Wakamatsu*[4]*; Hironari Tamiya*[4]*; Takaaki Tanaka*[4]*; Kenichiro Hamada*[3]*; Akira Myoui*[3]*; Nobuhito Araki*[5]*; Takafumi Ueda*[6]*; Hideki Yoshikawa*[3]*; Satoshi Takenaka*[3]*; Norifumi Naka*[4]

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Poster #291 3241614

CONTINUOUS INFUSIONAL IFOSFAMIDE FOR MANAGEMENT OF SOFT-TISSUE AND BONE SARCOMA: A SINGLE CENTRE RETROSPECTIVE COHORT ANALYSIS

Thomas Carter, MBChB, PhD*; Marina Milic; Joanna McDerra; Vasilios Karavasilis; Maria Michelagnoli; Rachael Windsor; Beatrice Seddon; Jeremy Whelan; Palma Dileo; Sandra J. Strauss*

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INFLAMMATORY TYPE UNDIFFERENTIATED PLEOMORPHIC SARCOMA TREATED WITH DOXORUBICIN, IFOSFAMIDE AND PREDNISOLONE. REPORT OF TWO CASES

Shigeki Kakunaga, MD, PhD; *Ikuo Kudawara; Takafumi Ueda*
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Poster #293 3248538

BCOR SARCOMAS: A CASE SERIES WITH A NEWBCOR/CCNB3 FUSION GENE VARIANT

Anastasios Kyriazoglou[1]; *Louisa Mahaira*[2]; *Alexandra Papakosta*[2]; *Flora Zagouri*[1]; *Michalis Liontos*[1]; *Dimitra Michali*[2]; *Natalia Tourkantoni*[3]; *Amalia Patereli*[4]; *Kaliopi Stefanaki*[4]; *Efthymios Dimitriadis*[2]; *Meletios Athanasios Dimopoulos*[1]; *Antonis Kattamis*[3]
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Poster #294 3252967

HEPATIC METASTASES FROM SOFT TISSUE SARCOMA

Masanori Okamoto, MD, PhD; *Masatake Matsuoka; Tamotsu Soma; Ryuta Arai; Hiroaki Hiraga*
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Poster #295 3253032

RETROSPECTIVE ANALYSIS OF ADJUVANT TREATMENT FOR LOCALIZED, OPERABLE UTERINE LEIOMYOSARCOMA

Jomjit Chantharasamee, MD[1]; *Karlton Wong*[1]; *Pasathorn Potivongsajarn*[2]; *Joshua Cohen*[3]; *Bartosz Chmielowski*[1]; *Sandra Brackert*[1]; *Anusha Kalbasi*[4]; *Neda Motamed*[2]; *Jianyu Rao*[2]; *Scott Nelson*[2]; *Arun Singh*[1]
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Poster #296 3253257

ASSOCIATIONS BETWEEN TREATMENT PATTERNS AND DISTANCE TO TREATING FACILITY AMONG PATIENTS WITH SOFT TISSUE SARCOMA OF THE EXTREMITY

Ambria S. Moten[1]; *Margaret von Mehren*[2]; *Sanjay Reddy*[2]; *Krisha Howell*[2]; *Elizabeth Handorf*[2]; ***Jeffrey Farma***[2]
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Poster #297 3253345

BRAIN METASTASIS FROM SARCOMA

Toshiyuki Takemori[1]; *Teruya Kawamoto*[2]; *Masayuki Morishita*[3]; *Ikuo Fujita*[3]; *Hitomi Hara*[2]; *Yohei Kawakami*[2]; *Shuichi Fujiwara*[2]; *Kazumichi Kitayama*[2]; *Shunsuke Yahiro*[2]; *Takuya Fujimoto*[3]; *Ryosuke Kuroda*[2]; *Toshihiro Akisue*[2]
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Poster #298 3253682

IDENTIFYING TUMOR SPECIFIC ANTIGENS IN SARCOMA PATIENTS WITH TUMOR REACTIVE T-CELLS: AN ANALYSIS OF MUTATIONS, NEOANTIGEN PEPTIDES AND EFFECTOR FUNCTIONS

Morten Nielsen[2]; Panagiotis Mantas[3]; Lars Rønn Olsen[4]; Inge Marie Svane[2]; ***Niels Junker, MD, PhD[1]***
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Poster #299 3253949

POPULATION PHARMACOKINETIC ANALYSIS FOR COMPARISON OF PEXIDARTINIB EXPOSURE IN ASIAN AND NON-ASIAN PATIENTS

Chia-Chi Lin[1]*; Jun Guo[2]; William D. Tap[3]; Andrew Wagner[4]; Silvia Stacchiotti[5]; Jih-Hsiang Lee[1]; Xiaoning Wang[6]; Jia Kang[6]; Hamim Zahir[7]; Shun-ichi Sasaki[8]; Ophelia Yin[7]*
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Poster #300 3254451

REAL WORLD CLINICAL PROGNOSITC FACTORS AND EFFICACY OF UPFRONT WEEKLY PACLITAXEL FOR ADVANCED ANGIOSARCOMA PATIENTS

Changhee Park, MD*; Miso Kim; Chan-Young Ock; Bhumsuk Keam; Tae Min Kim; Dong-Wan Kim; Dae Seog Heo*
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Poster #301 3242595

VALUE OF A COMMUNITY-BASED MULTIDISCIPLINARY SARCOMA CASE CONFERENCE IN AN INTEGRATED HEALTHCARE SYSTEM

Tiffany Seto, MD[4]*; Jeanette Yu[2]; Manpreet Sidhu[3]; Danny Sam[4]; Minggui Pan[1]*
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Poster #302 3245232

PROGNOSIS IN RECURRENT/METASTATIC SOFT TISSUE SARCOMA PATIENTS WI RETROPERITONEAL/INTRA-ABDOMINAL ORIGIN RECEIVING SYSTEMIC CHEMOTHERAPIES COMPARED TO THOSE WITH EXTREMITIES/TRUNK ORIGIN

Kenji Nakano[1]*; Yuki Funauchi[2]; Keiko Hayakawa[2]; Taisuke Tanizawa[2]; Keisuke Ae[2]; Seiichi Matsumoto[2]; Shunji Takahashi[1]*
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ESTABLISHMENT OF AN ACADEMIC TISSUE MICROARRAY PLATFORM AS AN EFFICIENT TOOL FOR SOFT TISSUE SARCOMA RESEARCH

Che-Jui Lee[1]; *Tom Van Cann*[2]; *Agnieszka Wozniak*[1]; *Jasmien Wellens*[1]; *Inti Zlobec*[3]; *Judith Bovee*[4]; *Christian Britschgi*[5]; *Raf Sciot*[6]; *Patrick Schöffski*[7]
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Poster #304 3253417

SURGICAL OUTCOMES IN ELDERLY PATIENTS OVER 80 YEARS OF AGE WITH SOFT TISSUE SARCOMAS

Kunihiro Ikuta, MD[1]; *Yoshihiro Nishida*[2]; *Eiji Kozawa*[3]; *Satoshi Tsukushi*[4]; *Hiroshi Urakawa*[1]; *Eisuke Arai*[1]; *Tomohisa Sakai*[1]; *Hiroshi Koike*[1]; *Naoki Ishiguro*[1]
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Poster #305 3254145

RAPID AND COMPLETE REMISSION OF CHEMOTHERAPY/TYROSINE KINASE INHIBITOR RESISTANT RELAPSED SPONTANEOUS AND RADIATION INDUCED ANGIOSARCOMA FOLLOWING TREATMENT WITH COMBINED ANTI-CTLA-4 AND ANTI-PD-1 THERAPY

Andrew L. Pecora[1]; *Melinda Weber*[1]; *Danielle Blair*[1]; *Eileen Beysel*[1]; *Themba Nyirenda*[2]; *Elli Gourna Paleoudis*[2]
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Poster #306 3254295

ADULT GENITOURINARY SARCOMA: CANCER INSTITUTE HOSPITAL OF JAPANESE FOUNDATION FOR CANCER RESEARCH EXPERIENCE

Tetsuya Urasaki[1]; *Kenji Nakano*[1]; *Junichi Tomomatsu*[1]; *Kyoko Yamashita*[3]; *Yutaka Takazawa*[3]; *Yoshinobu Komai*[2]; *Shinya Yamamoto*[2]; *Takeshi Yuasa*[2]; *Junji Yonese*[2]; *Shunji Takahashi*[1]
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Poster #307 3252932

ANALYSIS OF DEDIFFERENTIATED LIPOSARCOMA ARISING FROM THE EXTREMITIES AND SURFACE OF THE TRUNK

Tetsuro Yamagishi[1]; *Hiroshi Hatano*[1]; *Hiroyuki Kawashima*[2]; *Akira Ogose*[3]; *Takashi Ariizumi*[2]; *Naoki Oike*[2]
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Poster #308 3255188

SITES OF DISTANT METASTASES AND FACTORS AFFECTING OVERALL SURVIVAL: A STUDY OF 159 PATIENTS WITH METASTATIC LIPOSARCOMA

Nicholas Shannon; *Deanna Ng*
http://www.nccs.com.sg/, Singapore, Singapore

Poster #309 3212091

MOLECULAR PROFILE IN SOFT TISSUE SARCOMAS (STS): USEFULNESS FOR SPECIFIC DIAGNOSIS OF PLEOMORPHIC SARCOMA?

Tomás J. Soulé; Andres Rodriguez; ***Martin Angel****; Matias Chacon*
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Poster #310 3230196

EARLY BRAIN-ONLY METASTASES AFTER COMPLETE RESPONSE TO NEOADJUVANT THERAPY FOR HIGH-RISK LOCALIZED PLEOMORPHIC SARCOMA

Benjamin Powers, MD*[1]; Vickie Massey[2]; Howard Rosenthal[3]; Elizabeth Friedman[4]; Darren Lovick[5]*
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Poster #311 3240092

CLINICAL STUDY OF SOFT TISSUE SARCOMA WITH ANTECEDENT PRIMARY MALIGNANCIES

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Poster #312 3230600

PHASE II STUDY OF NEOADJUVANT CHECKPOINT BLOCKADE IN PATIENTS WITH SURGICALLY RESECTED UNDIFFERENTIATED PLEOMORPHIC SARCOMA AND DEDIFFERENTIATED LIPOSARCOMA-PRELIMINARY SAFETY DATA

Christina L. Roland, MD, MS*[1]; Emily Z. Keung[1]; Alexander Lazar[2]; Wei-Lien Wang[8]; Janice Cormier[1]; Ashleigh Guadagnolo[3]; Andrew J. Bishop[4]; Bilal Mujtaba[9]; Heather Lin[5]; Keila Torres[1]; Kelly Hunt[1]; Barry Feig[1]; Justin Bird[2]; Valerae Lewis[6]; Shreyaskumar Patel[7]; Jennifer Wargo[1]; Neeta Somaiah[7]*
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Poster #313 3256138

BONE CEMENT IMPLANTATION SYNDROME IN BONE TUMOR SURGERIES: INCIDENCE, RISK FACTOR, AND CLINICAL EXPERIENCE

Tsung-Han Yang*[1]; Tzu-Hao Tseng[2]; Chih-Peng Lin[2]; Rong-Sen Yang[2]*
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Poster #314 3256521

LONG TERM OUTCOMES AFTER SURGICAL MANAGMENT OF DERMATOFIBROSARCOMA PROTUBERANS: A SINGLE INSTITUTION EXPERIENCE

Erin Strong[1]; Justin Fazio[4]; Austin Livingston[1]; Julia Kasprzak[4]; Melanie Clark[4]; William Dzwierzynski[5]; John LoGiudice[5]; Meena Bedi[3]; John Charlson[6]; Kara Walton[4]; David King[2]; Donald Hakbath[2]; Michael Stadler[7]; Monica Shukla[3]; John C. Neilson[2]; ***Callisia N. Clarke, MD, MS****[1]*
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Poster Presentations Listing

Poster #315 3256560
REVISION RATES FOR MEGAPROSTHESES: REVIEW OF LITERATURE AND META-ANALYSIS
Jean-Camille Mattei, MD, PhD; *Arnaud Felden; Philippe Anract; David Biau*
AP-HM, Aix-Marseille University, Marseille, France

Poster #316 3256707
DISTRACTION OSTEOGENSIS SPECIFIC SURGICAL COMPLICATIONS IN RECONSTRUCTION OF OSSEOUS TUMORS
Daniel E. Prince, MD, MPH; *Eugenia Schwarzkopf; Molly Klima*
Orthopedic Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Poster #317 3223323
THE IMPACT OF SURVEILLANCE INTERVAL FOLLOWING RESECTION OF PRIMARY WEL DIFFERENTIATED LIPOSARCOMA OF THE RETROPERITONEUM
Emily Keung; *Nikita Rajkot; Janice Cormier; Neeta Somaiah; Keila Torres; Kelly Hunt; Barry Feig; Naruhiko Ikoma; Christina L. Roland*
MD Anderson, Houston, TX, USA

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CAN THE KATAGIRI SCORING SYSTEM PREDICT SURVIVAL FOR PATIENTS WITH METASTATIC BONE DISEASE TREATED SURGICALLY?
Hiten A. Doshi[1]; Elif Ugur[1]; Nicole L. Levine[1]; Janet Tingling[2]; Bang Hoang[2]; ***David Geller[2]***; *Rui Yang[2]*
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CAN WE PREDICT RECONSTRUCTIVE SURGERY FAILURE IN SARCOMA PATIENTS?
Christie G. Mellor[2]; *Daniel Saleh[1]; Kenneth Rankin[1]; T. Beckingsale; M. Ghosh; D. Lee; M. Ragbir*
[1]Plastic and Reconstructive Surgery, The Newcastle Upon Tyne Hospitals, Newcastle upon Tyne, United Kingdom; [2]Medical School, Newcastle University Medical School, Newcastle upon Tyne, United Kingdom

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INTRAOPERATIVE ANGIOGRAPHY FOR PREDICTING WOUND COMPLICATION IN SOFT TISSUE SARCOMA OF THE EXTREMITIES: A PILOT STUDY
Alexander L. Lazarides, MD; *Eliana Saltzman; Julia Visgauss; Suhail Mithani; William Eward; Brian Brigman*
Department of Orthopaedic Surgery, Duke University Medical Center, Durham, NC, USA

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RECONSTRUCTION AFTER SOFT TISSUE SARCOMA OF THE LIMB USING MUSCLE SPARIN LATISSIMUS DORSI
Audrey Michot; *Raphaël Blaquière; Eberhard Stoeckle*
Oncological Surgery, Institut Bergonie, Bordeaux, France

Poster #322 3255197
ULTRASONOGRAPHY-GUIDED TUMOR EXCISION FOR IMPALPABLE AND ILL-DEFINED MALIGNANT SOFT TISSUE TUMOR
Akihiko Takeuchi, MD, PhD; *Norio Yamamoto; Katsuhiro Hayashi; Shinji Miwa; Kentaro Igarashi; Yuta Taniguchi; Sei Morinaga; Yoshihiro Araki; Hiroyuki Tsuchiya*
Orthopaedic Surgery, Kanazawa University Graduate School of Medical Sciences, Kanazawa, Japan

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Poster #323 3255858

IMMEDIATE, ALL INTERNAL DISTRACTION OSTEOGENESIS AND BONE TRANSPORT AFTER TUMOR RESECTION

Nadine L. Williams; *Alex Mierke; Omar Ramos; Brendon Bauer; Stephen Morris; Lee M. Zuckerman*
Orthopaedic Surgery, Loma Linda University Medical Center, Loma Linda, CA, USA

Poster #324 3255974

MID- TO LONG-TERM CLINICAL OUTCOMES OF HEMICORTICAL RESECTION AND RECONSTRUCTION USING FROZEN AUTOGRAFTS IN OSTEOSARCOMA PATIENTS

Norio Yamamoto, MD, PhD; *Katsuhiro Hayashi; Akihiko Takeuchi; Shinji Miwa; Kentaro Igarashi; Yuta Taniguchi; Hirotaka Yonezawa; Yoshihiro Araki; Sei Morinaga; Hiroyuki Tsuchiya*
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Poster #325 3256384

HYPERTHERMIC ISOLATED LIMB PERFUSION (HILP) IN EXTREMITY SOFT-TISSUE SARCOMA (ESTS): SHIFTING FROM PALLIATION TO THE NEO-ADJUVANT SETTING – BUT NOW OUTDATED? A MONOCENTRIC 18 YEAR EXPERIENCE

Eberhard Stoeckle; *Audrey Michot; Maud Toulmonde; Raoul Perret; Paul Sargos; Antoine Italiano*
Institut Bergonié, Bordeaux , France

Poster #326 3256704

DOUBLE LEVEL BONE TRANSPORT FOR SARCOMA RECONSTRUCTION

Daniel E. Prince, MD, MPH; *Eugenia Schwarzkopf; Molly Klima*
Orthopedic Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Poster #327 3229449

DID THE PROPORTION OF SOFT TISSUE SARCOMAS PRESENTING AS UNPLANNED EXCISIONS INCREASE DURING THE GREAT RECESSION?

Duncan Ramsey; ***Kenneth R. Gundle, MD***; *James Hayden; Yee-Cheen Doung*
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Poster #328 3244000

HARLEQUIN SYNDROME FOLLOWING MICROWAVE ABLATION THERAPY IN A 20-MONTH-OLD WITH PARASPINAL MASS

Caleb Oh; *Anna L. Tamulonis; Paul Kent*
Hematology/Oncology, Rush Hospital, Chicago, IL, USA

Poster #329 3253130

OUTCOME OF SURGICALLY TREATED BONE METASTASES OF EXTREMITIES FROM RENAL CELL CARCINOMA

Hitomi Hara[1]*; Yoshitada Sakai*[2]*; Teruya Kawamoto*[1]*; Yohei Kawakami*[1]*; Shuichi Fujiwara*[1]*; Kazumichi Kitayama*[1]*; Shunsuke Yahiro*[1]*; Ryosuke Kuroda*[1]*; Toshihiro Akisue*[3]
[1]*Orthopaedic Surgery, Kobe University Graduate School of Medicine, Kobe, Japan;* [2]*Rehabilitation Medicine, Kobe University Graduate School of Medicine, Kobe, Japan;* [3]*Rehabilitation Science, Kobe University Graduate School of Health Sciences, Kobe, Japan*

Poster #330 3253972

IS NEOADJUVANT CHEMOTHERAPY BENEFICIAL IN CARDIAC SARCOMA

Robert J. Cusimano, MD
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REAMED VERSUS UNREAMED INTRAMEDULLARY NAILING FOR THE TREATMENT OF IMPENDING AND PATHOLOGICAL HUMERAL SHAFT FRACTURES: A RETROSPECTIVE COMPARATIVE STUDY

Manaf H. Younis, MD, MPH; *Spencer Barnhill; Sheila Conway; Juan Pretell-Mazzini*
Orthopedic Oncology, University of Miami, Miami, FL, USA

Poster #332 3255777

OUTCOME AFTER BIOLOGICAL RECONSTRUCTION FOLLOWING INTERCALARY RESECTION OF MALIGNANT BONE TUMORS

Manish Pruthi, MS, DNB[1]; *Jagandeep Singh Virk*[1]; *Gauri Kapoor*[2]; *Rajan Arora*[3]
[1]*Orthopaedics, Rajiv Gandhi Cancer Institute & Research Center, Delhi, Delhi, India;*
[2]*Pediatric Oncology, Rajiv Gandhi Cancer Institute & Research Center, Delhi, Dellhi, India;*
[3]*Plastic Surgery, Rajiv Gandhi Cancer Institute & Research Center, Delhi, India*

Poster #333 3256553

POST-RADIATION PATHOLOGIC FEMUR FRACTURES FOLLOWING RESECTION OF SOFT TISSUE SARCOMAS: IS ENDOPROSTHETIC RECONSTRUCTION A GOOD OPTION?

Ibrahim S. Alshaygy; *Georges Basile; Jean-Camille Mattei; Anthony Griffin; Peter Ferguson; Jay Wunder*
Orthopaedic Department, Mount Sinai Hospital, Toronto, ON, Canada

Poster #334 3256555

LONG TERM OUTCOMES OF VASCULAR RECONSTRUCTIONS IN SARCOMA SURGERY. WHAT TO EXPECT FROM VEIN RECONSTRUCTION?

Jean-Camille Mattei, MD, PhD; *Julia Visgauss; Curtis Woodford; Thomas Lindsay; Georges Basile; Anthony Griffin; Jay Wunder; Peter Ferguson*
AP-HM, Aix-Marseille University, Marseille, France

Poster #335 3214469

SANDWICH ISOLATION SURGERY PREVENTS LOCAL RECURRENCE IN PROGRESSIVE DESMOID TUMORS: A PILOT OBSERVATIONAL STUDY

Junqiang Yin; *Yiwei Fu; Changye Zou; Gang Huang; Jingnan Shen*
The First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, Guangdong, China

Poster #336 3255865

WHEN SHOULD LIMB SALVAGE SURGERY BE CONSIDERED DURING A MEDICAL MISSION?

Stephen Morris; Scott Nelson; ***Nadine L. Williams***; *Omar Ramos; Brendon Bauer; Alex Mierke; Lee M. Zuckerman*
Orthopaedic Surgery, Loma Linda University Medical Center, Loma Linda, CA, USA

Poster #337 3256401

CLINICAL STUDY TO EVALUATE SAFETY AND ACTIVITY OF AUTOLOGOUS T CELLS WITH ENHANCED NY-ESO-1-SPECIFIC T-CELL RECEPTOR (GSK3377794) IN HLA-A*02+ PREVIOUSLY-TREATED AND PREVIOUSLY UNTREATED PATIENTS WITH ADVANCED METASTATIC OR UNRESECTABLE SYNOVIAL SARCOMA AS PART OF A MASTER PROTOCOL DESIGN

Sandra P. D'Angelo, MD[1]*; Jean-Yves Blay*[2]*; Warren Chow*[3]*; George D. Demetri*[4]*; Fiona Thistlethwaite*[5]*; Michael J. Wagner*[6]*; David Loeb*[7]*; Steven Attia*[8]*; Albiruni Razak*[12]*; John Haanen*[9]*; Aisha N. Hasan*[13]*; Julia Billiard*[13]*; Laura Pearce*[13]*; Yuehui Wu*[13]*; Ran Ji*[13]*; Laura A. Johnson*[13]*; Chandra Srianth*[13]*; Aiman Shalabi*[13]*; Sandra J. Strauss*[10]*; Katherine Thornton*[4]*; Crystal Mackall*[14]*; William D. Tap*[1]*; Brian A. Van Tine*[11]

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Poster #338 3256432

EPIDEMIOLOGICAL STUDY IN A REFERENCE CENTER IN MEXICO FOR THE TREATMENT OF SARCOMA

Jorge L. Martínez Tlahuel, MsC[1]*; Jorge Alegria*[2]*; Alejandro Mohar*[2]*; Jaime de la Garza*[2]

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Poster #339 3224571

THE CLINICAL FEATURES OF GANGLIONEUROBLASTOMA IN ADULTS

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Poster #340 3241689

APPLICATIONS OF CARBON FIBER INTRAMEDULLARY NAILS IN ORTHOPAEDIC ONCOLOGY

Caleb Yeung, MD*; Nelson Merchan; Erik Newman; Joseph Schwab; Kevin Raskin; Santiago Lozano-Calderon*

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Poster #001 3241719

COMPARISON OF CACHECTIC AND NON-CACHECTIC SARCOMA PATIENTS REVEALS AN IMPORTANT ROLE OF NOTCH SIGNALING IN METASTASIS AND MYOGENESIS

Feiqi Lu[2]*; David Osei*[2]*; Jonathan Mandell*[1]*; Alejandro Morales*[1]*; Margaret L. Hankins*[1]*; Jared Crasto*[1]*; Ruichen Ma*[2]*; Vu Dinh*[2]*; Rebecca Watters*[1]*; Kurt R. Weiss*[1]

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Objective: Cancer cachexia is a wasting syndrome that affects up to 50% of cancer patients. It is defined as weight loss ≥5% over 6 months and characterized by muscle atrophy, fatigue, and anorexia that are refractory to nutritional supplementation. Sarcoma describes a diverse group of malignancies arising from the connective tissues and is often related to musculoskeletal impairment. Sarcoma patients are uniquely susceptible to cachexia given its origins in the musculoskeletal system, but little is known regarding the underlying mechanisms of sarcoma-associated cachexia (SAC). Our previous research suggests that sarcoma cells contribute to SAC via dysregulation of muscle stem cell homeostasis by abnormal Notch signaling. We hypothesized that 1) cachectic patient sarcoma samples would display upregulation of genes in the Notch signaling pathway compared with non-cachectic patient sarcoma samples and 2) that cachectic sarcoma patient samples would inhibit the differentiation of muscle-derived stem cells (MDSC), which is a potential mechanism for muscle atrophy.

Methods: After University of Pittsburgh IRB approval, sarcoma patient weights were collected from 6 months pre and post surgery. Linear regression was performed to evaluate weight loss. According to the definition of cachexia (weight loss over 6mo ≥ 5%), sarcoma samples were classified into either the cachexia group or the non-cachexia group. Twelve cachectic and ten non-cachectic patients were selected. The sarcoma samples were minced and enzymatically digested using a human tumor dissociation kit. Primary cell populations were cultured until cells reached 80-90% confluence. Cells were then harvested and cryopreserved. RT-qPCR was performed to evaluate the expressions of Notch pathway factors (*DLL1*, *JAG1*, *Notch1*, *Notch3*, *Hes1*) from primary tumors, tumor cell cultures, and muscle-derived stem cells (MDSCs). Data were normalized to the geometric mean of multiple internal control genes. Relative expression of mRNA was normalized to the non-cachectic group. The co-culture system was composed of MDSCs cultured in the lower chamber of a transwell plate and primary sarcoma cells in the upper chamber. After proliferation for 2 days and differentiation for 4 days, MDSCs were stained for f-MHC and DAPI (nuclear stain) to quantify fusion index and undergo RNA extraction. Data were analyzed using Mann-Whitney U test and presented as Mean ± SD. Statistical difference was defined by $p < 0.05$.

Results: There were significantly greater gene expression levels of *Notch1* and *Notch3* in fresh tumors from the cachexia group (Figure 1A). Gene expression levels of *Jagged1*, *Notch1* and *Notch3* were significantly increased in primary cultured cells from the cachexia group (Figure 1B). MDSCs co-cultured with primary sarcoma cells from both the cachexia and non-cachexia groups showed decreased fusion indices, increased Notch pathway gene expressions, and increased *Pax7* expressions (Figure 2). Interestingly, we also observed a statistically significant (p=0.0083) association of metastatic disease among the cachectic patients compared with the non-cachectic patients (Table 1).

Conclusion: Upregulation of the Notch signaling pathway is associated with SAC. Sarcoma cells from both cachectic and non-cachectic patients may elaborate factors and affect pathways that inhibit muscle differentiation independent of the Notch pathway. Further investigation is required to determine what these as yet undetermined factors might be, and if Notch inhibition is an effective strategy against SAC. Finally, the possible relationship between SAC and sarcoma metastasis must further be explored.

Table 1. Patient characteristics

	Cachexia (n=12)	Non-cachexia (n=10)	p-value
Age, median (range)	50.5 (14, 72)	61 (42, 78)	0.1741
Sex			
Male (%)	8 (67)	6 (60)	>0.9999
Female (%)	4 (33)	4 (40)	
Weight change% (Mean ± SD)	-13.22 ± 5.559	3.874 ± 6.677	<0.0001
Metastasis (%)	10 (83)	2 (20)	0.0083

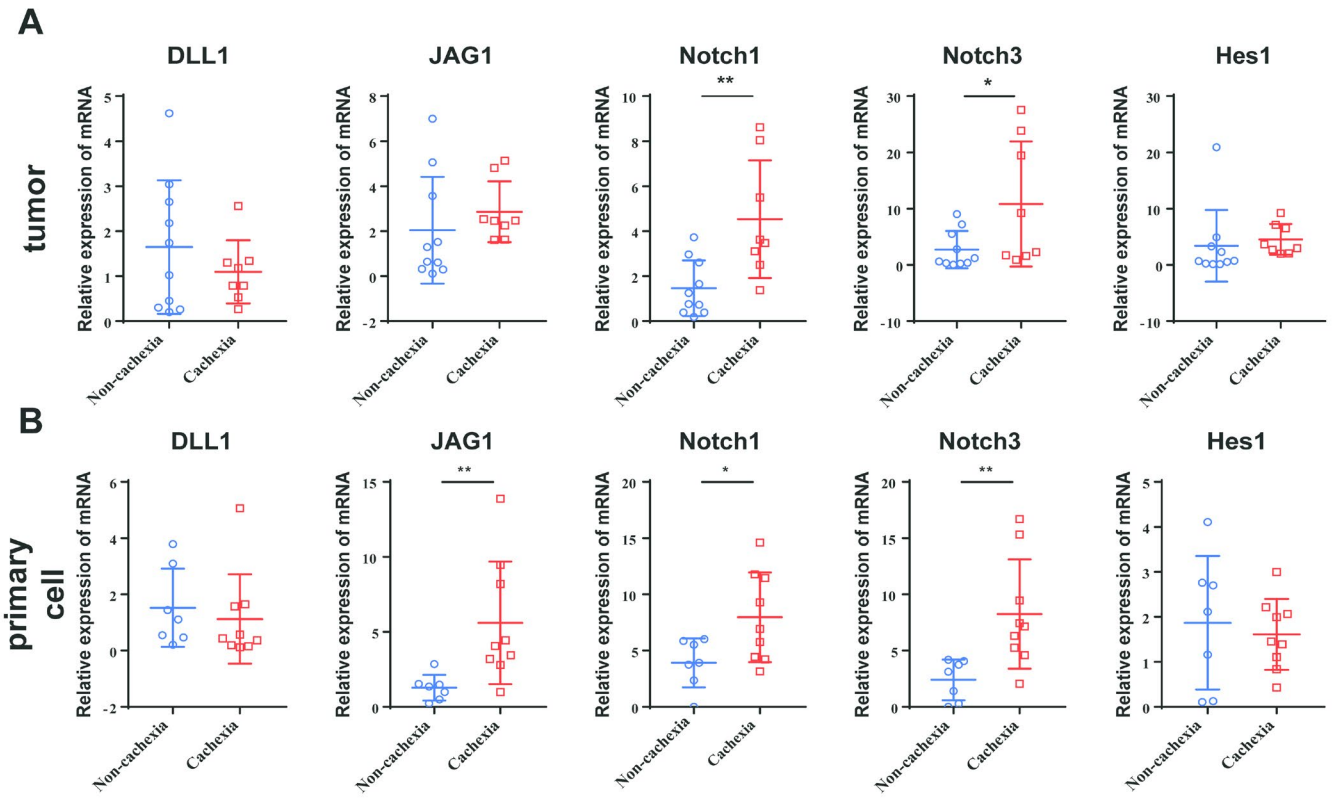

Figure 1. Notch signaling pathway was upregulated in the cachexia group. A) Gene expression levels of Notch1 and Notch3 were increased in the tumors from cachexia group. B) Increased JAG1, Notch1 and Notch3 were maintained in primary cell culture of cachectic tumors. Mann-Whitney test, $p<0.05$.

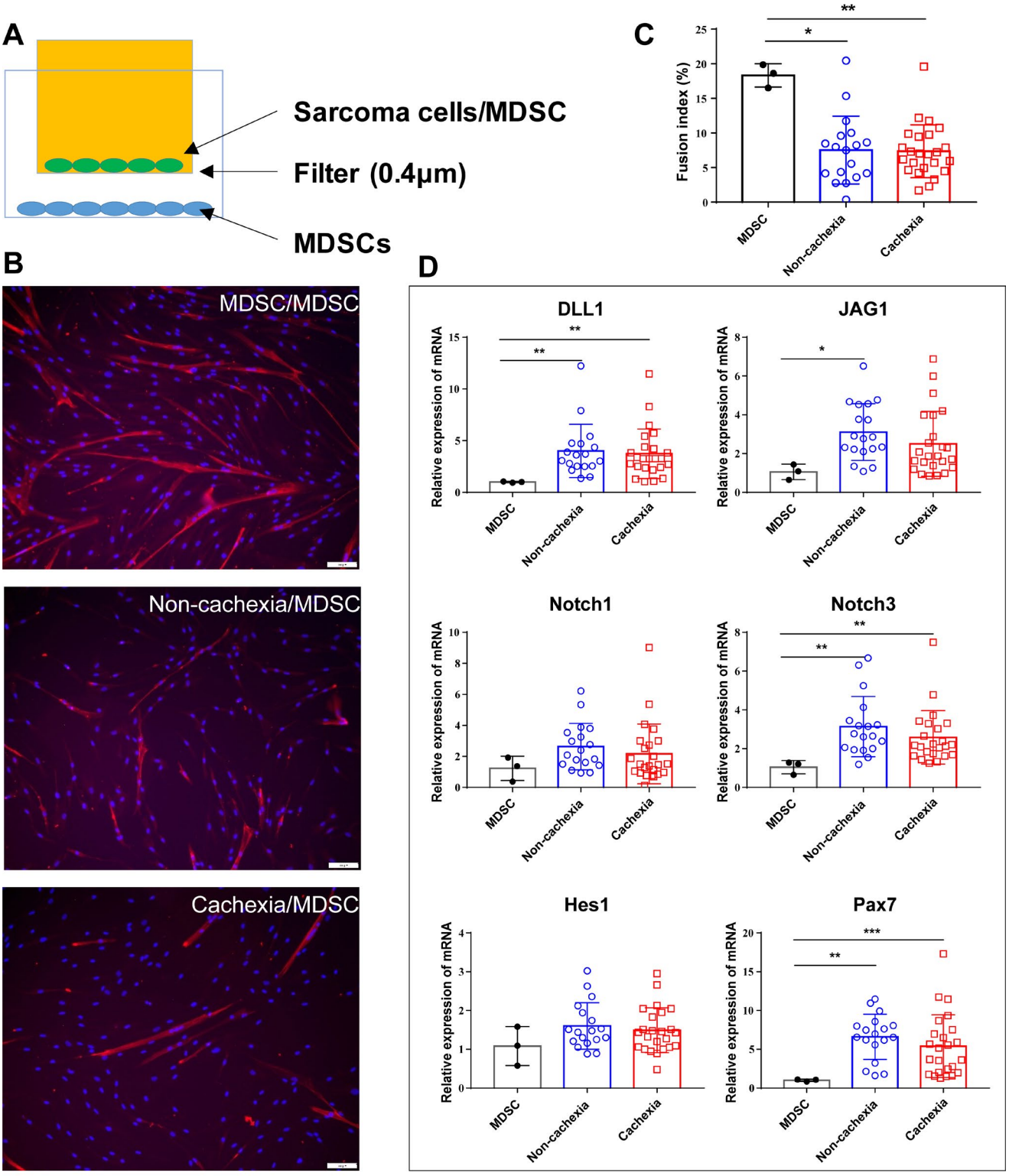

Figure 2. Cachectic and non-cachectic sarcoma primary cells inhibited muscle differentiation and upregulated Notch pathway and Pax7 in MDSCs. A) Schematic figure showing co-culture experimental design. MDSCs were co-cultured with cachectic, non-cachectic primary tumor cells or MDSCs (control group). B) Immunofluorescence images of MDSCs after co-culture (100x). C) MDSCs co-cultured with both cachectic and non-cachectic sarcoma primary cells showed decreased fusion index. D) Notch pathway and Pax7 were upregulated in MDSCs co-cultured with either cachexia (n=8) or non-cachexia (n=6) primary cells. All treatment groups were performed in triplicate.

Poster #002 3243870

METABOLIC REPROGRAMMING IN HIGH-GRADE SARCOMAS, REPURPOSING ANTI-CHOLESTEROL AGENTS AS A NOVEL THERAPEUTIC STRATEGY

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Objective: Soft tissue sarcomas (STS) are a diverse group of mesenchymal tumors with over 50 histologically distinct subtypes. Undifferentiated pleomorphic sarcoma (UPS), leiomyosarcoma (LMS) and liposarcoma (LPS), are three common types and comprise >50% of adult sarcoma. Current treatment includes chemotherapy, radiation and/or surgery, and survival rates remain largely unchanged in the last decade. Since the main patterns of failure are metastatic disease and multifocal local recurrence, development of more efficacious systemic therapy is essential to improve disease outcomes. To identify novel therapies for sarcoma that are effective and potentially less toxic, we screened patient derived cell lines with >3,300 compounds and identified that UPS cells were exquisitely sensitive to statins (simvastatin and pitavastatin). Statins inhibit the rate limiting enzyme in the mevalonate (MVA) pathway, HMGCR – critical for the production of cholesterol and other metabolites needed for post-translational modifications. Cancer cells can exploit this pathway through PI3K/mTOR signaling to enhance proliferation and survival. The use of statins as an anticancer agent has been tested in other solid tumors, however to date it has not been investigated in sarcoma. Thus, goals of our study are **to define the mechanism(s) responsible for statin sensitivity** in UPS and determine if LMS and/or LPS are also statin sensitive.

Methods: Hit validation with EC_{50} curves confirmed that both UPS and LMS, but not LPS, are sensitive to statins. To investigate the mechanism of action of statins in sarcoma cell lines, we performed immunoblots and qPCR. To analyze if simvastatin could be successfully combined with doxorubicin, the current standard of care, as a future therapeutic strategy, we performed a BLISS analysis, which demonstrated that these two agents are synergistic in vitro. To determine the best route of administration of simvastatin in vivo, we performed a pharmacokinetic study to ensure that simvastatin is bioavailable.

Results: To assess the activity of simvastatin in MVA pathway inhibition, the expression level of key components, such as HMGCR and INSIG1, were measured in UPS and LMS cell lines, which indicated an intact positive feedback response after statin treatment. To determine if dysregulation of the PI3K/mTOR pathway renders sarcoma cells statin sensitive, we assayed the activity of downstream effectors of PI3K/mTOR. In UPS, we found a decrease in phosphorylation of AKT and 4EBP1, indicating that simvastatin dysregulates PI3K/mTOR signaling. We are currently investigating if PI3K/mTOR signaling is similarly dysregulated in LMS cell lines to determine if this is a candidate mechanism of simvastatin sensitivity. Finally, as our laboratory has a panel of UPS and LMS xenografts, we are currently investigating if statin inhibition is an effective therapy in vivo and mechanistically dissecting the basis for tumor growth inhibition. During the pharmacokinetic study we treated mice for 5 days via oral gavage (n=5) or intraperitoneal injections (IP) (n=5), and found that simvastatin is present in the tumors treated by IP injections but not gavage. Thus, in our pre-clinical murine studies, we are administering simvastatin by IP injection alone and in combination with doxorubicin to assess efficacy and toxicity.

Conclusion: Taken together, we report the promising finding that primary UPS and LMS cells are highly sensitive to simvastatin. This work suggests that two common high-grade sarcomas rely on metabolic reprogramming to support the increased energy demand and proliferation through the PI3K/mTOR pathway. Simvastatin, a repurposed and well tolerated drug, is able to inhibit this process which may lead to treating sarcomas with this novel therapy. Future studies will focus on elucidating connections between major metabolic pathways and preclinical drug studies of UPS, LMS, and other sensitive sarcoma models.

Poster #003 3249741

DUAL INHIBITION OF DISTINCT METABOLIC FEATURES TARGETS OSTEOSARCOM STEM-LIKE CELLS BY PHYTOCHEMICAL PTEROSTILBENE AND C-MYC INHIBITORS

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Objective: Mitochondria are the places for the energy production of the cells, while reactive oxygen species (ROS) are also produced alongside of the ATP production. In recent years, it has been reported that cancer stem cells metabolize predominantly through oxidative phosphorylation (OXPHOS) rather than glycolysis in certain cancer cells. Targeting OXPHOS achieved by suppression of ATP synthesis through mitochondrial ATP synthase could be a potential therapeutic option against cancer stem cells. In the current study, we have identified the mitochondria metabolism as the potential therapeutic target in osteosarcoma (OS) stem cells, presenting the synergistic effects of combination of OXPHOS inhibition by pterostilebene (PTE) with c-Myc inhibitor, which target both OXPHOS-dominant cancer stem cells and glycolysis-dominant non-cancer stem cells as a 'two hit' or 'dual inhibition' of metabolic pathways, OXPHOS and glycolysis.

Methods: Using human OS cell lines of SaOS2, U2OS and MG63 cells, cell survival and the ability of sphere formation was assessed with or without PTE, and the expression of stem cell markers mRNA such as Oct3, NS, CD44 was examined by RT-PCR. Next, the activity of mitochondrial ATP synthase, mitochondrial respiration capacity of oxygen consumption rate, and the amount of ATP as well as ROS production were measured under the treatment of PTE. Furthermore, we examined the synergistic effect of PTE with cMyc transcription inhibitors of JQ1 or Honokiol (HNK). We then evaluated the role of PDZD8, which is associated with the tethering of endoplasmic reticulum (ER) and mitochondria, assessing cell viability, oxygen consumption rates and ROS generation by PTE treatment in combination with the knock-down of PDZD8 (PDZD8KD).

Results: PTE treatment on human OS cell lines reduced the viabilities of all cell lines in dose-dependent manner and expression of stem cell marker and the ability of sphere formation were also decrease in terms of sphere number and size. PTE reduced the activity of F0F1-ATP synthase; Complex V predominantly, and the mitochondrial oxygen consumption rates and synthetic amount of ATP were also decreased in spheroid condition. These results suggest that PTE possibly targets stem cell population which preferably relies on OXPHOS, suppressing ATP synthesis via F0F1-ATP synthase inhibition as well as increased ROS production in OS cells (Fig.1) and changes metabolic flax to glycolysis dependent feature. The dual inhibition of OXPHOS by PTE and c-Myc inhibition by HNK or JQ1 showed the synergistically inhibition of OS cell growth in a dose-dependent manner (Fig.2). PDZD8KD regenerated the decreased mitochondrial oxygen consumption rates by PTE and decreased cell viability through the increased ROS production suggesting that ER-mitochondria tethering by PDZD8 controls function of mitochondria and ROS homeostasis.

Conclusion: Prognosis of the patients with osteosarcoma has reached to plateau without any breakthroughs over the last quarter century, and nearly 30% of patients still have to face very severe poor prognosis, especially with metastatic disease. Current study suggests that modulation of metabolic flux by c-Myc and OXPHOS inhibitors showed a greater synergistic effect with 'two metabolic hit' or 'dual metabolic inhibition' of distinct metabolic features and it could be a novel therapeutic strategy against osteosarcoma, possibly targeting both stem-like cell population and general tumor cell population.

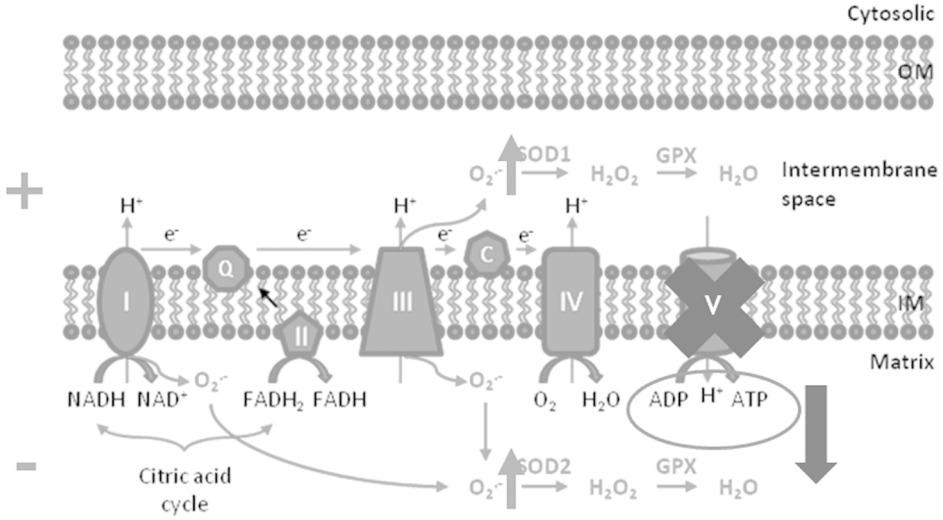

Fig.1. PTE inhibits mitochondrial complex V, reducing ATP production and generating ROS production, which changes metabolic flax to glycolysis dependent feature of osteosarcoma cells.

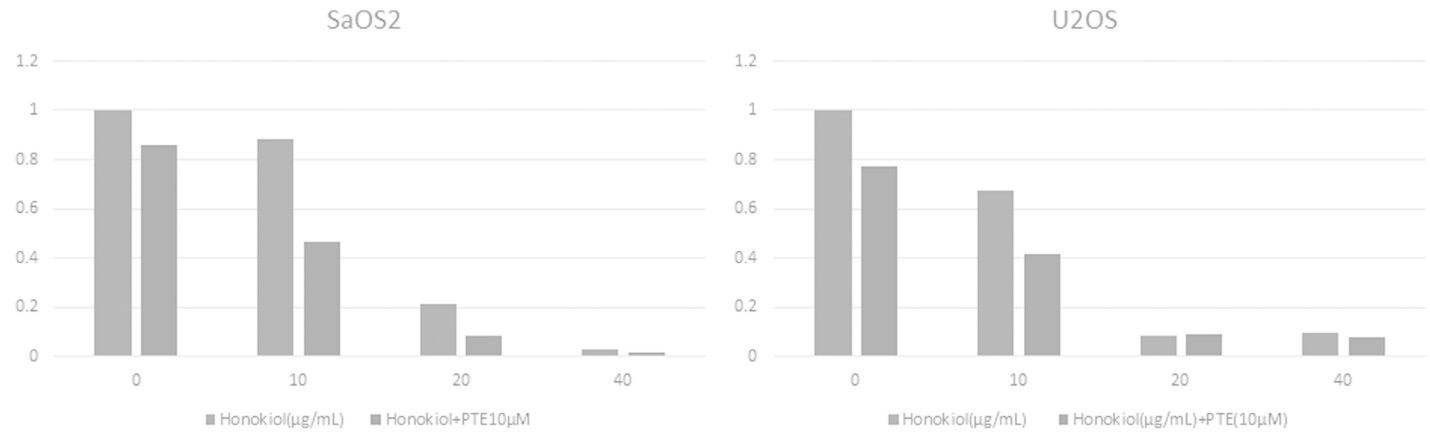

Fig.2. PTE potentiates the anticancer efficacy of Honokiol and other cMYC inhibitors.

Poster #004 3256372

IMPROVING ONCOLYTIC VIROTHERAPY USING VANADIUM-BASED COMPOUNDS IN SARCOMAS

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Objective: Immunotherapies like immune checkpoint inhibitiors and cancer vaccines have not yet translated into meaningful outcomes for sarcoma patients. Oncolytic virotherapy (OV) employs viruses with engineered oncotropism to selectively eradicate cancer cells and stimulate antitumor immunity. Despite promising results achieved with OVs, heterogeneity of response and resistance to monotherapies remains a clinical challenge. While OVs are immunotherapeutics in their own right, they can also synergize with small molecule « viral sensitizers » or checkpoint blockade to achieve increased efficacy. We reported that vanadium-based protein tyrosine phosphatase (PTP) inhibitors improve oncolysis as well as long-term antitumor immunity and survival when used in conjunction with oncolytic virus VSVD51 in various murine models of carcinoma. Thus, this project aims to evaluate the potential of vanadium compounds in combination with checkpoint inhibitors or oncolytic viruses to improve sarcoma immunotherapy and to determine the mechanism of action driving vanadate-mediated viral sensitization.

Methods: The vanadium, OV and immune checkpoint treatment regimens were tested in a murine rhabdomyosarcoma model. To identify PTPs and kinases involved in oncolysis and viral infection, two high-throughput screens were conducted using (1) a library consisting of 800 kinase inhibitors and (2) a library of small interfering RNAs targeting human PTPs. Primary hits were validated and tested in *ex vivo*-treated sarcoma tumors and normal tissues (i.e. brain, lung, spleen, muscle).

Results: The triple combination therapy of vanadium, OV and immune checkpoint inhibitor improved survival and lead to cures. We have found that kinase inhibitors targeting the EGFR pathway abrogate vanadate's viral sensitization suggesting that vanadium-based compounds rely on functional EGFR signaling to exert their pro-viral effects on cancer cells. Also, we discovered an unprecedented role for several PTPs in modulating oncolytic VSVD51 viral infection.

Conclusion: Overall, this project supports the translational potential of vanadium compounds paired with oncolytic virotherapy for the treatment of sarcomas. These discoveries also pave the way for innovative pharmaco-viral approaches and provide rationale in designing oncolytic viruses that selectively suppress host PTP to improve therapeutic efficacy.

Poster #005 3256542

INHIBITORY EFFECTS OF INDOMETHACIN ON HUMAN OSTEOSARCOMA TUMOR CELLS

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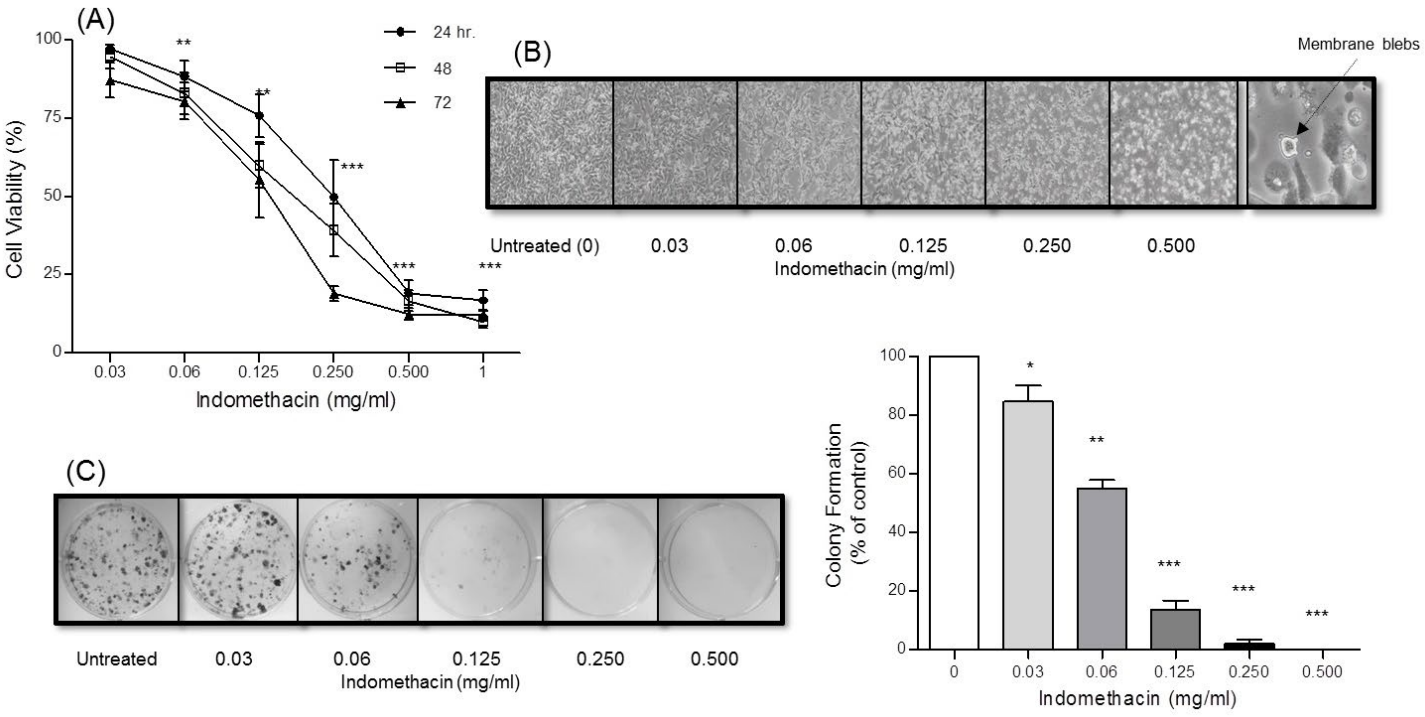
Objective: The purpose of this study was to assess whether a common nonsteroidal anti-inflammatory drugs (NSAIDs) such as indomethacin, a nonselective cyclooxygenase (COX) inhibitor, could induce apoptosis in human osteosarcoma (OS) cells and further to explore the possible underlying mechanisms.

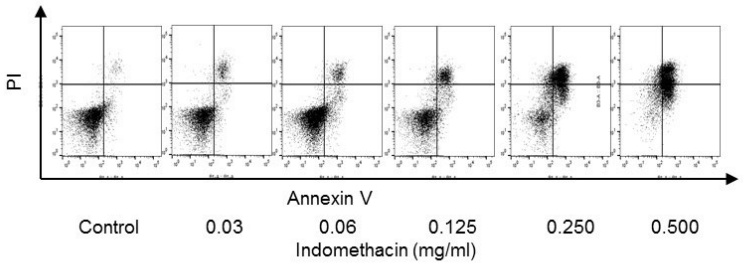
Methods: A human OS cell line (CRL-1547) was treated with various concentrations of indomethacin and compared to a control. Cell viability, cell morphology, apoptosis induction, cell cycle, surface expression of PD-L1 and the expression of apoptosis-related markers were examined by MTT assay, phase-contrast photomicrograph, flow cytometry, and western blot respectively.

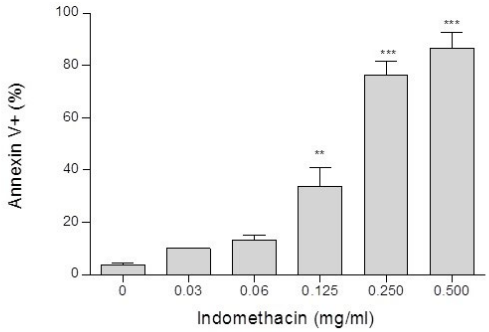
Results: Exposure to indomethacin significantly decreased viability and induced apoptosis in a dose-dependent manner in OS cells (Figure 1). Apoptosis was confirmed by morphological changes and percentage of Annexin V+ tumor cells (Figures 1 & 2). There was no cell cycle arrest in OS cells exposed to indomethacin. However, a dose-dependent increase in the sub-G1 fraction following the treatment was observed. In addition, indomethacin significantly down-regulated the expression of anti-apoptotic proteins such as Bcl-2, survivin, Mcl-1, pro-caspase-3, and PARP, and up-regulated the cleavage of both caspase-3 and PARP (Figure 3). Indomethacin did not down-regulate the expression of COX-2, which indicated that most likely the decreased cell viability and apoptosis induction was a COX- independent effect. The result also indicated that indomethacin could down-regulate the expression of PD-L1 on OS tumor cells.

Conclusion: These findings offer initial optimism that indomethacin can be used as a neoadjuvant or adjuvant treatment before and after tumor resection. Further in vivo studies are warranted.

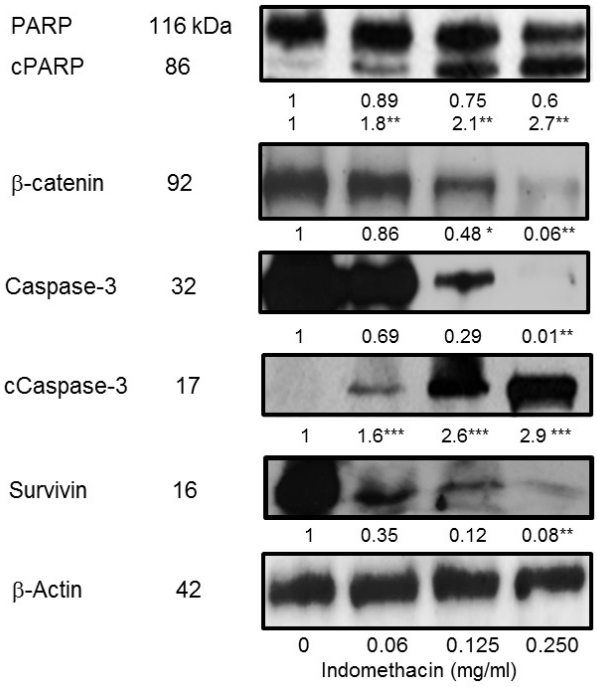


A) Indomethacin significantly decreased viability in a dose-dependent manner. B) Abnormal morphological changes characterized by cellular shrinkage, severe blebbing, turning round, undefined edges, floating and eventually death. C) Colony formation was decreased in both a time- and dose-dependent manner.





Quantitative analysis showed the total number of Annexin+ cells increased significantly with different doses of indomethacin. The total number of apoptotic cells increased from 7% to 48% and from 16% to 79% after exposure to indomethacin in a time- and dose-dependent manner.



Indomethacin significantly down-regulated the expression of anti-apoptotic proteins such as Bcl-2, survivin, Mcl-1, pro-caspase-3, and PARP, and up-regulated the cleavage of both caspase-3 and PARP

Poster #006 3243435

HUMAN BONE MARROW-DERIVED STEM CELLS INDUCE EPITHELILAL-MESENCHYMAL TRANSITION AND ENHANCE STEMNESS FEATURES IN LOW-INVASIVENESS LUNG CANCER CELLS

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Objective: The underlying mechanism(s) causing cancer metastasis remains a mystery despite decades of research. Carcinoma cells often undergo epithelial-mesenchymal transition (EMT) to acquire increased motility, so that they can escape from the primary tumor site. Recent studies have shown that bone marrow-derived mesenchymal stem cells (BM-MSCs) can be recruited into the tumor microenvironment and regulate cancer metastasis. However, BM-MSCs' influence on the primary tumor cells has not been well defined.

Methods: Mesenchymal stem cells (MSCs) were isolated from fresh human bone marrow in patients undergoing arthroplasty surgery. Conditioned medium (CM) was harvested from MSC culture after seventy-two hours. A549 lung cancer cells were functionally fractionated by transwell invasion assay. The cells that remained in situ were termed low-invasiveness cells, and then cultured in MSC-CM. The cytokines in this condition medium were screened by human cytokine antibody array. The activity of STAT3 signaling pathway was studied by western blotting and promoter reporter assay. The expression levels of EMT markers, stemness genes, and ABC drug transporter genes were measured by RT-PCR and promoter-luciferase reporter assay. Expression of the epithelial marker E-Cadherin was measured by promoter-luciferase reporter assay and western blotting. stemness-related phenotypic features, such as sphere-forming and migratory abilities, were studied with suspension culture and wound healing assay, respectively. A STAT3 mutant (STAT3-Y705F) was constructed through point-mutation at the STAT3 phosphorylation site Tyr705 in order to examine the effect of STAT3 blockade on low-invasiveness cells treated with MSC-CM.

Results: Human cytokine antibody array identified IL-6 in MSC-CM (fig.2A). After low-invasiveness cells were cultured in MSC-CM, phosphorylated STAT3 was detected on western blotting (fig.2B) and promoter reporter assay showed a 10-fold increase in STAT3 transcriptional activity (fig.2C). RT-PCR revealed that Twist1 gene had a 2.5-fold increase in expression after MSC-CM treatment (fig.2D), while reporter assay demonstrated that expression of E-Cadherin substantially decreased (fig.2E). Several stemness genes were upregulated 48 hours after MSC-CM treatment (CD133 1.8-fold; Oct4 1.4-fold; Nanog 1.2-fold) (fig.3A). Expression of some drug resistance genes were also increased (ABCA3 1.2-fold; ABCB1 1.3-fold; ABCC2 1.5-fold; ABCG1 1.8-fold) (fig.3A). The percentage of coverage on scratch wound healing assay at sixteen hours was 2.7-fold higher in the MSC-CM-treated group (control 15%; MSC-CM treatment 40%) (fig.3B). MSC-CM-treated group had better sphere-forming ability in suspension culture (fig.3C). When the STAT3-Y705F mutant of the low-invasiveness cells were treated with MSC-CM, Luciferase reporter assay confirmed minimal STAT3 transcription versus that of the STAT3 wild-type control (STAT3-Y705F mutant 2-fold; STAT3-WT 10-fold) (fig.4A). Meanwhile, the expression of Twist1, CD133, Nanog, ABCA3 and ABCG1 were down-regulated in the STAT3 mutant (Twist1 0.2-fold; CD133 0.5-fold; Nanog 0.8-fold; ABCA3 0.8-fold; ABCG1 0.6-fold) (fig.4B). Compared with the wild-type, the STAT3 mutant had less coverage on wound-healing assay (STAT3-Y705F 34%; STAT3-WT 45.5%) (fig.5A), indicating their worse migratory ability. The STAT3 mutants also formed less spheres per well in suspension culture (fig.5B).

Conclusion: Our results indicate that low-invasiveness lung cancer cells have enhanced IL-6-STAT3 signaling after MSC-CM treatment, with subsequent increase in the expression of EMT markers, stemness genes, and drug resistance genes. Phenotypically, the MSC-CM-treated low-invasiveness cancer cells showed heightened migratory and sphere-forming abilities. The above-mentioned effects were abolished after blockade of STAT3 signaling. Therefore, we propose that BM-MSCs may induce EMT and confer stemness properties to primary tumor cells, allowing them to become primed for metastasis.

Fig.1.

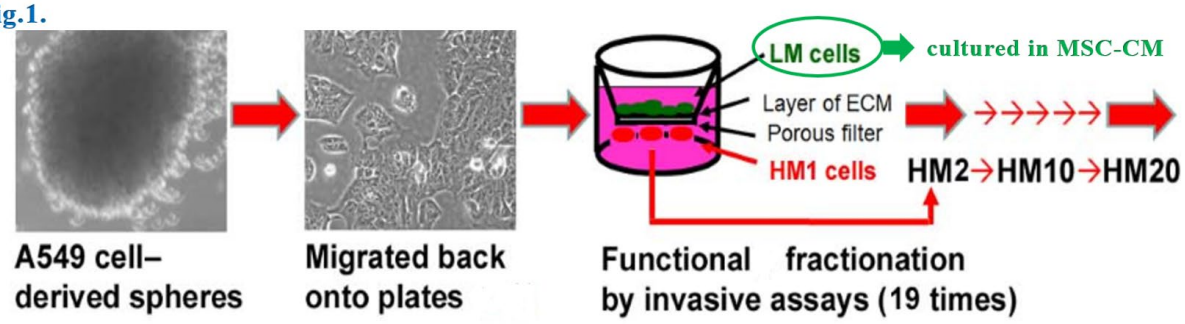


Fig.2

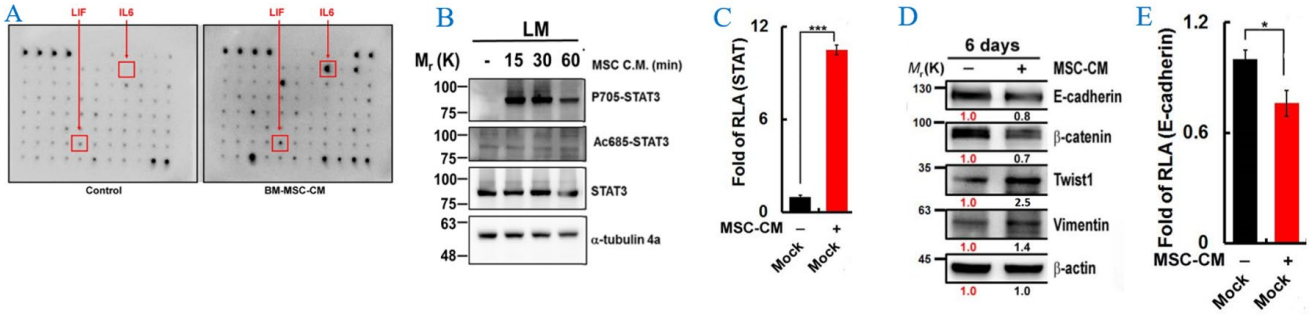


Fig.3

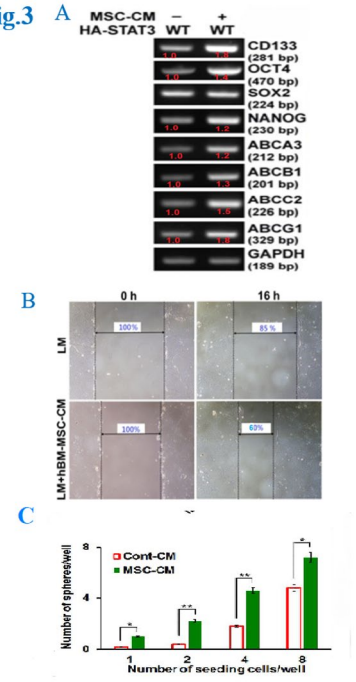
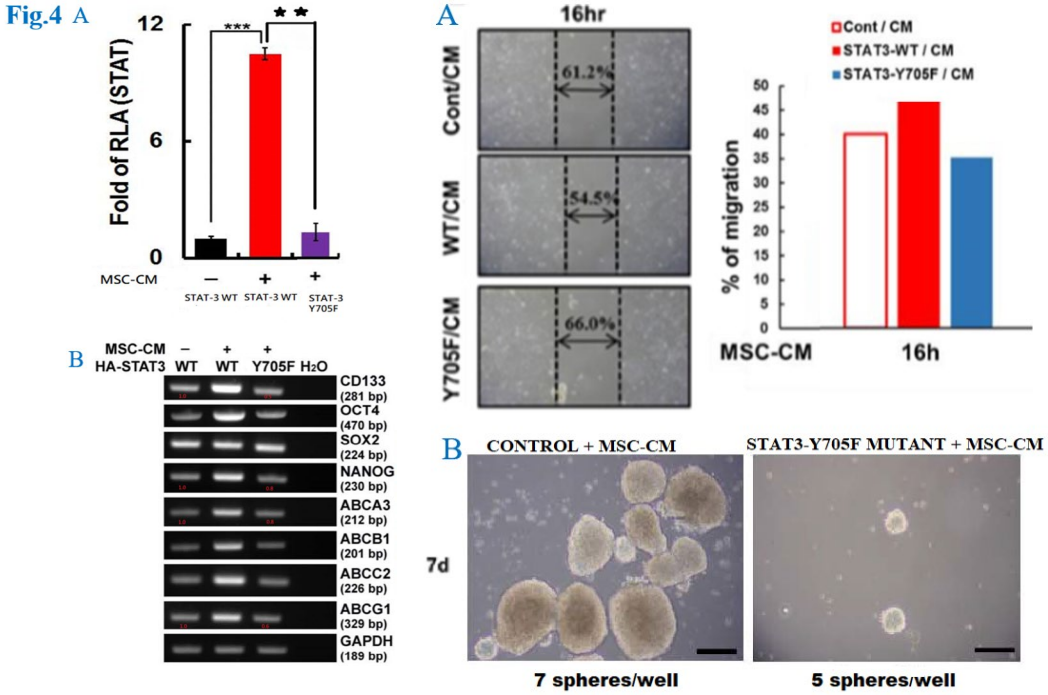


Fig.4



Poster #007 3220620

XANTHOHUMOL INDUCE APOPTOSIS THROUGH P38 MAPK SIGNALING PATHWAY IN HUMAN NASOPHARYNGEAL CANCER CELLS

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Objective: Nasopharyngeal carcinoma (NPC), arising from the squamous mucosal epithelium of the nasopharynx, is a unique malignant head and neck cancer, and it is endemic in a few areas including Southern China, Southeast Asia (Taiwan, Hong Kong, Singapore, and Malaysia), North Africa and the Arctic. With advances in radiation therapy (RT) and chemotherapy strategies, the survival rate of patients with NPC has improved, but the prognosis of patients with NPC remains poor. Therefore identification of mechanism of drug resistance involved in chemotherapeutic response is critical for predicting tumour response. Xanthohumol, derived from *Humulus lupulus*, has a wide range of beneficial effects, including anti-angiogenesis and anticancer properties.

Methods: The aim of the present study was to investigate the effect of xanthohumol in NPC cells and to understand the mechanism of its action.

Results: Our results revealed that the treatment of NPC-039 and NPC-BM cells with xanthohumol potently induce cell apoptosis, and which subsequently activated caspase-3, -8, and -9 and poly (ADP-ribose) polymerase. Moreover, xanthohumol induced apoptosis through the modulation of AKT, p38 mitogen-activated protein kinase, extracellular signal-regulated kinases 1 and 2, and jun N-terminal kinases 1 and 2 pathways.

Conclusion: In summary, our data show that xanthohumol induces apoptosis in human NPC cells and suggesting xanthohumol to be a promising candidate for NPC therapy.

Poster #008 3232396

OSTEONECROSIS OF JAW AFTER USE OF DENOSUMAB IN PATIENTS WITH GIANT CELL TUMOR OF BONE

Hiroshi Urakawa[3]*; Eisuke Arai*[1]*; Kunihiro Ikuta*[1]*; Tomohisa Sakai*[1]*; Hiroshi Koike*[1]*; Naoki Ishiguro*[1]*; Yoshihiro Nishida*[2]
[1]Orthopaedic Surgery, Nagoya University, Nagoya, Aichi, Japan; [2]Orthopaedic Surgery/ Rehabilitation, Nagoya University, Nagoya, Japan; [3]Orthopaedic Surgery/ Chemotherapy and Clinical Oncology, Nagoya University, Nagoya, Japan

Objective: The aim of this study is to investigate the incidence of osteonecrosis of the jaw (ONJ) after use of denosumab in patients with giant cell tumor of bone (GCTB).

Methods: We retrospectively reviewed 12 patients with GCTB who were treated with denosumab in Nagoya University Hospital from 2011 to 2019. We also used a prospective study dataset (UMIN000019700, n=40) of bone metastasis (BM) from 2014 to 2017, and comparison and integrated analysis were performed. The factors (disease (GCTB, BM), age (<60, ≥60), sex, dental consultation before treatment, use of loading dose, surgery for primary tumor, and total number of doses (<25, ≥25)) potentially affecting ONJ were analyzed. ONJ free survival was calculated using the Kaplan-Meier method and clinical factors which affect ONJ free survival were analyzed by log-rank test. Chi-square test and Mann-Whitney U test were used to compare paired samples. *p*-values of <0.05 were considered to indicate significance. The median follow-up period after use of denosumab was 46.7(0.1-91.0) months in GCTB and 15.9 (0.6-63.3) months in BM.

Results: The median age was 31 (13-70) years in GCTB and 68 (42-84) years in BM, and median total dose of denosumab was 24 (2-63) in GCTB and 11.5 (1-63) in BM (p=0.31 in Mann-Whitney U test). ONJ was seen in 2 of 12 patients (17%) with GCTB and 5 of 40 patients (13%) with BM (p=0.71 in Chi-square test). The median dose of denosumab at onset of ONJ was 46.5 (44-49) in GCTB and 21 (4-26) in BM (p=0.10 in Mann-Whitney U test). In GCTB and integrated cohort of GCTB and BM, no factors affecting ONJ free survival were identified. ONJ free survival rate at 60 months after the start of denosumab was 62.5% in GCTB and 55.2% in BM. Patients with ONJ were significantly more frequently given denosumab compared with patients without ONJ in GCTB and integrated cohort of GCTB and BM (p=0.03 and p=0.009 in Mann-Whitney U test, respectively).

Conclusion: In this study, the use of denosumab in GCTB showed almost the same occurrence of ONJ as the use in BM, and an increased incidence of ONJ was not observed with a loading dose. ONJ after use of denosumab in GCTB was more frequent than in previous prospective studies, the same as with BM. Patients with ONJ received denosumab much more frequently than patients without ONJ. In unresectable GCTB, it is expected that the total dose of denosumab will be larger than that of bone metastasis because of the long-term administration, and sufficient attention should be paid to the occurrence of ONJ.

Poster #009 3249808

TREATMENT OF OSTEOFIBROUS DYSPLASIA IN A 13-MONTH OLD CHILD WITH CURETTAGE AND PLACEMENT OF ALLOGRAFT BONE

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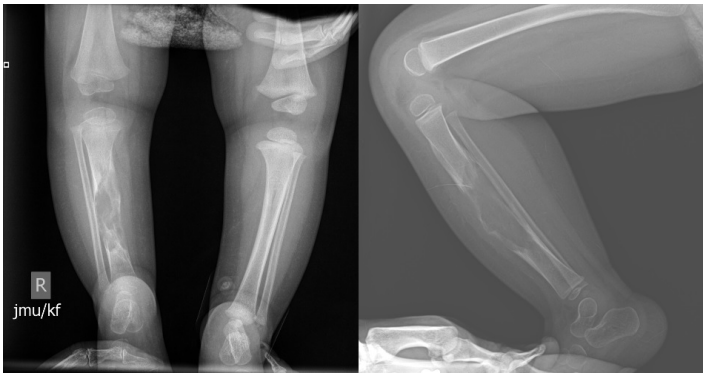
Objective: Osteofibrous dysplasia is an uncommon benign tumor with a predilection for the anterior tibia and fibula. Weakening of the bone can result in fracture and anterior bowing. There is also concern for progression to adamantinoma. Infantile osteofibrous dysplasia has been described with varying courses of treatment. We describe the case of a 13-month old female who presented with significant destruction of the tibia due to osteofibrous dysplasia treated with curettage and placement of allograft.

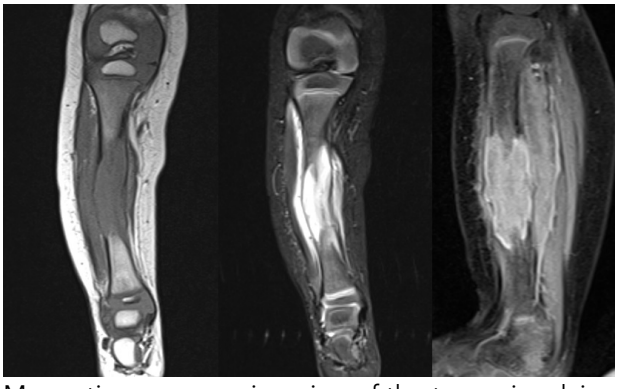
Methods: The patient presented to the Emergency Department with pain in the right leg and refusal to bear weight. X-rays demonstrated a destructive, lytic lesion involving the mid-tibia (Figure 1). A skeletal survey and whole body bone scan were negative for distant disease. Blood work including a complete blood count, sedimentation rate, C-reactive protein, and comprehensive metabolic panel were unremarkable except for the lactate dehydrogenase which was elevated to 337 U/L (74-250). On MRI, the tumor demonstrated dark signal on T1, bright signal on T2, and had diffuse enhancement with contrast (Figure 2). No soft tissue extension was identified.

Results: The patient underwent a biopsy which was consistent with osteofibrous dysplasia. She subsequently underwent a curettage resection of the tumor with placement of allograft bone. No adjuvant was used. The periosteum was preserved and repaired. The patient was kept non-weight bearing in a long leg cast for 6 weeks. She was transitioned to a short leg cast and allowed to walk and the cast was discontinued at 10 weeks. The patient has no evidence of recurrence or deformity with normal function 30 months after surgery. No complications were noted during treatment or follow-up.

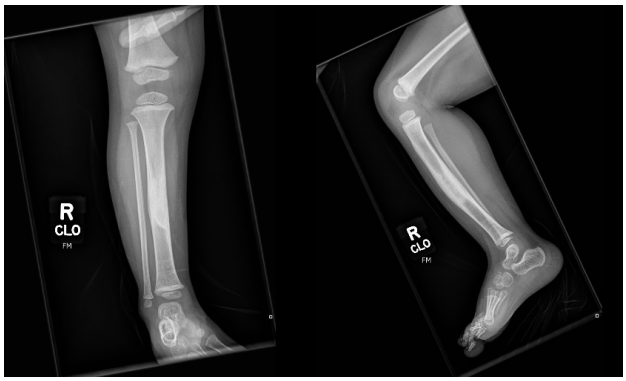
Conclusion: Osteofibrous dysplasia is a rare tumor that may occur at a very young age. Due to the scarcity of this tumor in this age group, treatment is uncertain. As demonstrated in this case, significant destruction of the bone may be found on presentation compared to the typical appearance in the anterior cortex of the tibia or fibula. The patient was successfully treated with a curettage resection and placement of allograft.



AP and lateral x-rays demonstrating a destructive, lytic lesion involving the mid-tibia.



Magnetic resonance imaging of the tumor involving the tibia. A biopsy confirmed the diagnosis of osteofibrous dysplasia.



AP and lateral x-rays 30 months after surgery demonstrating incorporation of the bone graft with no evidence of tumor recurrence.

Poster #010 3250654

DESMOID TUMOR VOLUMETRIC ANALYSIS FOR DISEASE RESPONSE POST ABLATION WITH MAGNETIC RESONANCE GUIDED HIGH INTENSITY FOCUSED ULTRASOUND (MR-HIFU)

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Objective: An objective measure of treatment response is an important feature of the clinical evaluation of cancer therapy. Response Evaluation Criteria in Solid Tumors (RECIST) is a unidimensional measurement that is currently the most widely accepted method of measuring treatment response. This may be suitable for more uniform, rapidly growing, malignant solid tumors; however, its limitations are most notable in irregularly shaped, heterogeneous tumors, particularly when treated using targeted or local therapies.

Desmoid tumors are benign, locally aggressive and irregularly shaped tumors that can cause significant deformity, morbidity and mortality resulting from local mass effects causing compression and pain, muscular contracture or obstruction of adjacent neurovascular structures. MR-HIFU ablation can be used to target specific areas within larger tumors that may be contributing most to this type of morbidity. The resultant ablation zone can be visualized as a volume of non-perfused and non-enhancing tissue on contrast enhanced MRI imaging. Measuring total tumor, perfused and non-perfused volumes using volumetric analysis may provide better objective measurements of tumor response to MR-HIFU local therapy compared to unidimensional measurements.

Methods: This is a retrospective review of MRI images from 9 patients with histologically diagnosed recurrent, refractory and symptomatic desmoid tumors from Children's National Medical Center (CNMC) and Cincinnati Children's Hospital Medical Center (CCHMC). All patients were treated with MR-HIFU on a clinical trial or compassionate use protocol. Unidimensional measurements were performed using digital calipers on Synapse workstation and Osirix workstation for patients from CNMC and CCHMC, respectively. Volumetric analysis was performed using Osirix software. Total tumor volume (TTV) was segmented and calculated by outlining the tumor in all axial planes on post-contrast T1-weighted images. Non-perfused volume (NPV) was similarly measured on axial planes using subtraction images that were generated from pre- and post-contrast T1-weighted images. Perfused tumor volume (PTV) was measured as the subtraction of NPV from TTV.

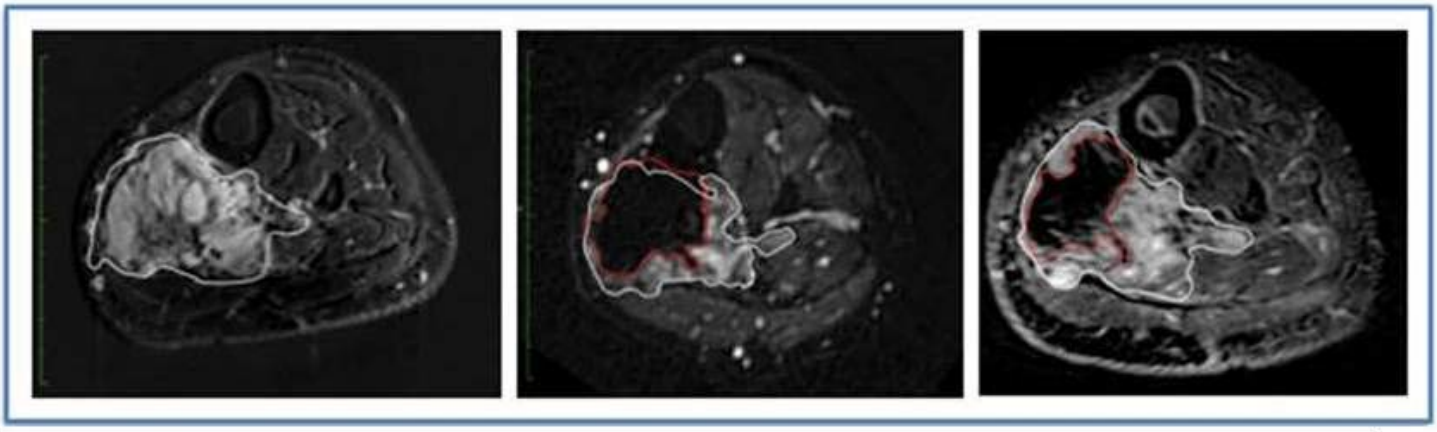
Results: Nine patients (median age 15.3 years, range 6-23 years; 4 males) underwent treatment (tx) with MR-HIFU (n=3, 1 tx; n=5, 2 tx; n=1, 3 tx). Tumors were axial (n=3) or located in the lower extremities (n=6). The median pretreatment TTV was 266.9 cm^3 (range 19.7 - 657.2 cm^3). NPV was not measurable pre-treatment and TTV equaled PTV. At one month post-treatment, the median TTV was 278.2 cm^3 (range 23 - 675.7 cm^3), median PTV was 214.3 cm^3 and median NPV was 64 cm^3. There were no objective RECIST responses immediately post treatment. Table 1 shows individual volumes for all patients. Figure 1 demonstrates volumetric analysis for patient 1 including outlined TTV (white) and NPV (red).

Conclusion: Volumetric analysis provides more detailed measurements of treatment effect including percentages of perfused and non-perfused tumor volume that is not reflected by unidimensional measurements, which may better determine treatment effects with HIFU therapy. Small increases in TTV are thought to be due to inflammation and edema post ablation treatment. These volumes are useful measurements that can be followed over time to establish how changes in TTV relate to perfused and non-perfused tumor components. Analysis of subsequent imaging at later follow up periods, as well as following retreatment, is ongoing and will be included at time of presentation.

Table 1: Volumetric Analysis of total tumor, perfused and non-perfused volume as well as RECIST response									
	Pretreatment 1		**Treatment 1 Day**			**One month Posttreatment 1**			
Pa-tient	TTV (cm3)	RECIST response (cm)	TTV (cm3)	PTV (cm3)	NPV (cm3)	TTV (cm3)	PTV (cm3)	NPV (cm3)	RECIST response (cm), percent change (%)
1	135.7	13.4	137.5	81.2	56.4	157.1	115.2	41.9	12.4, -7.5
2	80.5	9.6	76.4	47.3	29	87.3	62.7	24.7	9, -6.2
3	642.7	51	611.8	389.5	222.2	675.7	605.1	70.6	*N/A, N/A
4	19.7	4.4	25.4	17.6	7.8	23	19.8	3.2	4.4, 0
5	657.6	12.9	655.2	240.2	415	612	274.2	337.8	12.7, -1.6
6	176.4	8.5	182.3	161.4	20.9	181.3	7.6	173.8	9, +5.9
7	96.9	12.2	91.8	81.9	9.9	111.1	104.3	6.8	*N/A, N/A
8	262.8	17.2	**218.6	157.2	61.4	286.6	244.7	41.9	17.8, +3.5
9	329.8	11.1	352.8	192.6	160.2	370.1	328.7	41.4	11.7, +5.4
TTV = Total tumor volume, PTV = Perfused tumor volume, NPV = Non-perfused tumor volume *Unable to perform due to image acquisition/quality **MRI does not include entire tumor									

Table 1: Volumetric analysis of total tumor, perfused and non-perfused volume as well as RECIST response

Figure 1: Patient 1 Volumetric Analysis before treatment, immediately following treatment and at 1 month follow up



White: TTV, Red: NPV

Figure 1: Patient 1 volumetric analysis before treatment, immediately following treatment and at 1 month follow up

Poster #011 3253315

CLINICAL FEATURES OF CHONDROBLASTOMA: A REVIEW OF 19 CASES

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Objective: Chondroblastoma is a benign bone tumor that typically affects the epiphyses of the long bones. Curettage, either alone or in conjunction with bone grafting, is the main surgical treatment for chondroblastoma. The rate of recurrence of chondroblastoma after these procedures has been reported to be approximately 10%. This retrospective study aims to analyze the clinical features and rate of recurrence of chondroblastoma after surgical treatments.

Methods: We performed a retrospective study of 19 patients with chondroblastoma who had been referred to our affiliated hospitals between 2003 and 2017 with a minimum 1-year follow-up after the operation. The age at presentation, gender, anatomical site, and surgical treatment were noted along with the operation records and postoperative complications.

Results: A total of 16 men and 3 women of age range 9–42 years (median age: 16 years) were followed-up for an average follow-up period of 48 months (range: 13–138 months). Tibia was the most frequent location (n = 6 cases), followed by the femur and patella (n = 3 cases, respectively). The other lesions included the humerus (n = 2 cases), temporal bone, radius, ischium, talus, and calcaneus (n = 1 case, respectively). The average size of the lesion was 2.9 cm (range: 2–5 cm). A total of 18 patients were treated with curettage (including 6 cases treated with a wide curettage using a high-speed burr). In addition to this procedure, 13 patients underwent bone grafting (artificial bone, n = 9 cases; allograft, n = 3 cases; autograft, n = 1 case). Local recurrence occurred in 1 case (5.2%) who was a 14-year-old girl with a 4.5-cm chondroblastoma of the calcaneus treated with a wide curettage and autogenous bone grafting. Five years after the operation, local recurrence occurred and was successfully treated with curettage and allogeneic bone grafting. Postoperative complications occurred in 2 cases (10%) as infection in 1 case and deafness and trismus in another case.

Conclusion: As observed in other studies, the rate of recurrence in our study was approximately 10%. Age before epiphyseal fusion, inadequate curettage, tumor size, and location in the proximal femur or tarsal bones are reported to be the risk factors of recurrence after surgical treatment. We also confirmed the recurrence in large chondroblastoma of the calcaneus in a child. Although chondroblastoma is benign and not many recurrent cases have been reported, long-term follow-up is recommended because of appearance of recurrent cases 5 years after the surgery in this and several other studies.

Recurrence of Chondroblastoma

Year	Authors	No. of cases	Age (mean or median)	Rate of recurrence (%)	Time to recurrence (months)
1972	Dahlin DC et al	125	5-59	10	11-24
1985	Springfield DS et al	70	10-40	14	5-84
1985	Bloem JL et al	104	10-70 (16)	16	7 cases within the 1st year
1993	Turcotte RE et al	70	8-68	29% in flat bone 11% in long bone	34
2000	Ramappa AJ et al	47	11-56 (22)	15	NA
2005	Suneja R et al	53	8-48 (18)	13.2	4-17
2005	Lin PP et al	82	10-69 (16)	8.3	5-51
2007	Atalar H et al	28	11-41	21.4	10
2009	SailHan F et al	87	(12.5)	32	NA
2015	Xu H et al	145	9-35 (18.8)	5	5-24
2019	This study	19	9-42 (16)	5.2	60

Poster #012 3254301

TARGETABLE DRIVER MUTATIONS IN MULTICENTRIC RETICULOHISTIOCYTOSIS

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Objective: Multicentric reticulohistiocytosis (MRH) is a very rare systemic disease, characterized by multiple destructive arthritic and papulonodular skin lesions that can also affect other organs including the lungs and heart. Because of the rarity and similarity of histological features, it is occasionally misdiagnosed as tenosynovial GCT, eosinophic granuloma or other disease, and only local treatment may be performed by the involved physicians. Given its similar clinical manifestations to those of rheumatoid arthritis (RA), MRH has been suspected to be an autoimmune or inflammatory disease, and patients receive treatments similar to that of RA including administration of corticosteroids, methotrexate, bisphosphonates, and several biological anti-inflammatory agents. Although spontaneous remission is occasionally observed during the initial 10 years after diagnosis, the functional prognosis of patients is generally poor; joint replacement surgery is often required because of the progression of destructive arthritis. Together, current treatment is not satisfactory for patients, particularly in severe cases.

Methods: To clarify the genetic background of MRH, we performed whole exome sequencing and RNA sequencing in two patients with MRH. A 60-year-old woman (UPN1) visited our hospital because of multiple skin lesions. At the age of 54, a subcutaneous nodule appeared on her left little finger, and other lesions followed gradually in other fingers, toes, foot, ankles, knees, chin, and vocal cords. Resection and histopathological analyses of her nodules were performed six times without any diagnostic yields. We performed biopsies of periarticular lesions of a finger and a skin lesion in the chin and diagnosed the patient as having MRH based on the clinical and pathological features.

UPN2 was a 39-year-old man who visited our hospital because of disturbances in his ADL caused by polyarticular nodular lesions and arthralgia in addition to multiple skin lesions. At the age of 30, abnormal chest shadows were found on X-ray images at routine medical examination. A bronchoscopic biopsy revealed infiltration of histiocytic cells. From the age of 33, multiple symmetric arthralgia of shoulders, knees, wrists, fingers, and hands appeared and worsened gradually. We performed a biopsy of a periarticular lesion of the left elbow and diagnosed him as having MRH based on the typical histological findings similar to those of UPN1. The patient's disease had been resistant to RA-like immunosuppressive therapies, and he had undergone total joint replacements of the left knee and bilateral hips because of intractable pain emanating from destructive arthritis.

Results: We identified a FGFR1 tyrosine kinase fusion (KIF5B-FGFR1) in UPN1 and a MAP2K1 (MEK1) gain-of-function mutation in UPN2, suggesting the neoplastic nature of this disease caused by the activation of the RAS-MAPK pathway similar to that present in patients with LCH. We hypothesized that chemotherapy resembling that for LCH might be effective in these patients, and upon approval by our institutional review board, we performed a chemotherapy used for LCH to patient UPN2 who harbored MAP2K1 and TET2 mutations in his histiocytes. After starting the chemotherapy, the periarticular masses containing histiocytic cells gradually decreased in size and became soft and the subjective symptoms including the right knee pain improved. As a result of this response, the patient's right knee did not require the joint replacement surgery that had been considered inevitable before the chemotherapy initiation.

Conclusion: Our results indicate that MRH should be considered a neoplastic disease and suggest promising effects of chemotherapy for its treatment. Further studies are warranted to contribute to the development of optimal therapeutic approaches for MRH, possibly including molecular targeted therapies.

Poster #013 3254342

TWO WEEKS INTERVAL OF METHOTREXATE AND VINBLASTION CHEMOTHERAPY SHOWS THE SIMILAR EFFECT AS WEEKLY ADMINISTRATION

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[1]Rehabilitation, Orthopaedic surgery, Nagoya University Hospital, Nagoya, Aichi, Japan; [2]Orthopaedic Surgery, Nagoya University Graduate School and School of Medicine, Nagoya, Aichi, Japan; [3]Medical Oncology, Nagoya University Graduate School and School of Medicine, Nagoya, Japan; [4]Orthopaedic Surgery, Tonokosei Hospital, Mizunami, Japan

Objective: Several studies have shown efficacy of low-dose chemotherapy with methotrexate (MTX) and vinblastine (VBL) for desmoid-type fibromatosis (DF). Many regimens in these studies used a weekly dosing regimen to demonstrate their effectiveness. Since 2003, meloxicam, which is a selective COX-2 inhibitor, has been administered consecutively and prospectively, as a first line treatment. We have used MTX + VBL chemotherapy in a regimen of once every two weeks, which was different from that used in previous reports, for refractory patients. The aim of this study was to reveal the clinical outcome of low-dose chemotherapy with MTX+VBL in a regimen of once every two weeks, additionally to determine the useful factors to predict the efficacy of this chemotherapy including CTNNB1 mutation status.

Methods: Since 2003, 167 cases were histologically diagnosed as DF. Among them, 36 cases were treated with MTX (30mg/M2) +VBL (6mg/M2) chemotherapy. Treatment interval was basically 2 weeks according to our previous study. However, the dosing interval was extended to once every 3-4 weeks depending on the patient's side effects and preference, and tumor reduction effects. Effectiveness was evaluated with MRI and/or CT every 3 months according to Response Evaluation Criteria in Solid Tumors (RECIST). Frozen or FFPE (Formalin-Fixed Paraffin-Embedded) specimens obtained at biopsy or previous surgery were subjected to the analyses for CTNNB1 mutation status by Sanger method. Clinical outcome with this 2-weeks interval regimen was investigated, and factors correlating with the efficacy were analyzed.

Results: Male was 13, female was 23 cases, mean age at the treatment was 36±18 years. Mean maximum diameter of tumor was 15±18 cm. Twenty-nine cases (81%) had CTNNB1 or APC mutation. Mean treatment duration and cycles of MTX+VBL were 20 months and 29 cycles, respectively. According to RECIST, PD in 2, PR 1n 15, and SD in 19. Response rate (PR) was 42%, and clinical benefit rate (PR+SD) was 94%. It took an average of 10 months to show a response in PR cases. According to CTCAE, Grade 3 or more adverse events were observed in only one case (2.8%) As factors relating to the response rate, CTNNB1 mutation status, gender, age, size, and location did not affect the outcome with RECIST evaluation. Longer treatment duration and cycles of chemotherapy were significantly associated with the outcome (P=0.003 and 0.005, respectively). In 15 cases of PR, recurrent tumors significantly took longer time to get efficacy (P=0.027), and tumors arising in trunk and extremities tended to take longer time (P=0.1).

Conclusion: Every 2-weeks' regimen showed 42% of response rate, which was similar to those (40-52%) reported in previous studies (every week regimen). Rate of grade 3-4 toxicity was 2.8% in our study, which was lower than those (13-40%) reported in previous studies (every week's regimen). On the other hand, time to response in the present study was 10 months (mean), which was longer than that (6 months, mean) reported with every week's regimen. Low-dose MTX+VBL chemotherapy with 2-weeks' regimen is effective treatment for refractory DF regardless of various clinical factors and CTNNB1 mutation status. It will take time to obtain objective response.

Poster #014 3254507

PRIMARY BONE ROSAI-DRFMAN DISEASE ARISING IN INFANTILE ILEUM

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Objective: Rosai-Dorfman disease (RDD) is an extremely rare benign histiocytic disorder that usually affects young adults. Extranodal involvement of the RDD is common and may occur in more than 40% of patients, but bone involvement occurs in less than 10% of cases. Furthermore, primary bone RDD is extremely rare. We herein report a case of primary bone RDD arising in the infantile ileum. We describe the clinicopathological details of this rare case and review the relevant literature.

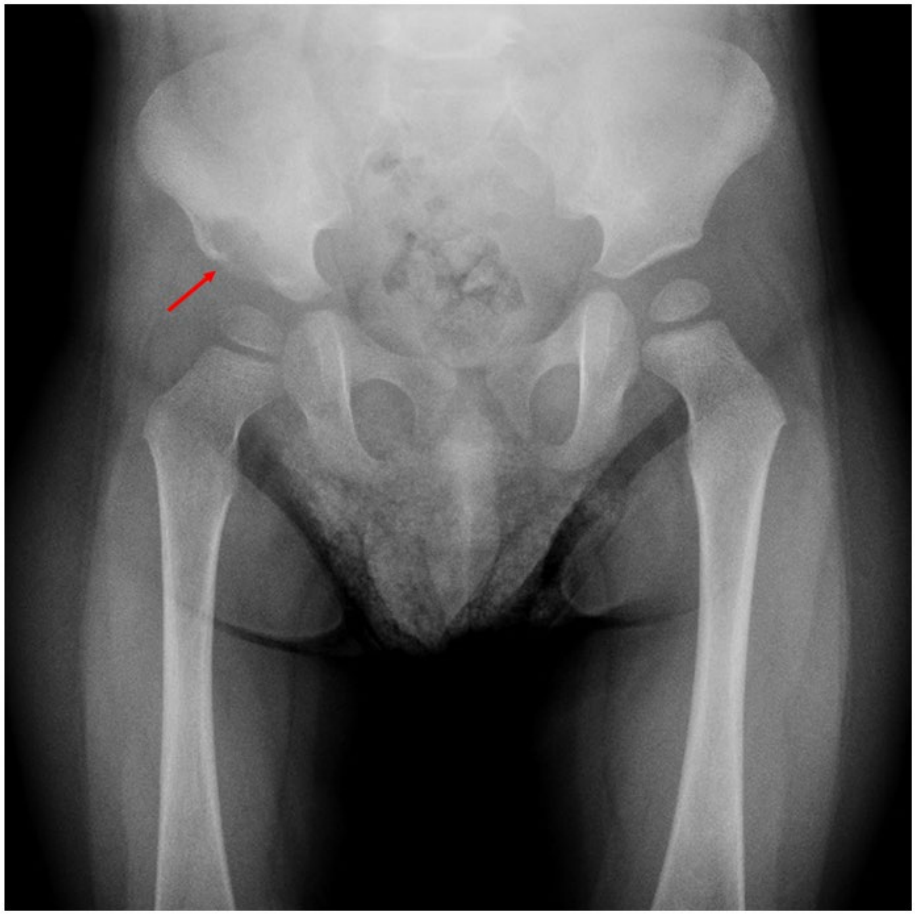
Methods: A 2-year-old boy presented with limping of the right lower extremity, which persisted for two months without obvious pain. He had no perinatal medical problems.

Plain radiographs showed an osteolytic lesion at the peri-acetabular lesion of the patient's right ilium. We examined the boy by imaging and pathological diagnostic method.

Results: A physical examination showed slight limitation in the range of motion of his right hip joint without a leg length discrepancy. A laboratory examination revealed no abnormalities.

Plain radiographs and CT images showed an osteolytic lesion at the peri-acetabular lesion of the patient's right ilium. Fluorodeoxyglucose positron emission tomography (FDG-PET) indicated abnormal accumulation only in the right iliac bone, without any other accumulation. An incisional biopsy was performed to obtain a definite pathological diagnosis. Microscopy showed numerous large histiocytes interspersed with different amounts of lymphocytes, neutrophils, and plasma cells. Emperipolesis was observed in the cytoplasm of the large histiocytes. Immunohistochemistry was positive for CD68, CD163, and S-100, and negative for CD1a. The patient was diagnosed with primary bone RDD of the ileum. The bone lesion showed spontaneous regression on radiography, and he could walk without any limping or pain at 8 months after the biopsy. After 18 months of follow-up, the bone lesion had completely disappeared and no joint deformity was observed on radiography and CT.

Conclusion: Primary bone RDD is extremely rare. In the present case, the osteolytic lesion of the RDD showed spontaneous remission without residual bone deformity after curettage of the lesion at the incisional biopsy. However, previous reports reported that some cases, eventually developed additional extraosseous manifestations, including testicular, lymph node, and subcutaneous lesions. Thus, careful and long-term follow-up is necessary.



Poster #015 3255103

NANOSTRING ANALYSES OF TYROSINE KINASE FUSION GENES IN INFLAMMATORY MYOFIBROBLASTIC TUMOR/ INFLAMMATORY PSEUDOTUMOR

Taisei Kurihara; *Yoshiyuki Suehara; Kei Sano; Keisuke Akaike; Takuo Hayashi; Nobuhiko Hasegawa; Tatsuya Takagi; Taketo Okubo; Takashi Yao; Kazuo Kaneko; Tsuyoshi Saito*
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Objective: Inflammatory myofibroblastic tumor (IMT)/inflammatory pseudotumor (IPT) is an intermediate malignancy and histologically characterized by admixed proliferation of myofibroblasts and inflammatory cells such as, lymphocytes, plasma cells and eosinophils. Approximately half of IMTs are considered to have *ALK*fusion and recently other fusions such as *ROS1, PDGFRB* and*NTRK3*have also been reported in addition to *ALK*. In this study, we conducted comprehensive TK fusion screening to identify novel fusions in these tumors.

Methods: We enrolled 9 cases of IMT and 26 cases of IPT. RNA of these cases was extracted, and the imbalance of 5′-side/3′-side of the gene expression was comprehensively measured for 90 TK（Tyrosine Kinase）genes by Nanostring. Cases with imbalanced expressions were further analyzed by either IHC, FISH, RT-PCR and RNA sequencing.

Results: Among 35 cases, 11 cases (2 for IMT, 9 for IPT) were excluded by statistical analyses (including normalization) due to sample qualities, and 9 cases (4 for IMT, 5 for IPT) were emerged as imbalanced cases (2 for *NTRK3*, 6 for *ALK*and 1 for *ROS1*). Further analysis confirmed *ETV6-NTRK3*fusion by RT-PCR in 2 IPT cases, *ALK*rearrangement by IHC and FISH in 5 cases (4 IMTs and 1 IPT). *ROS1*- rearrangement was detected by RNA sequencing and was confirmed by RT-PCR (1 IPT). Interestingly, 2 cases with *ETV6-NTRK3*fusion were not positively stained by pan-trk IHC which has been shown as a sensitive IHC marker for *NTRK*fusion-positive tumors.

Conclusion: We could identify 7 cases (30%) with TK fusions from among 24 informative cases of IMT/IPT. IMT and IPT were found to be difficult to distinguish only by pathological findings. Pan-trk IHC in IMT/IPT might be less sensitive than previous studies, especially for *NTRK3*fusions. Alternatively, this staining might not be suitable to identify *NTRK*fusion for this type of tumor often having only few myofibroblastic cells with predominant inflammatory cells.

Poster #016 3255260

FACTOR ANALYSIS ASSOCIATED WITH LOCAL RECURRENCE AND LIMB FUNCTION OF 105 PATIENTS WITH DIFFUSE-TYPE TENOSYNOVIAL GIANT CELL TUMOR: A MULTINATIONAL STUDY OF AN ASIAN POPULATION

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Objective: A diffuse tenosynovial giant cell tumor (D-TGCT) is a rare, locally aggressive benign, synovial tumor predominantly involving the knee, followed by the hip, ankle, elbow, and shoulder. It is usually difficult to complete excision and resulted in high recurrence. Due to its low incidence of disease, the long-term clinical outcome and the factor associated with local recurrence (LR) and limb function were not fully clarified in Asian populations. This study was aimed to evaluate the long-term clinical outcome of D-TGCT and analyze the factors associated with LR and limb function in an Asian population by a multinational and multi-institutional retrospective study.

Methods: Data regarding age, gender, location, status (primary or referred), type of surgery, time to local recurrence, treatment of recurrence, number of recurrences, distant metastasis, malignant transformation, term of follow-up, the Musculoskeletal Tumor Society (MSTS) scoring system and oncological outcome were collected by questionnaire from the 14 cancer centers and university hospitals that participate the cooperative study group. Patients with biopsy-proven D-TGCT in large joints with minimum 3-year follow-up without medical treatment were included. Local recurrence (LR) was defined as recurrence following complete resection, or residual tumor progression following incomplete resection. Local recurrence-free survival (LRFS) and predictive factors associated with LRFS were analyzed by log-rank test. The predictive factor of MSTS scores was determined by chi-square test and logistic analysis.

Results: One hundred five patients were included, 82 with primary and 23 with recurrent tumors (41 men, 64 women). The mean age was 40 years (8 to 82), and the mean follow-up was 80 months (36 to 231). The types of initial surgery were open synovectomy in 90 patients and arthroscopic synovectomy with or without open synovectomy in 15 patients. Thirty-six patients (34.3%) developed LR after initial treatment. The 5- and 10-year-LRFS was 71.5% and 50.2% (Fig.1). The complete tumor excision was significantly correlated with better local control (P=0.01) (Fig.2). Joint replacement was eventually performed in 9 patients (8.6%). Malignant transformation was observed in one patient and managed by the amputation. The final oncological status was 47 in continuous disease-free (CDF), 21 in no evidence of disease (NED), and 37 in alive with disease (AWD). The mean MSTS score was 26.4 (13 to 30). There was no significant difference between the oncological status (27.7 in CDF, 26.6 in NED, and 24.8 in AWD). Age (>40 y.o.) (P=0.03), pre-operative bone invasion (P=0.04), open synovectomy (P=0.04) and incomplete resection (P=0.05) were independent risk factor of worse MSTS score (<75%) (Table 1). Moreover, there was a significant difference in MSTS score between progressive (20.4) and stable (26.2) AWD (P<0.001) (Fig.3).

Conclusion: Complete excision may lead to favorable oncological and functional outcomes although the possibility of it is determined by the tumor extension. Although the local recurrence rate was still high after surgical treatment, alive with stable disease contributed to the better limb-function. Novel approach (such as anti-CSF-1R inhibitor) to keep the stable disease after local recurrence is urgently needed.

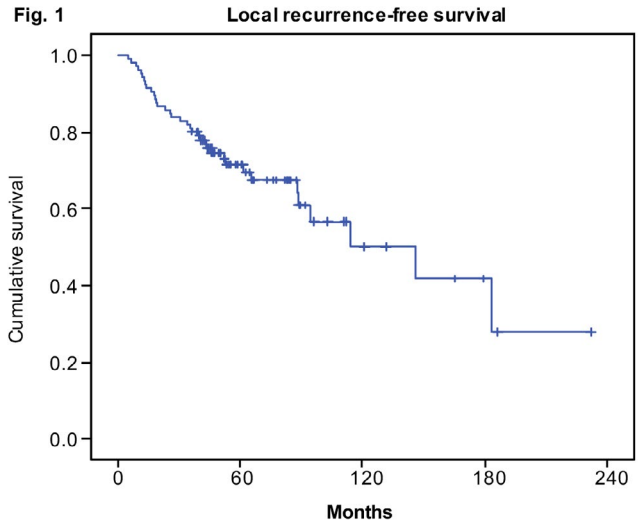

Fig.1: The 5 and 10-year- local recurrence-free survival rate by Kaplan-Meier analysis was 71.5% and 50.2%.

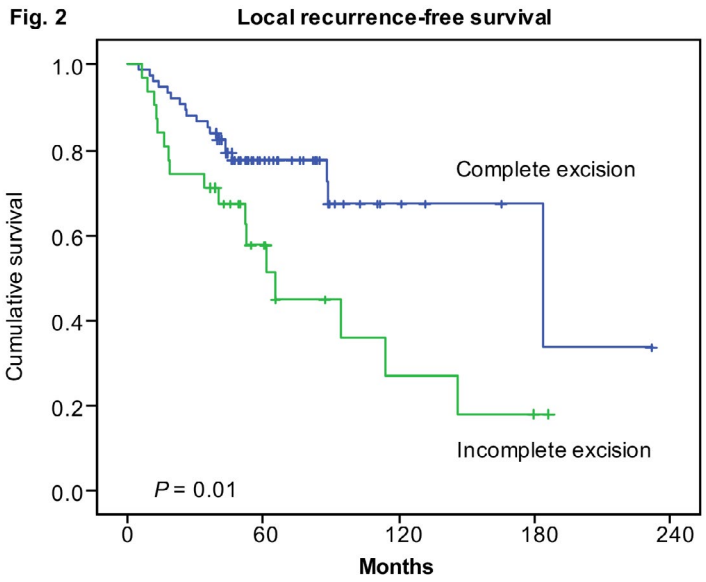

Fig.2: The local recurrence-free survival was shown for patients who were treated by complete excision and incomplete excision. The complete tumor excision was significantly correlated with better local control (P=0.01).

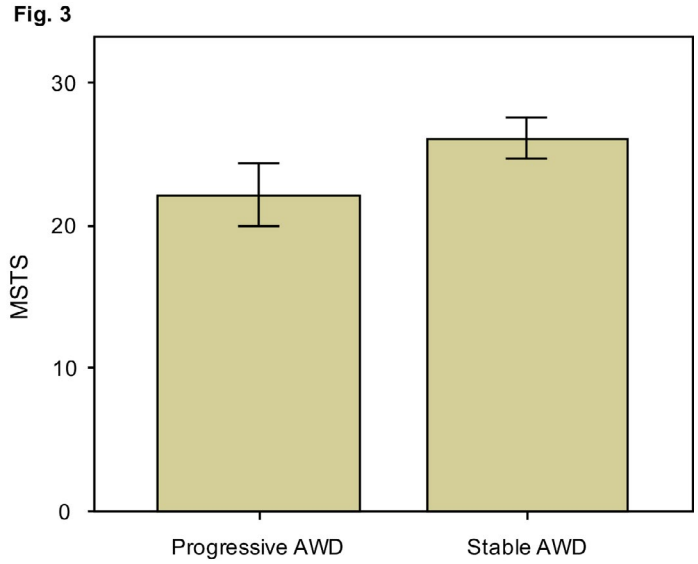

Fig.3: The data represent the mean MSTS score of progressive AWD and stable AWD. Statistical significance determined by Student's t-test. There was a significant difference in MSTS score between progressive (20.4) and stable (26.2) AWD (P<0.001).

Poster #017 3255673

SIMPLE BONE CYSTS TREATED BY INJECTION OF AUTOGENOUS BONE MARROW

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Objective: Since 2007, we have been treating simple bone cysts (SBC) in children before epiphyseal closure by injection of autogenous bone marrow. This technique is a minimally invasive treatment that does not require skin incision. We present a review of clinical experience at our hospital to verify the validity of this treatment for SBC.

Methods: From 2007 to 2016, 20 patients (gender, 16 males and 4 females; mean age, 10.5 years) who were diagnosed with SBC prior to epiphyseal closure, injected with autogenous bone marrow, and followed up for more than two years were included in this study. The site of occurrence included the humerus (n = 9), femur (n = 4), and calcaneus (n = 7). The radiological assessment of treatment outcomes was performed according to the classification described by Chang et al. The effect of treatment, operation time, postoperative hospitalization period, and complications were examined.

Results: The radiological results of SBC after initial treatment were: healed or healing with defect, 11 cases (humerus, n = 5; calcaneus, n = 6); persistent or recurrent cysts, nine cases (humerus, n = 4; femur, n = 4; calcaneus, n = 1). One of nine cases with persistent or recurrent cysts in the humerus resulted in a pathological fracture, but has since healed with conservative therapy. The remaining eight cases underwent a second treatment. The radiological results of SBC after second treatment were: healed or healing with defect, three cases (humerus, n = 1; femur, n = 2); persistent or recurrent cysts, five cases (humerus, n = 2; femur, n = 2; calcaneus, n = 1). Cases evaluated as healed or healing with defect after the second treatment were as follows: humerus, 67%; femur, 50%; calcaneus, 86%. Of the five cases with persistent or recurrent cysts, two cases in the femur resulted in pathological fractures. One of these two cases was treated with external fixation, while the other was treated with curettage and artificial bone grafting, and both of these cases have healed. The remaining three cases underwent decompression therapy with cannulated screws and were evaluated as healing with defect.

The mean operation time was 28.2 minutes, and the mean postoperative hospitalization period was 2.1 days. There were no complaints of postoperative pain, and all patients were discharged with physical activity levels that were comparable to preoperative levels.

Conclusion: Like other forms of treatment, the injection of autogenous bone marrow may require reoperation for cases occurring in the humerus or femur; however, we believe it is an appropriate initial treatment for younger patients due to its lower invasiveness and shorter hospital stay.

Poster #018 3255781

DEVELOPMENT OF MULTIFOCAL EXTRA-ABDOMINAL DESMOID FIBROMATOSIS AFTER SURGICAL RESECTION

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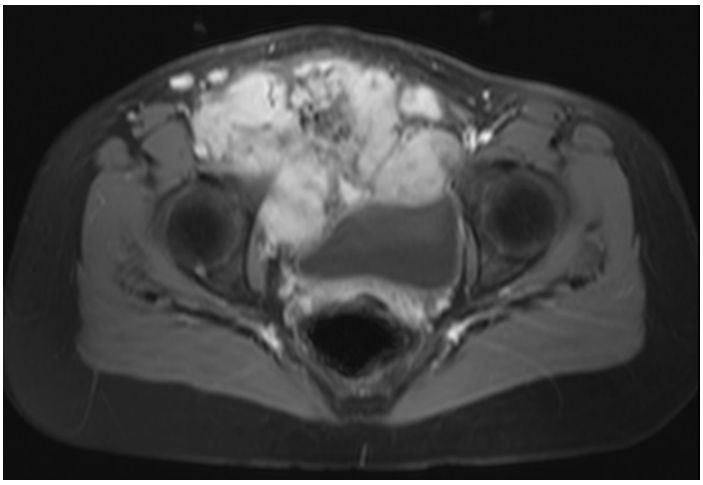
Objective: Multifocal extra-abdominal desmoid fibromatosis is a rare entity. Both sporadic and hereditary entities have been described. Trauma has been described as a possible etiology of sporadic fibromatosis. We report on two cases of solitary, sporadic fibromatosis that developed multifocal disease after surgery.

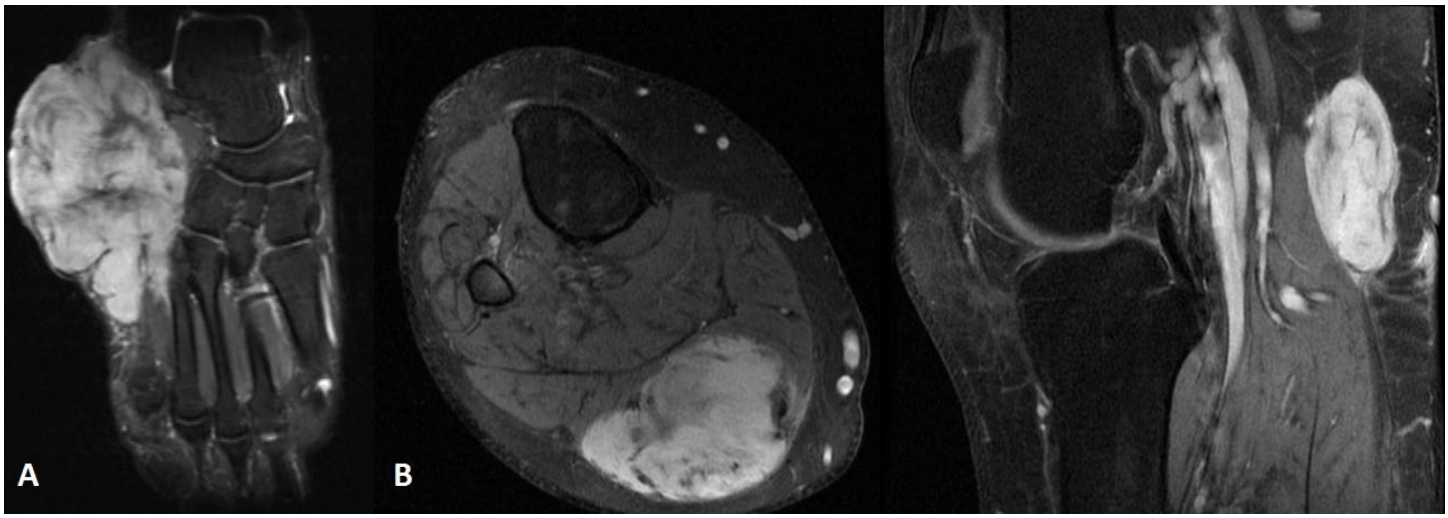
Methods: The cases of a 21-year-old female with fibromatosis involving the right hemipelvis (Figure 1) and a 20-year-old male with involvement of the right ankle (Figure 2a) were reviewed. Both patients had a negative evaluation for Gardner syndrome including a colonoscopy. Biopsy was performed on two separate tumors that developed after surgery to confirm multifocal disease.

Results: Both patients developed distant multifocal disease in the extremity affected by the surgery. Neither patient had multifocal disease prior to their last surgery. The 21-year-old female underwent a single surgery with resection of the primary tumor including ligation and en bloc resection of the femoral vein and lymphatics. She developed significant lymphedema post-operatively. Five years after surgery she was found to have multiple tumors in her right leg below the knee (Figure 3). The 20-year-old male presented after multiple resections at an outside institution with local recurrence and fungation of the tumor. Multiple procedures were performed in order to attempt limb-salvage surgery. The patient elected to proceed with a below the knee amputation after multiple recurrences. Post-operatively the patient developed sores and folliculitis multiple times under his prosthesis due to sweating while working. Thirty-two months after amputation, the patient developed tumors at the posterior aspect of his stump and the popliteal fossa where his prosthesis was irritating the soft tissues (Figure 2b). Both patients elected for non-surgical management and the tumors are stable 2.5 and 3 years after the diagnosis of multifocal disease. No evidence of disease outside of the affected extremity has developed.

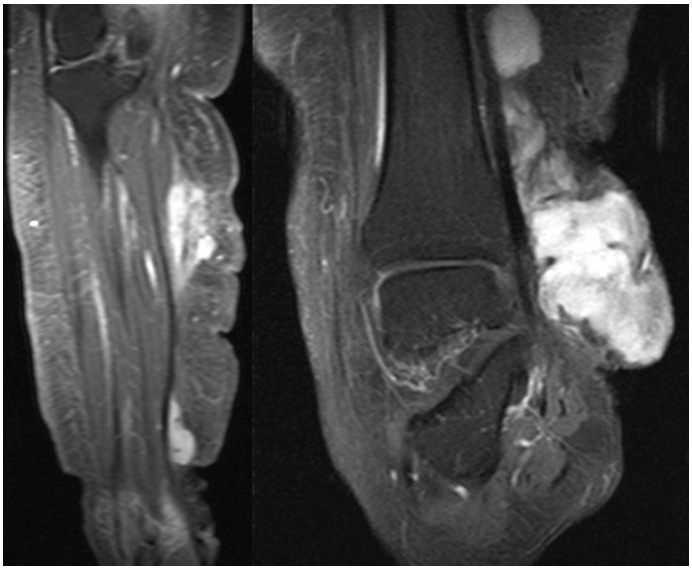
Conclusion: Multifocal fibromatosis is rare. These two cases are felt to have developed after chronic irritation and trauma to the soft tissues due to significant lymphedema and from use of a prosthesis. Chronic inflammation and repetitive trauma may be considered a risk factor for developing multifocal disease.



Axial MRI of the pelvis demonstrating fibromatosis involving the right hemipelvis in a 21-year-old female.



A) Fibromatosis involving the ankle region in a 20-year-old male. B) Post-below the knee amputation development of multifocal disease involving the popliteal fossa and distal stump region.



Demonstration of postsurgical development of multifocal disease in the leg of a 21-year-old female who underwent resection of fibromatosis from the pelvis. Multiple tumors are noted in the lower leg and ankle region.

Poster #019 3255783

MASSIVE LOCALIZED LYMPHEDEMA (MLL) ASSOCIATED WITH MORBID OBESITY: A RARE, BENIGN CLINICAL ENTITY RESEMBLING A GLUTEAL LIPOSARCOMA

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Objective: MLL is a rare benign fatty entity that occurs in morbidly obese patients. It is felt to develop from chronically obstructed lymphatics within the morbidly obese. This obstruction is believed to cause the excessive growth of lymphoproliferative tissue resulting in a large, pedunculated fatty mass typically in the lower legs, but also in the suprapubic tissue, genitalia, and upper arms. Given the progressive enlargement of these tumors as well as the large size, these tumors are commonly misdiagnosed as sarcomas. We present a case of massive localized lymphedema localized to the left gluteal muscle with radiographic and pathologic similarities to liposarcoma.

Methods: Our patient is a 136kg, 73-year-old male being worked up for bariatric surgery. During presurgical work-up, the patient had a CT scan of the Abdomen and Pelvis. From that scan, a fatty tumor was seen in the left buttock in the deep soft tissues involving the left gluteus maximus muscle. A follow up MRI demonstrated an ovoid fat-containing lesion measuring 10.1x5.4cm in the left posterior gluteal region (Fig 1). Lesion showed heterogeneous peripheral and central enhancement. Image characteristics were concerning for liposarcoma. Patient underwent core needle biopsy. Pathology demonstrated an atypical lipomatous tumor. Patient was taken to the operating room for radical resection. However, final pathology demonstrated MLL and no malignancy was identified.

Results: Lesion consisted of adipose tissue with areas of fat necrosis, sclerosis and scattered cells with microvesicular fat which resembles brown fat. DDx include – well differentiated lipomatous neoplasm with areas of fat necrosis and possibly a component of a hibernoma. No definitive lipoblasts or overt malignancy were identified in the biopsy. Multiple FISH markers for MDM2 were negative. Fluorescence in-situ hybridization (FISH) was performed on interphase nuclei using probes localized to the MDM2 (12q13-q14) and CEP12 (D12Z3) regions.

Conclusion: While massive localized lymphedema is considered a rare entity (~1:1500 patients), as the incidence of obesity increases in our population, there is an increased likelihood that this tumor may become more prevalent. This tumor is most often located in the thigh or suprapubic location. We report a rare case of a gluteal presentation. Thus, it is necessary to consider a large fatty mass in the morbidly obese, anywhere in the body, to be a benign MLL instead of a sarcoma.

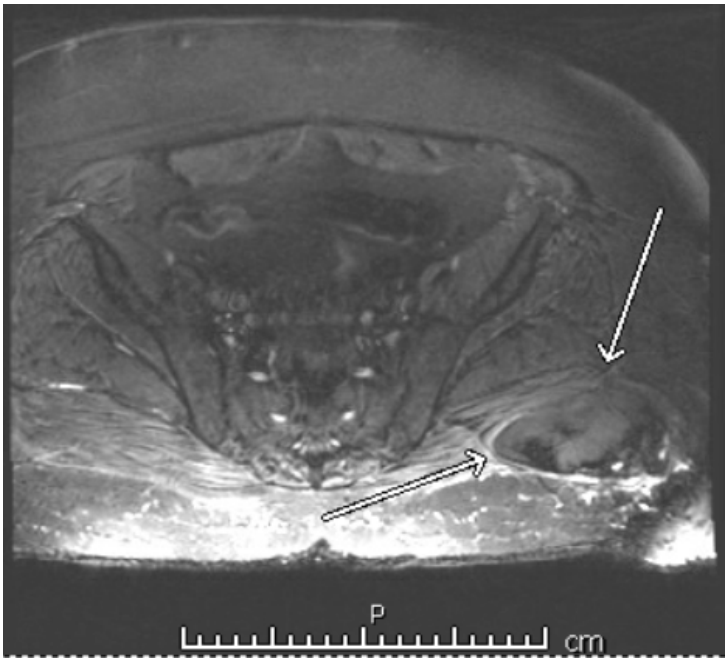

Figure 1. Left gluteal mass (axial)

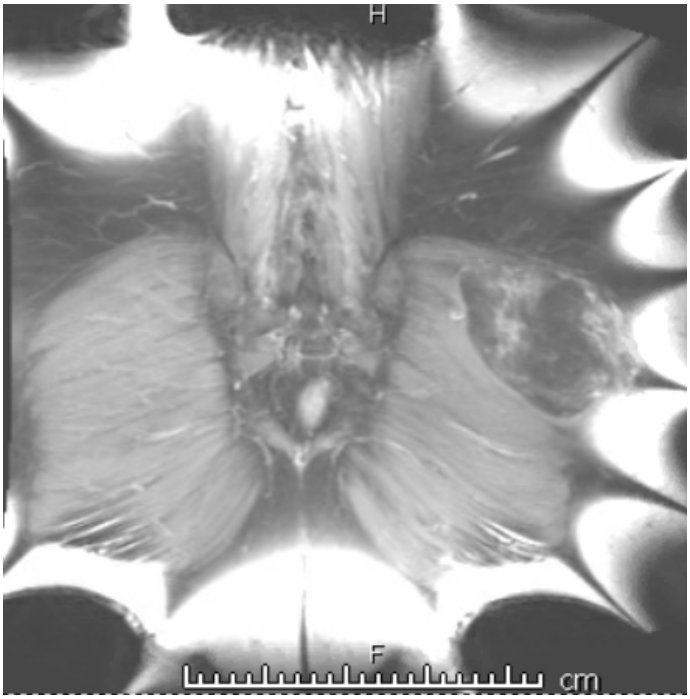

Figure 2. Left gluteal mass (coronal)

Poster #020 3255921

NOVEL TREATMENT OF ZALTOPROFEN FOR DIFFUSE-TYPE TENOSYNOVIAL GIANT CELL TUMOR: A PILOT STUDY

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Objective: Diffuse-type tenosynovial giant cell tumor (D-TGCT) is a locally aggressive benign synovial tumor which involves the inner lining of a joint. Surgical removal is the only radical treatment, however, the local recurrence rate is still high. Recently, a selective inhibitor of the colony-stimulating factor (CSF1)/CSF1 receptor (CSF1R) has been developed as a novel treatment. In the previous study, the authors have revealed that zaltoprofen, a nonsteroidal anti-inflammatory drug possessing the ability to activate peroxisome proliferator-activated receptor gamma (PPARγ), can inhibit the proliferation of tenosynovial giant cell tumor (TGCT) stromal cells, and got the patent in Japan. PPARγ is a ligand-activated transcription factor that belongs to the nuclear hormone receptor superfamily. Therefore, we conducted this pilot study to evaluate whether zaltoprofen is safe and effective for patients with Diffuse TGCT (D-TGCT).

Methods: Patients with advanced primary and recurrent D-TGCT arising in knee and ankle joints were enrolled in this study. Zaltoprofen (240mg) was given orally, daily for 48 weeks or until progressive. The response was assessed using the Response Evaluation Criteria in Solid Tumors (RESIST), which was measured by MRI every 3 months. The functional status of the patients was assessed using Ogilvie-Harris score for knee and MSTS score for ankle D-TGCT. Adverse effects were evaluated using the Common Terminology Criteria for Adverse Events v4.0 (CTCAE).

Results: Twelve patients were enrolled. The mean age was 44 years (range, 16 to 67 years). The mean tumor size was 59 mm (range, 31 to 93 mm). Mean follow-up periods were 76 weeks (range, 12 to 143 weeks). Tumor locations were knee in 7 and ankle in 5 pts. Mean tumor size reduction was 2.9% (range, -9.5% to 16.4%) (Fig. 1). Eleven patients kept the stable disease (Fig. 2) and one patient showed progressive disease after 72 weeks. Surgery was performed in 3 patients due to their request Mean pre- and post-treatment Ogilvie-Harris score was 64% and 80%. Mean pre- and post-treatment MSTS score 96% and 99.3%. No adverse effect (>Grade 3) was observed. Surgery was performed for 3 patients with ankle D-TGCT due to their request at 12, 24 and 48 weeks.

Conclusion: Zaltoprofen was well tolerated and kept stable disease with improving the limb-function. It could be a novel treatment in patients with TGCT. The results of this study contributed to the development of a randomized, placebo-controlled, double-blind, multicenter invaestigator-initiated clinical trial (UMIN000025901) granted by Center for Clinical Trials, Japan Medical Association (JMACCT), which is currently on-going.

Fig.1

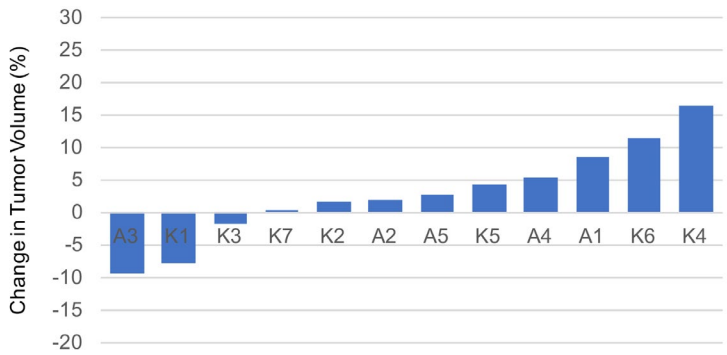

Fig.1: Percentage change in tumor volume during the treatment. All cases showed stable disease in RECIST response classification.

Fig.2

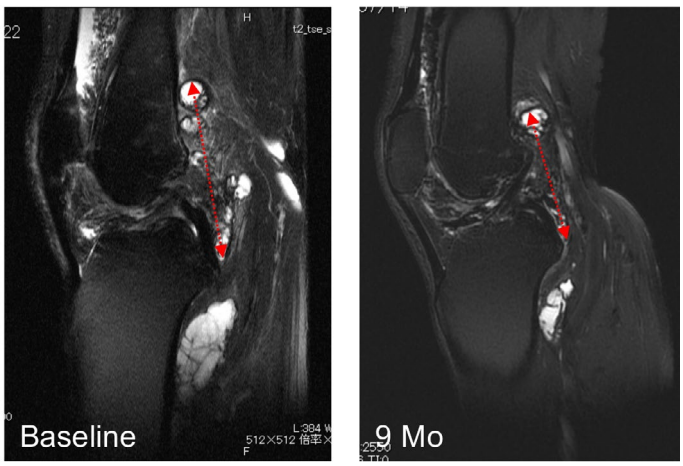

Fig.2: Case K5. The baseline MRI showed the large D-TGCT occurred in the suprapatellar pouch and the popliteal fossa. The longest diameter of the posterior lesion (dashed red line) decreased from 81.1mm to 76.1 (6.2%) at 9 months. Synovial fluid was also decreased.

Poster #021 3256403

COMBINATION DRUG THERAPY AND AGGRESSIVE FIBROMATOSIS

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[1]Orthopaedic Surgery, Duke University, Durham, NC, USA; [2]Developmental & Stem Cell Biology, The Hospital for Sick Children, Toronto, ON, Canada; [3]MD Anderson, Houston, TX, USA; [4]Broad Institute, Cambridge, ME, USA; [5]Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, USA; [6]Lunenfeld-Tanenbaum Research Institute, Toronto, ON, Canada

Objective: Aggressive fibromatosis (AF), commonly referred to as Desmoid tumor, is a locally aggressive lesion. Surgery is associated with a high recurrence rate, and in recent years there has been increased interest in non-surgical management. Clinical studies are limited by small patient numbers and the need for long term follow up. As such, preclinical studies to assess possible therapies are useful in informing treatment approaches. Prior studies investigated single agent therapies through both in vivo and in vitro studies; however, there is a paucity of literature available on multi-drug regimens. A multicenter drug screen has identified numerous medications that show promising activity in AF. Therefore, we sought to investigate various combination regimens from the drug screen to determine drug synergies and the utility of multidrug therapy in AF.

Methods: Our mouse model, APC1638N, develops AF tumor that is structurally similar to human AF tumor. In this study, we chose male mice that develop around 25 tumors per mouse by the age of 6 months. The treatment was started when the mice are around 8 weeks old (2 months) and continued until sacrificed at the age of 6 months. At which, an observer who is blinded to the groups, manually counted the tumors and measured tumor volume. Mice were treated with either monotherapy or combination therapy. Drugs which were effective as single agents in initial analyses were studied in combinations. Dexamethasone (Dex), Dasatinib (Das), AV-412 tosylate (AV), FAK inhibitor 14 (FAK), IKK-16 (IKK), PF-03084014 (PF), KB-R7943 mesylate (KB), Nefopam (Nef), and Y26763 (Y267) were selected for therapy. AF tumors were also evaluated through immunohistochemistry (IHC) for markers of proliferation and apoptosis (KI67 and caspase).

Results: Gross tumor analysis from Apc+/Apc1638N mice has shown a significant decrease in tumor number with most combinations. We found that the following combinations significantly reduced tumor number or the volume in the APC1638N mice without adversely affecting the mouse: Dex + FAK, Dex + Das, Dex X Y267, Dex X AV, Dex X IKK, Das X FAK, Das X AV, Das X Y267, Das X PF, Das X KB, AV X FAK, AV X PF, AV X KB, AV X IKK, FAK X Y267, FAK X KB, FAK X IKK, IKK X PF, IKK + KB, PF + KB, KB + Nef, Y267 + Nef. IHC demonstrated increased caspase activity and decreased KI67 activity for the combination chemotherapy treatments.

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 appears to be effective treatment options, which may warrant further evaluation with clinical trials.

Poster #022 3256572

CRYOABLATION FOR DESMOID TUMORS: THE FRENCH NATIONWIDE CRYODESMO-01, CURRENT PRACTICE AND PERSPECTIVES

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Objective: Desmoid tumors (DT) are rare tumors (2-4 cases/million/year) that originate from musculoaponeurotic structures, and related so APC or beta-catenin gene alterations. Cryoablation is a promising interventional radiology technique that is suitable for DTpts. The procedure is based on repeated cycles of freezing/passive thawing of the tumor, leading to cell death. CRYODESMO-01 was a nationwide phase II study assessing cryoablation in advanced DT. Retrospective data for cryoablation in expert centers with long-term follow up are also available in patients treated before CRYODESMO, and provide useful data for further developement of the technique.

Methods: CRYODESMO-01 was the first prospective, open-label, non-randomized, non- comparative, multicentric pilot study assessing cryoablation in non-abdominopelvic DT pts progressing after two lines of treatment. The study was funded by the French National Cancer Institute and supported by the French Sarcoma Group and the SOS Desmoid pts advocacy group.The primary endpoint was the rate of non-progression at 12 months; secondary endpoints included safety, time to disease progression (TDP), quality of life (QoL), assessment of pain and functional status. Inclusion criteria were: pts 18 y.o., confirmed DT deemed accessible by the cryoablation operator , progressive disease after at least two lines of adequate medical therapy or with functional symptoms/pain, adequate biological parameters, informed consent and affiliation to social security. Data from CRYODESMO will be compared to a series of patients treated in an expert center to provide longer follow-uo experience and additional data, to support further development of cryoblation.

Results: 50 pts were enrolled from in 4 centers (78% female). The mean age was 41 y.o (range 19-73). Tumor location included limbs (36%); trunk (60%) and cervical area (4%). The median tumor volume was 111cm^3(range 0.6-1 068). The rate of non-progressing disease +12 months was 86% (CI95% 73%-94%). Grade 1 and 2 toxicity occured in 32.8 and 44.5% of cases, whereas 11 pts (22%) had grade 3 and 4 AEs, all with a favorable outcome. Overall, 63% and 83% of pts experienced an improvement in functional status (better utility) and pain scores, respectively. Data from our expert center reinforce the feasibility of cryoablation in large tumors, as well as DT of the extermities, showing functional benefit and strong reduction of analgesics intake, suggesting that a cure might be achievable with this innovative technique.

Conclusion: Cryoablation is feasible in progressive DT pts, and has a favorable safety profile. The primary endpoint of the study was met and coupled with expert centers retrospective experiencen support the future incorporation of cryoablation. Cryoablation will soon challenge medical therapy as front-line therapy in the forthcoming randomized trial (CRYODESMO-02).

Poster #023 3257659

CAN WAIT AND SEE BE THE STANDARD OF CARE FOR INITIAL APPROACH TO PRIMARY SPORADIC DESMOID TUMORS? PRELIMINARY DATA FROM MULTICENTER EUROPEAN PROSPECTIVE STUDIES

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[1]Fondazione IRCCS Istituto Tumori Milano, Milan, Italy; [2]IRCCS Istituto Candiolo, Candiolo, Italy; [3]Ospedale di Treviso, Treviso, Italy; [4]Erasmus MC Cancer Institute, Rotterdam, Netherlands

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

Methods: This study comes from the combination of 2 prospective European multicenter (Italian and Deutch centers) observational studies aimed at evaluating the progression rate in patients affected by primary SDT managed with a front-line conservative approach (W&S). β- catenin mutational status was analyzed.
Inclusion criteria were:
-Pathological diagnosis of SDT
-Primary disease at diagnosis or incompletely resected residual disease (R2 resection)
-Histological diagnosis confirmed by expert sarcoma pathologists according to the WHO criteria
-Measurable disease evaluated by on contrast-enhanced MRI (ce-MRI) T1 and T2 weighted images or contrast enhanced CT scan (for intra-abdominal location) or ultrasound

Patient and tumor-related factors, treatment variables, follow up findings, time to progression and status at last follow-up were recorded. Follow-up (FU) schedules were identical in the 2 studies and required clinical evaluation and ce-MRI (or CT scan or ultrasound) at 3, 6, 9, 12 months, then every 6 months until the third year. Upon progression (RECIST or not), defined as tumor growth proven by imaging and/or clinical examination, active treatments were proposed according to physician's preference and registered in the clinical database.

Results: Between 2013 and 2018 a total of 199 patients with CTNNB1 mutational status available (except one for which the analysis is pending) entered the study (81% female, 19% male); median age 39 (IQ, 33-48) years; sites distribution: abdominal wall (46%), trunk (27%), extremity (18%), intra-abdominal (3%), head/neck (6%). Median follow-up was 18 (IQ, 10-28) months. At the time of last follow up: 11/199 had spontaneous complete regression, 41/199 spontaneous partial regression, 86/199 stable disease, 61/199 progression. 31/71 patients started an active treatment for PD. The median time to an active treatment was 8 (IQ range, 5-13) months. A preliminary analysis on the correlation between β-catenin mutational status and outcome revealed that 9/26, 8/108, 2/25 and 4/39 patients with DT harboring 45F, 41A, WT or other mutations had to start an active treatment for progression, respectively. Ten patients required surgery after enrollment.

Conclusion: This study prospectively confirmed that W&S for primary SDT is safe in light of the high rate of regressions and spontaneous growth arrest. SDT have a favorable course in more than 60% of patients. A higher risk of worse outcome for patients harboring 45F was observed on the initial analysis but needs further validation on a longer FU. Upon progression, active treatments were considered on an individualized basis, while persisting in the W&S could still pay off.

Poster #024 3232140

ANLOTINIB, VINCRISTINE AND IRINOTECAN(AVI) FOR ADVANCED EWING SARCOMA AFTER FAILURE OF STANDARD MULTIMODAL THERAPY: A MULTICENTER, TWO - COHORT, PHASE IB/II TRIAL (NCT03416517)

Jie Xu[1]*; Wei Guo*[1]*; Lu Xie*[1]*; Xin Sun*[1]*; Kuisheng Liu*[1]*; Bingxin Zheng*[1]*; Tingting Ren*[1]*; Yi Huang*[1]*; Taiqiang Yan*[1]*; Xiaodong Tang*[1]*; Rongli Yang*[1]*; Jin Gu*[2]

[1]Peking University People's Hospital, Beijing, China; [2]Peking University Shougang Hospital, Beijing, China

Objective: Both protracted irinotecan and anti-angiogenesis therapy have shown promising results in Ewing sarcoma. We did this phase Ib/II trial to first define the proper dose of irinotecan in combination with anlotinib in Ewing sarcoma (phase Ib) and then evaluate efficacy (phase II).

Methods: Patients diagnosed with recurrent or refractory Ewing sarcoma were enrolled and sub-classified into cohort A (≥16y) or cohort B (<16y). In the dose-defining phase Ib portion, anlotinib was given at a fixed dose of 12mg $D_{1\text{-}14}$ every 21 days, while the de-escalated 3+3 design was used to detect the recommended dose of irinotecan in each cohortfrom an initial level of 20mg/m^2/d dx5x2. Recommended phase 2 dose (RP2D) was defined as the highest dose at which no more than 30% patients experience a DLT in the first two courses. In the next dose-expanding phase II portion, the primary endpoint was objective response rate at 12 weeks (ORR_{12w}). A conventional two-stage study design model was used.

Results: 41 patients were finally enrolled with 29 in cohort A and 12 in cohort B. For cohort A, first 5 patients were treated at initial level in phase Ib portion, two of whom subsequently experienced delayed diarrhea as dose-limiting toxicity (DLT). Additional six patients were then treated at a lower dose of 15mg/m^2. Since no more DLT was recorded, it was used as RP2D. 23/24 patients in cohort A phase II were available for response evaluation at 12 weeks, with one complete response (CR), 14 partial response (PR) (including two CMR who has a negative PET/CT scan but still abnormal lesions in MR scan), 2 stable disease (SD) and 6 progressive disease (PD). ORR_{12w} was 62.5%. For cohort B, no DLT was noticed in the first six patients treated at the initial level which was used as RP2D later. Finally, 12 patients were included in cohort B. ORR_{12w} was 83.3% with two CR, 8 PR (including two CMR) and two PD. Although effective, cohort B were closed because of slow enrollment. Most common grade 3/4 adverse events were leukopenia (28.5%), neutropenia (24.4%), anemia (8.7%) and diarrhea (3.7%). The genotype of UGT1A1*1 and UGT1A1*28 were not associated with the risk of diarrhea.

Conclusion: The combination of irinotecan and anlotinib demonstrated an acceptable toxicity profile with promising evidence of clinical efficacy in advanced Ewing sarcoma.

Result of phase Ib

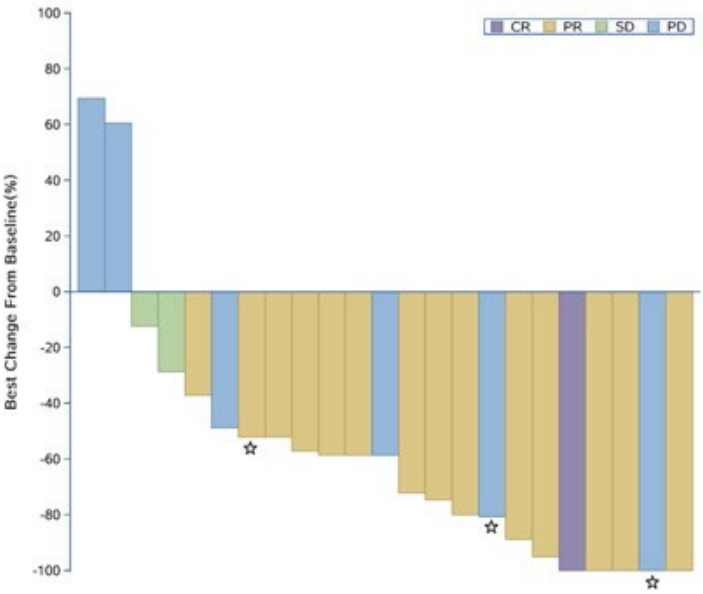
Cohort	Total number (DLT)		Recommended phase 2 dose
	Irinotecan level 0	Irinotecan level 1	
A	5 (2)	6 (0)	Level 1
B	6 (0)	-	Level 0

level 0 = 20 mg/m2/d; level 1= 15 mg/m2/d

Result of phase 2 portion

Cohort	CR (%)	PR (%)	SD (%)	PD (%)	NA	ORR at 12 weeks
A	1 (4.2%)	14 (58.3%)	2 (8.3%)	6 (25.0%)	1 (4.2%)	62.5%
B	2 (16.7%)	8 (66.7%)	0 (0%)	2 (16.7%)	0 (0%)	83.3%

CR, complete response; PR, partial response; SD, stable disease; PD, disease progression; NA, not available; ORR, objective response, ORR=CR+PR


CR
PR
SD
PD
Best Change From Baseline(%)
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60
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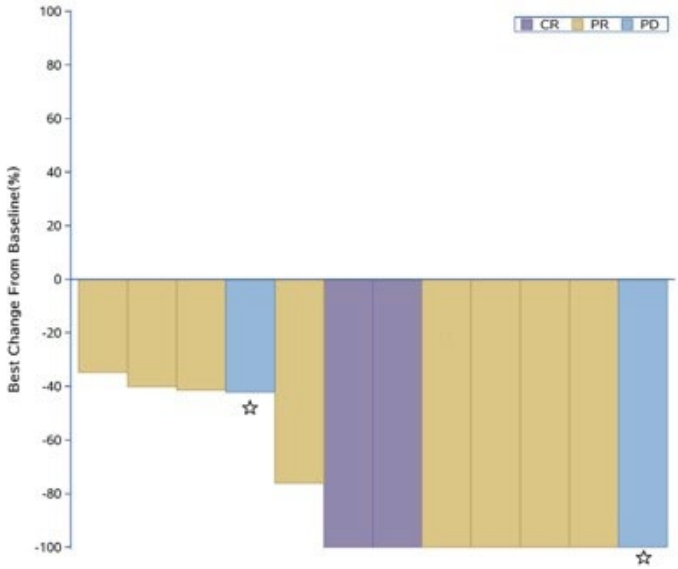
20
0
-20
-40
-60
-80
-100


CR
PR
PD
Best Change From Baseline(%)
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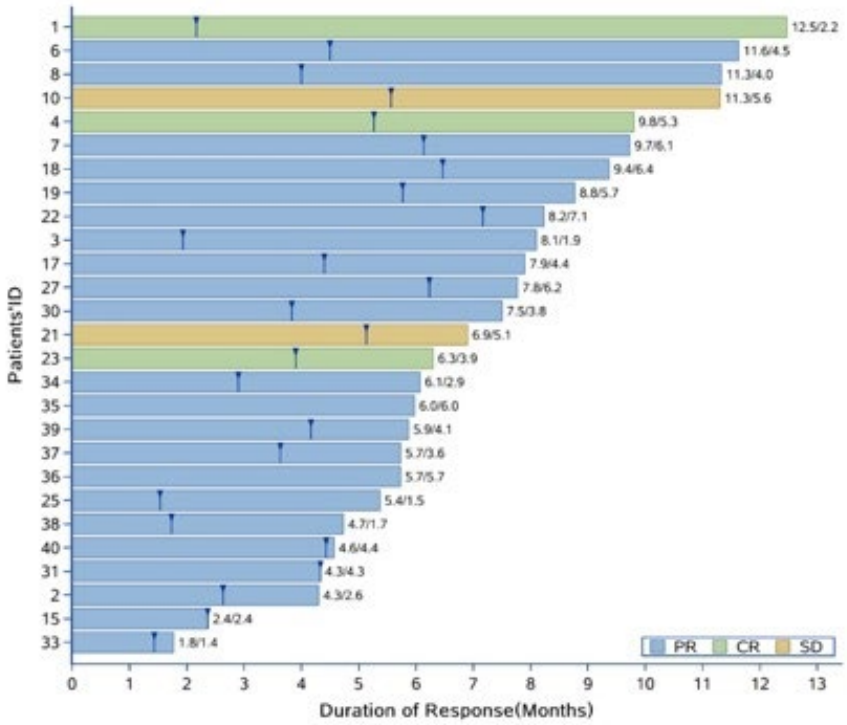
Patients'ID
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9.4/6.4
8.8/5.7
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8.1/1.9
7.9/4.4
7.8/6.2
7.5/3.8
6.9/5.1
6.3/3.9
6.1/2.9
6.0/6.0
5.9/4.1
5.7/3.6
5.7/5.7
5.4/1.5
4.7/1.7
4.6/4.4
4.3/4.3
4.3/2.6
2.4/2.4
1.8/1.4
PR
CR
SD
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12
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Duration of Response(Months)

Poster #025 3256530

TWO YEARS IN, WHAT HAVE WE LEARNED ABOUT *ATRX* MUTATION IN OSTEOSARCOMA? THEY INCREASE AGGRESSIVENESS THROUGH MULTIPLE MECHANISMS

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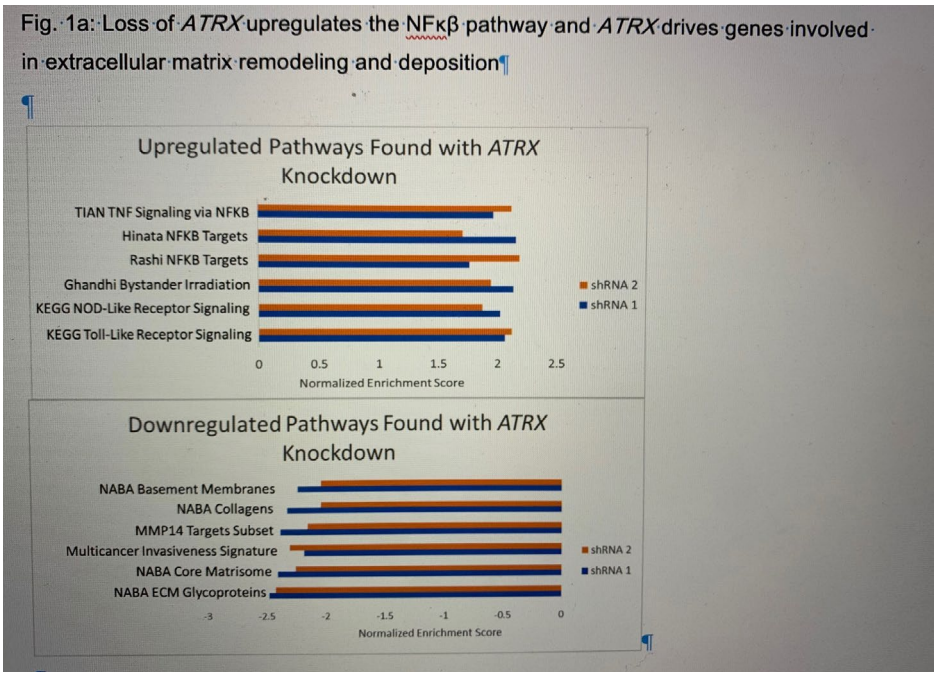
Duke University Medical Center, Durham, NC, USA

Objective: To understand how ATRX loss contributes to the aggressive features of osteosarcoma.

Methods: To better understand the mechanisms by which *ATRX* contributes to osteosarcoma (OS) aggressiveness, we used both *in vitro* and *in vivo* methods to examine changes in tumor initiation, growth and proliferation, and metastasis that correspond with loss of *ATRX* expression. Human 143B OS cells were stably transduced with non-silencing shRNA or one of two independent shRNA constructs for *ATRX* knockdown, and an ATRX knockout 143B cell line was generated using CRISPR-Cas9. *ATRX* knockdowns/knockouts were confirmed via qPCR, immunofluorescence, Sanger sequencing, and western blotting. CRISPR-Cas9 also was used to knock out *ATRX* in the human MG63 osteosarcoma cell line, and the wild-type or knock out MG63 cell lines were screened with 2,100 bioactive small molecule inhibitors to identify drugs for which *ATRX* loss of function led to increased drug efficacy. Additionally, an *Osterix-Cre* driven genetically engineered mouse model of OS was developed to examine tumor development in mice with loss of *Rb* and *p53* compared to loss of *Rb*, *p53*, and *ATRX*. Control and *ATRX* knockdown/knockout cells were injected subcutaneously in SCID-beige mice, and tumor growth rates were compared. In parallel, RNA-Seq was performed on the *ATRX* knockdown cell lines.

Results: *In vitro*, whole transcriptomic profiling of the *ATRX* knockdown cell lines by RNA-Seq showed significant upregulation of the NF-κβ pathway, which has been shown to play a role in cancer cell proliferation, decreased apoptosis, and increased angiogenesis (Fig 1a). Unexpectedly, this sequencing showed significant downregulation of several extracellular matrix pathways, supporting a role for *ATRX* in matrix remodeling and invasion (Fig 1a). Consistent with this data, a drug screen of 2,100 bioactive small molecule inhibitors showed significant sensitization of the *ATRX* knockout to an integrin inhibitor (Fig 1b). Interestingly, integrins are known key interactors with extracellular matrix components, a previously unknown domain to be influenced by *ATRX*. In the genetically engineered mouse model, *ATRX* loss correlated with increased tumor initiation relative to wild-type *ATRX* expression (Fig 2a). In the immunodeficient mouse model, *ATRX* shRNA knockdown and CRISPR knockout of the 143B human OS cells resulted in enhanced growth and more robust local invasion of the xenograft tumors established in these mice (Fig 2b).

Conclusion: Our results support the conclusion that decreased *ATRX* expression in OS is associated with more aggressive tumors that exhibiting enhanced initiation, proliferation, and invasion. Results from both RNA-Seq and the bioactive drug screen support altered extracellular matrix remodeling, which may suggest a change in invasive properties of OS cells with *ATRX* expression loss. In the future, we plan to use both *in vitro* and *in vivo* methods to further explore these underlying mechanisms and test the integrin-inhibitor as a potential new therapeutic for OS tumors with loss of *ATRX* expression.



¶Fig. 1b: Drug screen finds *ATRX* loss sensitizes OS cells to integrin-inhibitor; ¶confirmed with IC50 assays¶

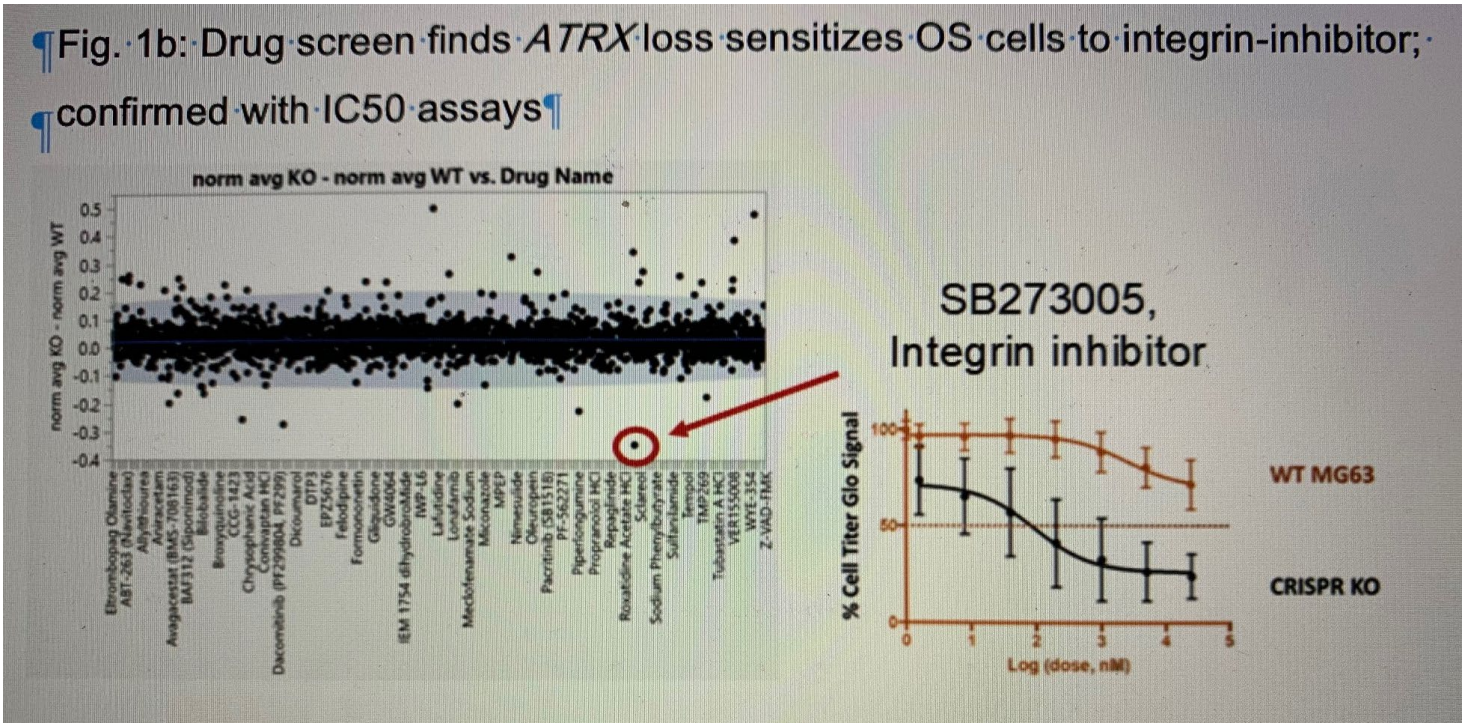


Fig 2a: In an *Osterix-Cre* driven genetically engineered mouse model of OS, *ATRX* loss correlated with increased tumor initiation relative to wild-type *ATRX* expression.

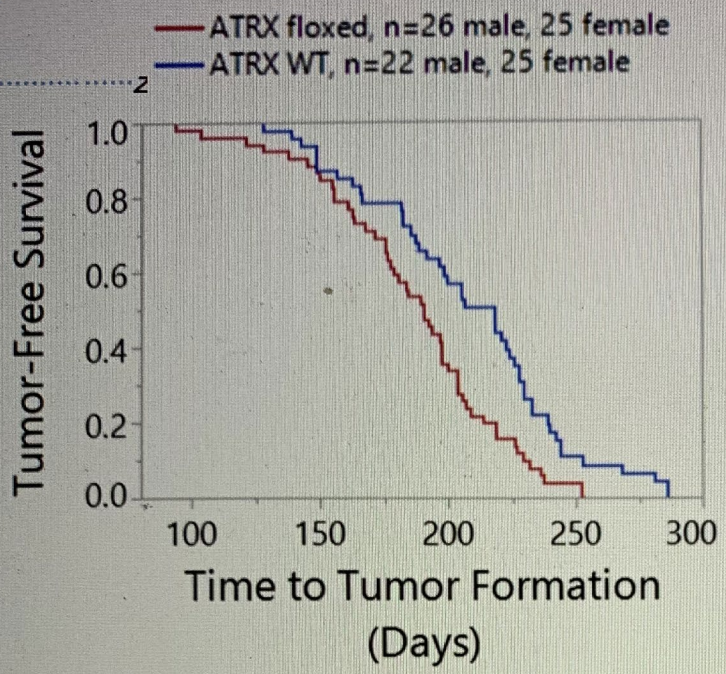
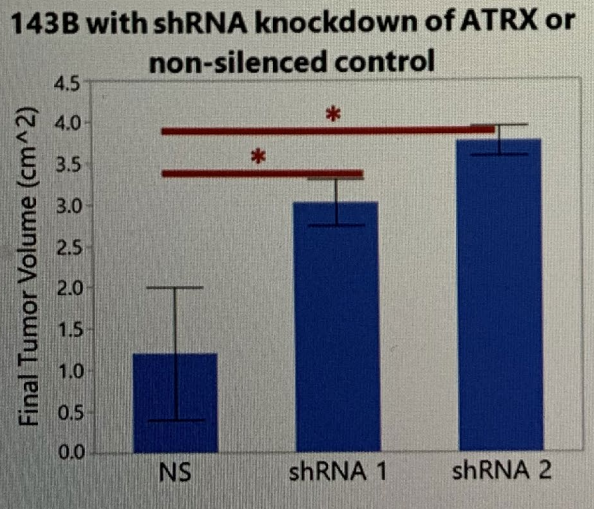
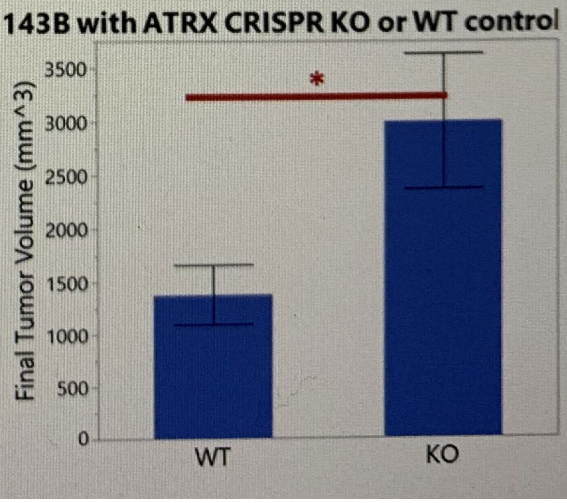


Fig 2b: *ATRX* shRNA knockdown and CRISPR knockout in the 143B human OS cell line enhanced growth and local invasion of established xenograft tumors.





Poster #026 3254140

MONOCLONAL ANTIBODY BLOCKADE OF SEMA4-PLXNB2 AXONAL GUIDANCE SIGNALING REDUCES TUMOR PROGRESSION AND METASTASIS IN ANIMAL MODELS OF OSTEOSARCOMA

Branden Smeester[1]*; Kelsie Becklin*[1]*; Garrett Draper*[1]*; Emily Pomeroy*[1]*; Nicholas Slipek*[1]*; Joseph Peterson*[1]*; Eric Rahrmann*[2]*; Margaret Crosby*[1]*; Branden Moriarity*[1]

[1]*University of Minnesota, Minneapolis, MN, USA;* [2]*University of Cambridge, Cambridge, United Kingdom*

Objective: Osteosarcoma (OSA) is the most common primary malignant bone tumor, usually occurring in children and adolescents. Derived from mesenchymal origins in the pre-osteoblastic lineage, OSAs arise from the failure of osteoblasts to differentiate into mature bone-building cells. OSAs are commonly typified by their heterogeneity, genomic instability, and frequency of systemic metastasis primarily to the lungs. Lack of effective therapeutic options across individual patients with metastatic disease is the number one problem plaguing the OSA research field and curative treatmentsare desperately needed. Semaphorins are a family of membrane-bound and soluble proteins that modulate a whole host of normal cellular functions including differentiation, cytoskeletal rearrangement, and motility. Semaphorins, specifically type IV, are important regulators of axonal guidance and have been increasingly implicated in poor prognoses for a variety of solid tumor types including breast, ovarian, and colorectal cancers. Type IV Semaphorins have been shown to function through their cognate PLXNB family receptors to mediate oncogenic functions necessary for tumor development and malignant spread. Recently, a new pathway has been identified using the *Sleeping Beauty* (SB) mutagenesis system in mice which implicated the SEMA4-PLXNB2 axonal guidance signaling network as a major driver of tumorigenesis in a subset of OSA cases. This work seeks to build upon our previous work that contributed to a Phase 1/2 Trial of VX15/2503 in pediatric patients with relapsed or refractory solid tumors at the University of Minnesota (see NCT03320330).

Methods: The complex signaling of SEMA4-PLXNB2 members was functionally, mechanistically, and therapeutically evaluated through a series of *in vitro* and *in vivo* assays. Knockdown of key pathway members was achieved through transient pooled siRNA technology. Functional validation of these effects was carried out using MTS proliferation, transwell migration, and colony formation assays. Downstream mechanistic studies and cell cycle analysis were conducted in siRNA-silenced heterogeneous cell populations. Cell lines harboring inducible shRNA vectors targeting SEMA4-PLXNB2 members were examined in orthotopic mouse models of OSA for their potential anti-tumor effect. We also conducted studies utilizing therapeutic antibody blockade in cultured cell lines and evaluated response in similar orthotopic *in vivo* models.

Results: Here, we present novel preclinical data on targeting the SEMA4-PLXNB2 signaling axis in OSA. Our results suggest targeting this axis is therapeutically advantageous in the treatment of metastatic OSA. Our studies demonstrate 1) a novel heterodimeric interaction between PLXNB2 and oncogenic RTK MET, which has never been reported, 2) reductions in cellular proliferation, colony formation, and migration when members of this axis were genetically targeted, 3) downregulation of ERK and AKT pathways and cell cycle arrest associated with knockdown of pathway members and lastly 4) genetic and therapeutic antibody blockade studies in *in vivo* orthotopic OSA mouse models demonstrating tumor-reducing capabilities and less metastatic burden. Excitingly, many of these results are also mirrored in analogous studies in other types of sarcomas such as rhabdomyosarcoma, Ewing's sarcoma, and malignant peripheral nerve sheath tumors (MPNSTs) extending further support for the importance of this signaling network in pan sarcomas.

Conclusion: Together, our results support further preclinical exploration of the SEMA4-PLXNB2 signaling axis and a strong basis for a phase I/II clinical consideration of antibody blockade of PLXNB2 for the treatment of OSA.

Poster #027 3220213

PRECLINICAL TESTING OF A NOVEL TARGETED TRAIL THERAPEUTIC FOR DEDIFFERENTIATED CHONDROSARCOMA

Zakareya Gamie[1]*; Martin Siegemund*[2]*; Craig Gerrand*[4]*; Anja Krippner-Heidenreich*[3]*; Roland Kontermann*[2]*; Kenneth Rankin*[1]

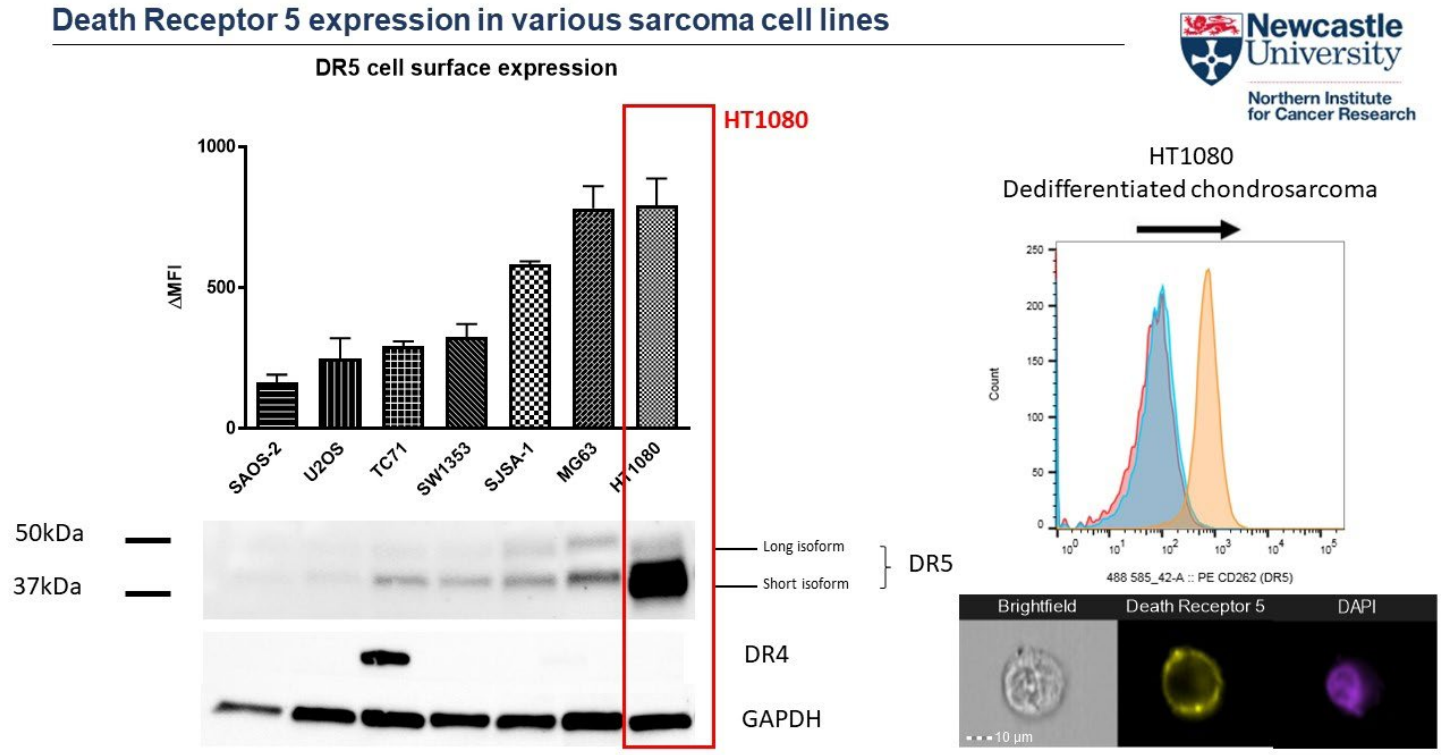
[1]*Northern Institute for Cancer Research, Newcastle University, Newcastle upon Tyne, United Kingdom;*
[2]*University of Stuttgart, Stuttgard, Germany;* [3]*Prinses Máxima Center for Pediatric Oncology, Utrecht, Netherlands;*
[4]*The Royal National Orthopaedic Hospital, Stanmore, United Kingdom*

Objective: TNF-related apoptosis-inducing ligand (TRAIL) can induce apoptosis in cancer cells after binding to its Death Receptors (DRs) while sparing non-malignant cells. TRAIL provides an approach that can potentially overcome drug resistance and toxicity associated with high doses, when administered alone or combined with conventional therapies. Enhancing the cytotoxic effect of TRAIL involves targeting a Tumour Associated Antigen (TAA). We aimed to characterise bone sarcoma cells for DR expression and to assess *in vitro* and *in vivo* the effectiveness of a novel TRAIL construct engineered to target a TAA we have identified.

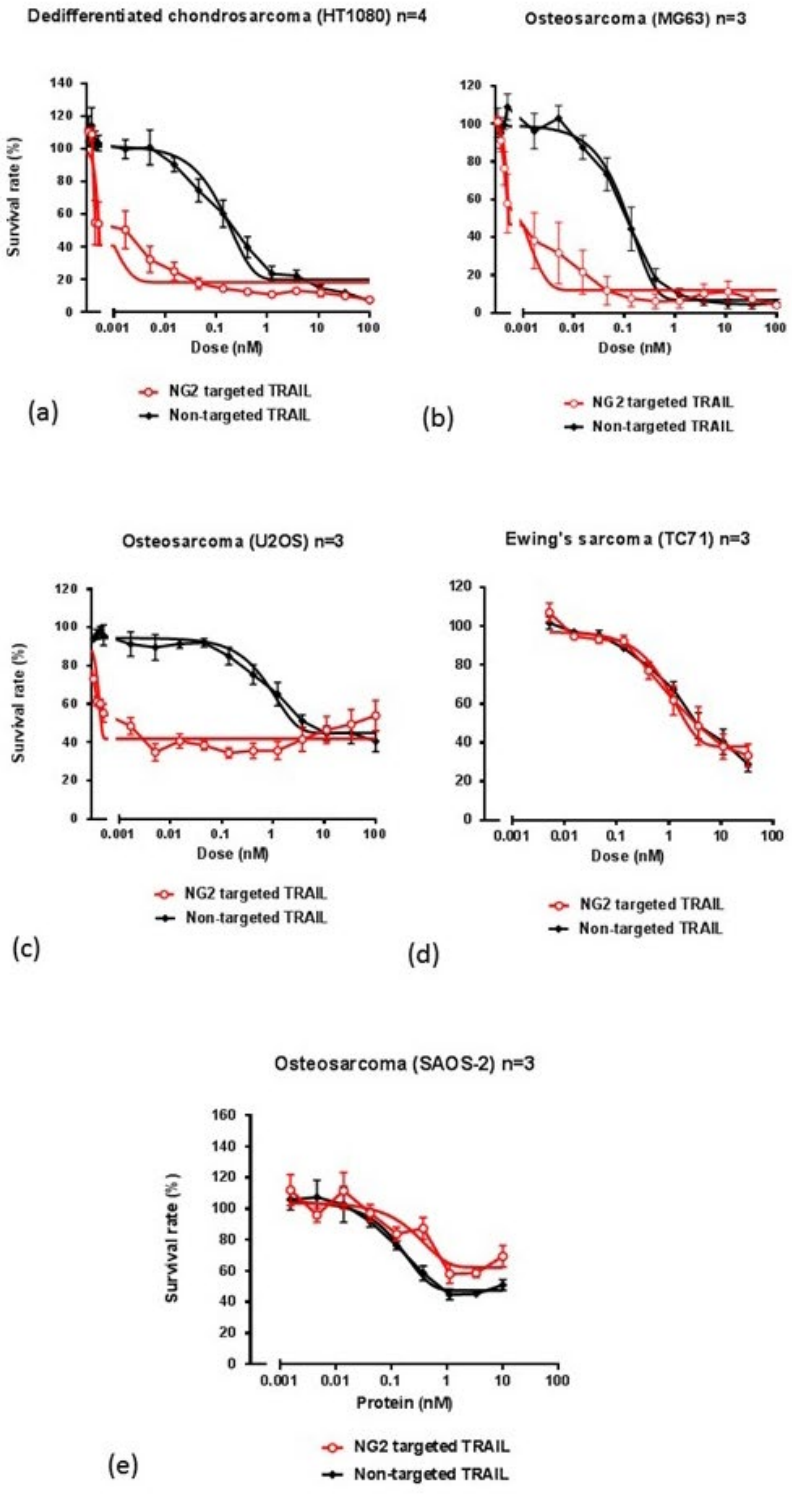
Methods: Bone sarcoma cell lines were characterised for DR and TAA expression at RNA and protein levels. Together with non-malignant cell lines, they were exposed to the novel TRAIL therapeutic *in vitro* and tested *in vivo* in a xenograft model of dedifferentiated chondrosarcoma.

Results: Surface DR5 was expressed in all the cell lines (Very high: HT1080, MG63; moderate: SW153, U2OS, TC71) (Image 1). The TAA was also expressed (Very high: SW1353, MG63; moderate: U2OS, HT1080). The novel TRAIL therapeutic demonstrated enhanced cytotoxicity in DR5 and the TAA expressing cell lines (MG63>HT1080>U2OS) (Image 2), increased further with doxorubicin. Similar results were demonstrated *in vivo* when engrafting the HT1080 cell line in a dedifferentiated chondrsarcoma mouse model (Image 3).

Conclusion: The novel TRAIL therapeutic tested has a significant cytotoxic effect on cell lines expressing both DR5 and the TAA of interest, which can be enhanced further with doxorubicin. Such combinations would minimise the risk of treatment failure due to drug resistance, a commonly observed problem of single agent approaches.

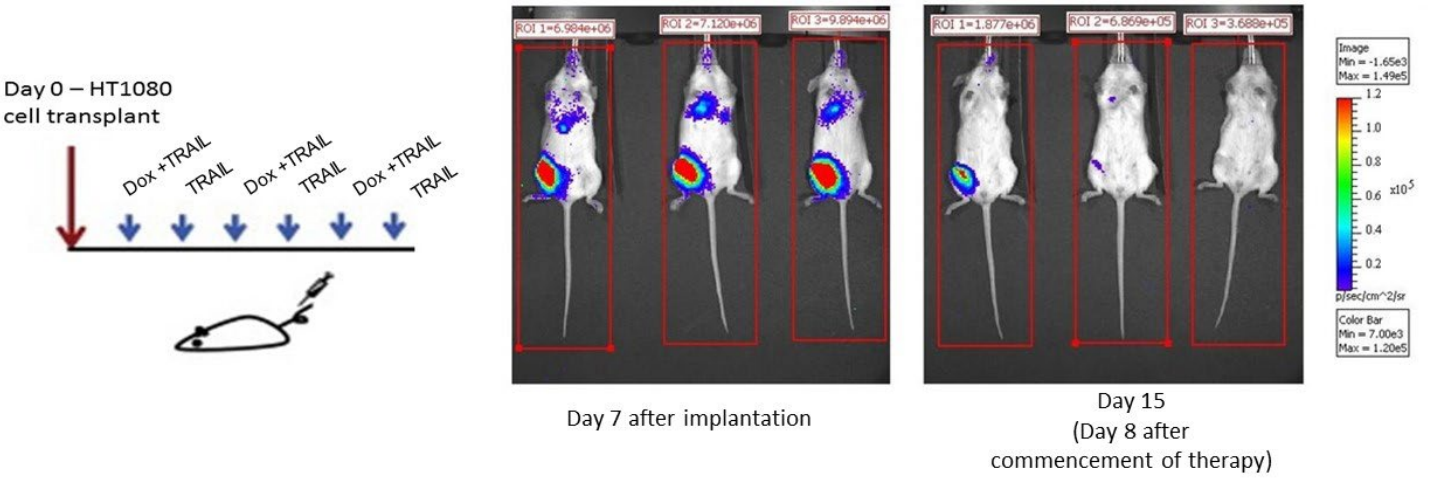


DR5 expression in bone sarcoma cell lines. The HT1080 dedifferentiated chondrosarcoma cell line expresses very high levels.



Bone sarcoma cell lines that express both NG2 and DR5, (a) HT1080, (b) MG63 and (c) U2OS are sensitive to the NG2 targeted TRAIL (scFvNG2(9.2.27)-IgG1Fc-scTRAIL). The TC71 Ewing's sarcoma line (d) and SAOS-2 osteosarcoma cell line (e) are negative for NG2 and therefore has the same response to the targeted TRAIL as the non-targeted TRAIL (mean +/-SEM, n=3).

Bone sarcoma cell lines expressing DR5 and the TAA are more responsive to targeted TRAIL.



Day 7 after implantation

Day 15
(Day 8 after
commencement of therapy)

HT1080 dedifferentiated chondrosarcoma mouse model and response to targeted TRAIL with doxorubicin.

Poster #028 3224408

PEMBROLIZUMAB IN ADVANCED OSTEOSARCOMA: RESULTS OF A SINGLE-ARM, OPEN-LABEL PHASE 2 TRIAL

Boye Kjetil, MD, PhD[1]*; Alessandra Longhi*[2]*; Tormod Guren*[1]*; Stine Næss*[1]*; Michela Pierini*[2]*; Ingeborg Taksdal*[3]*; Ingvild Lobmaier*[4]*; Marilena Cesari*[2]*; Anna Paioli*[2]*; Elisabetta Setola*[2]*; Ivar Hompland*[1]*; Kirsten Sundby Hall*[1]*; Emanuela Palmerini*[2]

[1]Department of Oncology, Oslo University Hospital, Oslo, Norway; [2]IRCCS Istituto Ortopedico Rizzoli, Bologna, Italy; [3]Department of Radiology, Oslo University Hospital, Oslo, Norway; [4]Department of Pathology, Oslo University Hospital, Oslo, Norway

Objective: To evaluate the activity and safety of the PD-1 antibody pembrolizumab in patients with advanced osteosarcoma.

Methods: We have performed a single-arm, open-label, phase 2 trial in patients with unresectable osteosarcoma with disease relapse or progression after at least one line of systemic treatment. Patients received pembrolizumab 200 mg intravenously every 3 weeks. The primary endpoint was clinical benefit rate (CBR) at 18 weeks of treatment, defined as complete response (CR), partial response (PR) or stable disease (SD) at week 18, according to RECIST version 1.1. The trial had a Simon's two-stage design, and ≥3 of 12 patients with CR, PR or SD in stage 1 were required to proceed to stage 2. The trial is registered with ClinicalTrials.gov, number NCT03013127.

Results: Between May 31, 2017 and Sept 27, 2019, 12 patients were enrolled, six at Oslo University Hospital in Oslo, Norway and six at Rizzoli Orthopedic Institute in Bologna, Italy. The median number of cycles of pembrolizumab administered was 2 (range 1-6). No patients had clinical benefit at 18 weeks of treatment, and patient enrollment was thus stopped after completion of stage 1. Nine patients (75 %) had PD before week 18, two patients discontinued study treatment due to clinical progression without confirmed PD and one died of disease progression prior to radiological evaluation. Estimated median progression-free survival was 1.7 months (95% CI 1.2 to 2.2). At time of data cut-off, seven patients were dead, all from osteosarcoma. After an estimated median survival follow-up of 10.0 months, median overall survival was 6.6 months (95% CI 4.2 to 9.0). Grade 3 or 4 adverse events occurred in seven of 12 patients (58 %), and included anemia (two patients), and hypoxia, increased alkaline phosphatase, medulla compression, pneumothorax and tumor-related pain (all one patient each). No treatment-related deaths or drug-related grade 3 or 4 adverse events were observed.

Conclusion: In this single-arm, open-label, phase 2 study in advanced osteosarcoma, pembrolizumab did not show any clinically meaningful activity.

Poster #029 3241057

PHASE I COMBINATION DOSE-FINDING/PHASE 2 EXPANSION COHORTS OF LENVATINIB + ETOPOSIDE + IFOSFAMIDE IN PATIENTS AGED 2 TO ≤25 YEARS WITH RELAPSED/REFRACTORY OSTEOSARCOMA

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Objective: Lenvatinib (LEN) is a multikinase inhibitor of vascular endothelial growth factor (VEGF) receptors 1–3 and other targets. We report data from phase 1b dose-finding and phase 2 expansion cohorts of LEN + etoposide + ifosfamide in patients with relapsed/refractory osteosarcoma.

Methods: Patients were aged 2 to ≤25 years with relapsed/refractory osteosarcoma and <2 prior VEGF-targeted therapies. The phase 1b starting dose was LEN 11 mg/m^2/day + ifosfamide 3000 mg/m^2 + etoposide 100 mg/m^2 daily/3 days. On determination of the recommended phase 2 dose (RPh2D) of LEN + chemo, patients were enrolled into the phase 2 expansion cohort. Primary end points: phase 1b, RPh2D; phase 2, 4 months' progression-free survival (PFS-4).

Results: In the phase 1b dose-finding cohort (n=22), patients received LEN 11 mg/m^2 (n=7) and 14 mg/m^2 (n=15) + chemo. Dose-limiting toxicities were: grade 4 thrombocytopenia (n=1; LEN 11 mg/m^2), grade 4 thrombocytopenia and grade 3 epistaxis (n=1; LEN 14 mg/m^2), grade 2 oral dysesthesia, grade 3 muscle spasm, and grade 2 back pain (n=1; LEN 14 mg/m^2). RPh2D was LEN 14 mg/m^2 + chemo. In the expansion cohort (n=20), the median number of LEN cycles received was 4 (range: 1–7). As reported in the database, the most frequent treatment-emergent adverse events (TEAEs) were platelet count decreased/thrombocytopenia (50%/30%), neutropenia/neutrophil count decreased (45%/25%), anemia (45%), nausea (40%), alanine aminotransferase level increased, diarrhea, and white blood cell count decreased (30% each). Most frequent grade ≥3 TEAEs were neutropenia/neutrophil count decreased (45%/25%), platelet count decreased/thrombocytopenia (40%/20%), white blood cell count decreased (30%), and anemia (25%). Pneumothorax was observed in the dose-finding cohort (n=6) and expansion cohort (n=1); 2 (dose-finding cohort) were ≥ grade 3; and 1 was post-thoracotomy. In the dose-finding cohort, 4 patients discontinued treatment due to TEAEs. There were no treatment-related fatal serious AEs. In the dose-finding combination cohort, 12/18 evaluable patients (66.7%) achieved PFS-4. In the phase 2 expansion cohort, 5/8 evaluable patients (62.5%) achieved PFS-4.

Conclusion: The combination of RPh2D LEN (14 mg/m^2) + chemo had a manageable safety profile with promising preliminary evidence of efficacy.

Poster #030 3241713

IDENTIFICATION OF NOVEL THERAPEUTIC TARGETS FOR METASTATIC OSTEOSARCOMA

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Objective: Osteosarcoma (OS) is the most common primary bone malignancy and predominantly affects children and adolescents. One third of patients develop lung metastasis (LM), which portends a poor prognosis with survival rates of less than 30%. OS mortality has remained unchanged for 30 years, which is largely attributable to a poor understanding of the mechanisms of metastatic spread. We aimed to identify OS-specific gene alterations with a focus on those that drive LM in a genetic comparison of primary and metastatic human tissue.

Methods: Patients with OS treated surgically at our institution between 2000 and 2017 were identified and archived samples from primary and metastatic tumors were obtained. Chart review was performed to evaluate the clinical characteristics of each patient. Eighteen samples from 14 patients passed quality control and were included in the transcriptomic analyses, including seven samples from primary tumors in patients that never developed LM, four samples from primary tumors in patients that did develop LM, and seven LM samples. RNA was extracted from FFPE samples and total RNA library preparation was performed, followed by sequencing on an Illumina NextSeq 500. Greater than 50 million, 150 bp paired-end reads were generated for each sequenced tumor. RNA transcript abundance was quantified and normalized from paired-end FASTQ files and then mapped to hg38 build via Salmon algorithm. Differential gene expression was calculated by correlating Salmon gene-level counts with the effective lengths of target transcripts between the primary tumors and LM via DESeq statistical software. Ingenuity Pathway Analysis (Qiagen) was utilized for prediction of upstream regulators and to determine pathways that were significantly enriched or lost in LM.

Results: Patient characteristics were reviewed and are illustrated in Table 1. Eight of the 14 patients were male. In this cohort, male patients exhibited more aggressive disease: all patients who died and all who developed LM were male. Heat map and principal component analysis both demonstrated notable clustering of distinct genes in primary tumors and LM (Figure 1). In LM, we observed clear, defined clusters of upregulated genes not found in primary tumors. Pathway analysis revealed upregulation of 55 genes involved in cell motility and migration in the LM samples. Gene network reconstruction predicted androgen receptor (AR) as an upstream regulator of some of the most highly upregulated genes in LM (Figure 2).

Conclusion: We observed a male predominance in our cohort which is characteristic of OS. Additionally, we observed a more aggressive phenotype in male patients. Genetic comparison of primary tumors and LM demonstrated notable upregulation of many genes in LM. In two patient-matched pairs, we observed that primary tumors from different patients exhibited more similarities than the primaries shared with their own LM. This supports the hypothesis that significant genetic changes occur during the metastatic process and may be prime targets for new therapies. Additionally, for the first time, upregulation of the AR pathway was identified in metastatic tissue. This novel finding is particularly promising in the context of OS. This disease affects males more often than females at a rate of 1.5:1 and usually occurs during adolescence, when androgen activity is highest. Future studies will validate the genetic targets identified here in tissue microarray using frozen patient samples from our biobank. AR can be easily targeted with FDA-approved inhibitors and tested *in vitro* and *in vivo*. As such, identification of AR pathway upregulation in human LM tissue samples may provide a target for novel therapeutics for patients resistant to conventional chemotherapy.

Patient Demographics

SAMPLE ID	AGE AT DIAGNOSIS	GENDER	LIVING STATUS	SAMPLE TYPE	CELLULARITY
OS-01-LM1	15	Male	Deceased	lung met	50%
OS-01-LM2	15	Male	Deceased	lung met	50%
OS-02-LM	5	Male	Alive	lung met	90%
OS-04-R(M)	14	Male	Alive	primary (met'd)	90%
OS-05-LM	16	Male	Deceased	lung met	60%
OS-06-LM	17	Male	Deceased	lung met	60%
OS-10-LM	17	Male	Deceased	lung met	90%
OS-10-R(M)	17	Male	Deceased	primary (met'd)	60%
OS-14-R(L)	9	Female	Alive	primary	60%
OS-15-R(L)	15	Female	Alive	primary	90%
OS-17-B(M)	14	Male	Deceased	biopsy (met'd)	20%
OS-17-LM	14	Male	Deceased	lung met	80%
OS-17-R(M)	14	Male	Deceased	primary (met'd)	80%
OS-25-R(L)	15	Female	Alive	primary	70%
OS-27-B(L)	15	Female	Alive	biopsy	60%
OS-28-R(L)	16	Female	Alive	primary	40%
OS-38-B(L)	38	Female	Alive	biopsy	60%
OS-40-B(L)	13	Male	Alive	biopsy	50%

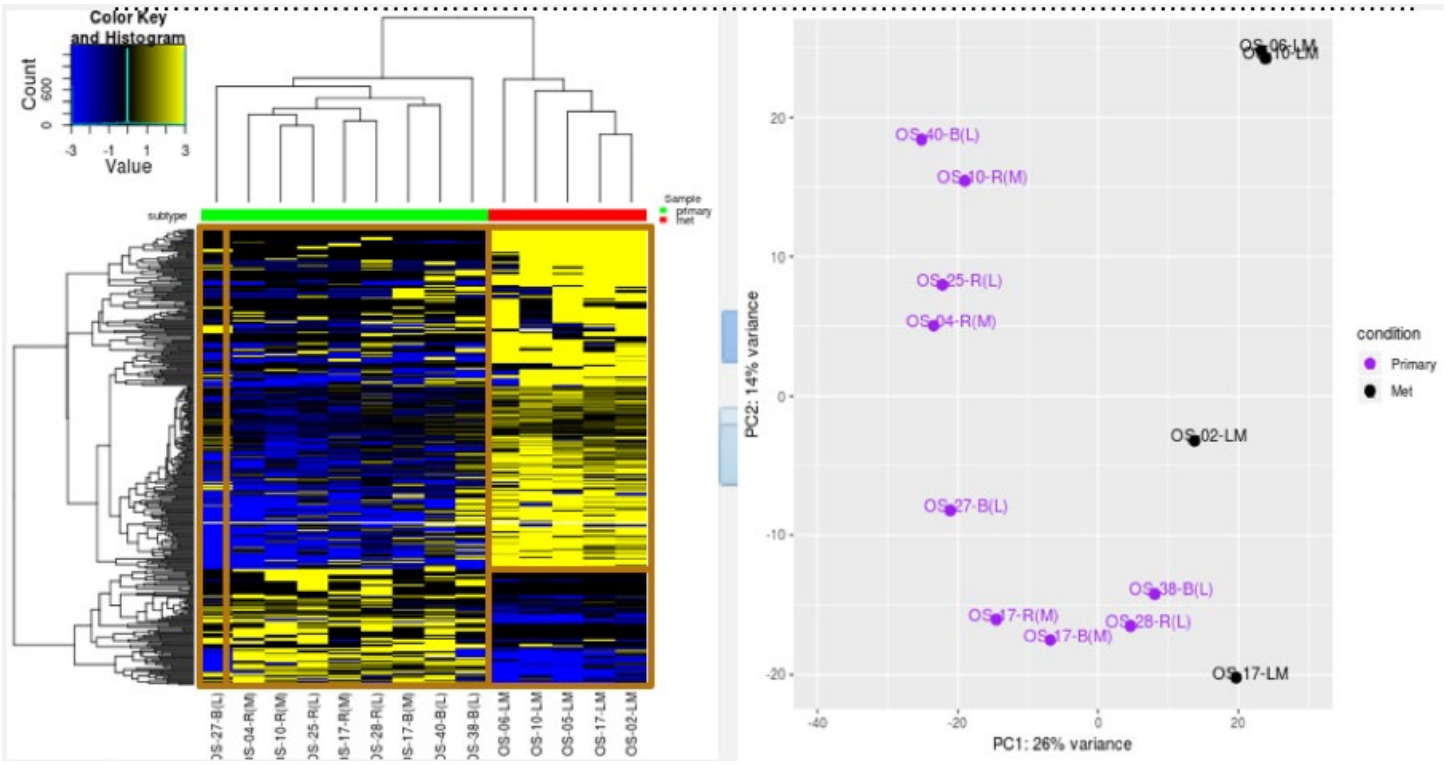

Figure 1. A heat map (left) and principal component analysis (right) were generated to compare all primary tumors to all lung metastases. The heat map demonstrates that LM, below the red bar, exhibit defined clusters of upregulated genes. Principal component analysis also demonstrates distinct clustering of LM samples (black) and primary tumor samples (purple).

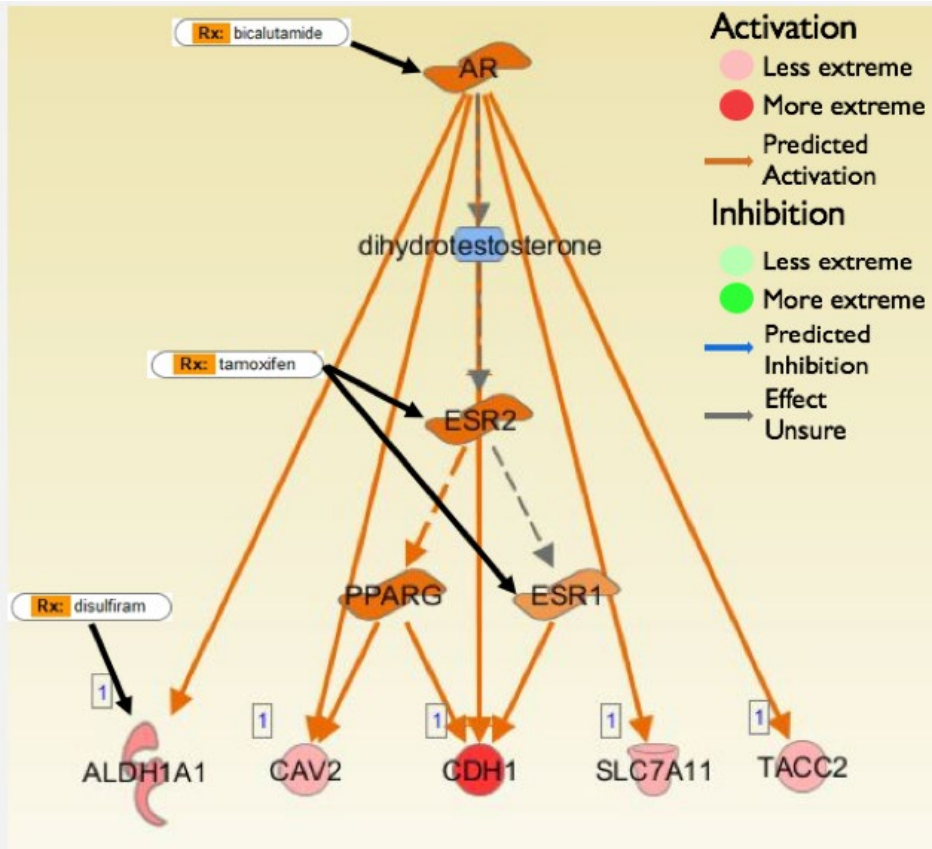

Figure 2. Several genes downstream of AR were found to be significantly upregulated in LM tissue compared to primary tumors, including aldehyde dehydrogenase (ALDH) and estrogen receptor (ER). AR, ALDH, and ER can all be targeted by known, FDA-approved drugs, as indicated here.

Poster #031 3245110

CLINICAL UTILITY OF BRCANESS TESTING OF PEDIATRIC OSTEOSARCOMA PATIENTS AT DIFFERENT STAGES OF THE DISEASE

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Objective: The finding of BRCAness in osteosarcoma is a prime example of how the use of mathematical abstraction can provide new rationales for individualized treatment strategies. Here, we aim to provide the basis for poly-ADP-ribose polymerase inhibitor treatment in osteosarcoma patients by determining when exactly BRCAness occurs during cancer evolution, whether linear or branching models better explain the acquisition of BRCA-like traits and how bottlenecks of chemotherapy and metastatic spread affect BRCAness prevalence.

Methods: We analyzed exomes and genomes of 13 time-series comprising tissue of chemotherapy-naïve osteosarcoma biopsies and/or resection specimens, locally recurring tumors and metastases. Signatures of mutation processes were interrogated from sequencing data and were reconciled with clonal maps and phylogenetic trees, thus building and evolutionary history of each tumor. Where possible, we searched for evidence of selection on mutation that could be therapeutically exploited and used molecular clock signatures to estimate timing of the occurrence of individual cancer cell clones.

Results: BRCAness was detected in at least one specimen in 8/13 patients with osteosarcoma. In three patients, BRCAness occurred after an early branching event had shattered an ancestral cancer cell population into highly-rearranged fast-growing clones that formed the primary tumor, whilst slow-growing BRCAness-negative cells evolved independently and clinically manifested years later. More commonly, however, BRCAness was present in a subpopulation of cancer cells that were closely related to the main clone and must have developed through late branching. Whenever these cells pass conventional chemotherapy and resection bottlenecks, the composition and frequencies of different cancer clones change, and BRCAness-positive cancer cells occasionally become the major clone in recurring tumors. Rarely, we observed an evolution of a BRCAness-positive clone through a genome catastrophy in a population of cancer cell was genetically stable for years.

Conclusion: Our data underline the need for more individualized treatment approaches in osteosarcoma. We provide insight into how different evolutionary trajectories impact the clonal composition of tumors over time. More importantly, we provide a rationale for poly-ADP-ribose polymerase inhibition in patients with osteosarcoma provided that up-to-date sampling and integrative genomic analysis is available.

Poster #032 3253025

ABCA6 AND ABCA7 ARE NOVEL BIOMARKERS OF PROGNOSIS IN EWING SARCOMA: ROLE OF INTRACELLULAR LEVELS OF CHOLESTEROL

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Objective: The molecular mechanisms of drug resistance in Ewing sarcoma are still poorly defined. Here we focus our attention on still poorly understood members of ABC transporters in order to highlight their role as potential biomarkers of risk and response. Therapy of Ewing sarcoma is still entrapped with the use of high-dose conventional chemotherapeutic agents and the definition of validated biomarkers is required to offer a more personalized treatments to patients who are in most of the cases children and adolescents.

Methods: Patients with localized Ewing sarcoma who were enrolled in prospective neoadjuvant studies and treated at the Rizzoli Institute were included in the present analysis. Based on biobank availability and after tissue and quality control checks a total of 130 primary tumors were studied by qPCR to evaluate ABC expression (27 as training set; 103 as validation set). Correlations with survival were performed according to log-rank test and Kaplan-Meier curves. Cox proportional hazards model using stepwise selection was used for multivariate analysis. Cell lines derived from human tumors or patient-derived xenografts were used for functional studies. Parameters of in vitro malignancy such as proliferation/survival/migration tests, spheroid formation, chemosensitivity to drugs used in the treatment of patients were considered. ChIP analysis was used to evaluate mechanisms of ABCA6/7 transcriptional regulation. The impact of cholesterol was analyzed by: 1. using Filipin III, a fluorescent dye staining membrane bound cholesterol specifically; 2. exposing cells to exogenous cholesterol or to subtoxic doses of the cholesterol-lowering drugs, such as simvastatin.

Results: High Expression of ABCA6 and ABCA7 transporters in primary tumors predicts favorable outcome of Ewing sarcoma patient. In patients with high expression of ABCA6 or ABCA7, adverse events occurred in 13 of 51 (25.5%) or 9 of 51 (17.6%), while in patients with low expression of ABCA6 or ABCA7 they occurred in 28 of 52 (53.8%) or 24 of 52 (46.2%), respectively ($P = 0.0002$ for ABCA6; $P = 0.04$ for ABCA7; Fisher's exact test). Expression levels of ABCA6 correlate with those of ABCA7 in our series of samples (Spearman 's test $r= 0.42$; $P < 0.0001$). Cox proportional hazard regression analysis confirmed the low expression of both the transporters as independent risk factor of poor outcomes (HR = 6.927; 95% CI = 1.542-31.108; $P = 0.012$ for EFS (HR = 5.437; 95% CI = 1.174-25.183; $P = 0.030$ for OS). Expression of ABCA6 and ABCA7 is regulated at transcriptional level by FOXO1/3 or p53 respectively. Expression of ABCA6 and ABCA7 influences malignancy and chemo-sensitivity of Ewing sarcoma cell lines through imbalanced distribution and enhanced cell efflux of cholesterol.

Conclusion: We described for the first time the impact of a series of ABCA6 and ABCA7 transporters on the prognosis of Ewing sarcoma. Overexpression of the two transporters is associated to better outcome, likely linked to their role in cholesterol and lipid efflux. Our data provide the rationale for using cholesterol lowering drugs in association with conventional treatments.

Poster #033 3253251

UPFRONT SURGERY FOLLOWED BY ADJUVANT CHEMOTHERAPY MAY IMPROVE METASTASIS-FREE SURVIVAL OF PATIENTS WITH STAGE IIB OSTEOSARCOMA OF EXTREMITY

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Objective: Despite numerous chemotherapy trials, survival of patients with localized osteosarcoma has not improved. We hypothesized upfront surgery before the tumor shows chemo-resistance may minimize the number of resistant cells, thereby, improve survival. To test our assumption, we performed a cohort study.

Methods: We investigated whether (1) surgical timing is a viable prognostic factor of survival in localized extremity osteosarcomas, (2) survival and local recurrence (LR) rate differed between patients with similar preoperative characteristics who undergo upfront and delayed surgeries, (3) metastasis pattern and response to treatment differed between case and control groups. *Patients and Methods* In 710 localized extremity osteosarcomas, we analyzed whether surgical timing is a prognostic factors of survival (597 delayed- and 113 upfront surgery). In the subgroup analysis, we selected 226 of 597 patients as control group matched in terms of age, initial tumor size, and tumor location. We compared survival and LR rates between two groups.

Results: The 113 patients with upfront surgery showed better 10-year overall survival than the 597 patients with delayed surgery ($p=0.0002$). In the cohort study, poor surgical margin ($p<0.0001$) and delayed surgery ($p<0.0001$) predicted poor survival. In the subgroup analysis, upfront case group showed better 10-year metastasis-free survival than the delayed surgery group ($p=0.003$). Upfront surgery group showed a LR rate of 5.3% which was lower than the 13% in the delayed surgery group ($p=0.03$). The response to metastasis treatment between two groups showed difference. Overall, 56 % (15/27) of patients in case and 28% (28/99) of patients in the control group showed no evidence of disease after metastasis treatment ($p = 0.01$).

Conclusion: By reviving the old treatment principle, we confirmed a survival gain. Immediate surgery is worth trying to break through the stagnant survival status in osteosarcoma.

Poster #034 3254188

SINGLE-CELL TRANSCRIPTOMIC ANALYSES OF MUTANT IDH1 GROWTH PLATE CHONDROCYTES REVEAL DISTINCT CELL POPULATIONS

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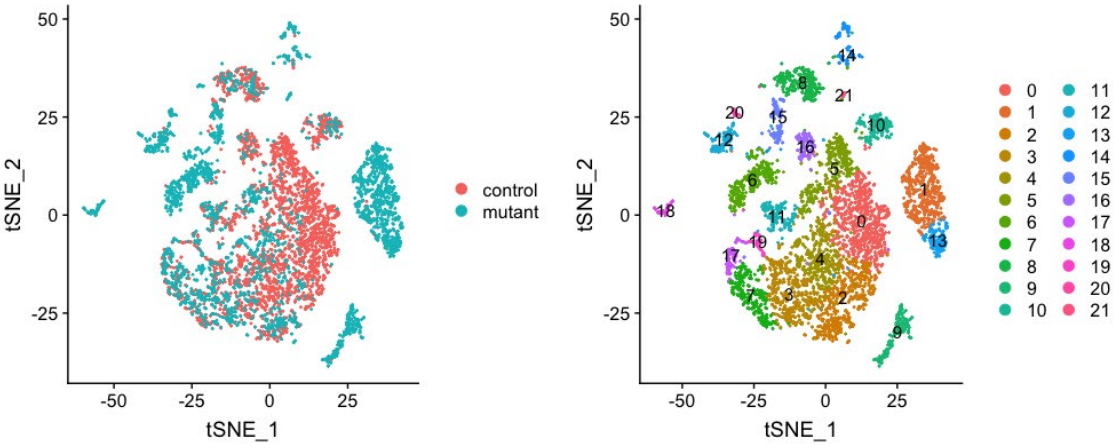
Objective: To understand the cellular and molecular changes in chondrocytes from *Idh1/2*-mutant enchondroma and chondrosarcoma, we examined the transcriptomic profiles caused by *Idh1*-mutation in our mouse model using single-cell RNA sequencing approach.

Methods: Mouse Strains:
All animals were used according to the approved protocol by the Institutional Animal Care and Use Committee of Duke University. Col2a1-Cre transgenic mice (*Ovchinnikov et al*, *2000*) and Idh1 KI mice carrying point mutation at amino acid 132 from R to Q, Idh1R132Q (Hirata et al, 2014). All mice were bred under specific-pathogen-free conditions. Col2a1-Cre males were crossed with Idh1R132Q flox/flox females to obtain Col2a1-Cre(+ve);Idh1R132Q flox/+ and Col2a1-Cre(-ve);Idh1R132Q flox/+ as controls. Embryonic development was defined based on the date of vaginal plug formation as embryonic day (E) 0.5.
Growth plate chondrocytes isolation, flow cytometry, and cell sorting:
E18.5 embryos were collected from the uterus and washed with PBS. Femur growth plate cells from both limbs were dissociated using the protocol described in *Mirando et al, 2014*. Cell suspensions were centrifuged at 1000 rpm for 5 min and then resuspended in flow staining buffer sorted cells live cells which were subjected to single-cell preparation.
scRNA library preparation and sequencing:
Approximately, 10,000 cells were loaded on the 10x Genomics Chromium Controller Single-Cell Instrument (10x Genomics) mixed with reverse transcription reagents along with gel beads and oil to generate single-cell gel bead in emulsions (GEMs). GEM-RT was performed. After RT, GEMs were broken and the single-strand cDNA was purified with DynaBeads MyOne Silane Beads. cDNA was amplified. Amplified cDNA product was purified with the SPRIselect Reagent Kit. Indexed sequencing libraries were constructed using the reagents in the Chromium Single-Cell 3' Library Kit, following these steps: (1) fragmentation, end repair and A-tailing; (2) SPRIselect cleanup; (3) adapter ligation; (4) post-ligation cleanup with SPRIselect; (5) sample index PCR; (6) Post-indexPCR cleanup. The barcoded sequencing libraries were quantified by quantitative PCR (cat#KK4824, KAPA Biosystems Library Quantification Kit for Illumina platforms). Sequencing libraries were transferred to the Duke University Center for Genomic and Computational Biology (GCB) and were loaded on a Novaseq 6000 (Illumina) for sequencing. The primary analytical pipeline for the SC analysis followed the recommended protocols from 10X Genomics. The 10X Cell Ranger output matrix file was analyzed by Seurat R package.

Results: In our analyses, we identified total of 21 cell populations for the mutant and control chondrocytes. Among them, our data show that there were some overlapping cell populations between Idh1-mutant and Idh1-wildtype chondrocytes. These cells express markers of endochondral ossification. Importantly, there were 9 distinct cell populations specific for the Idh1-mutant group, but no groups were specific for the Idh1-wildtype. The distinct cell population lack the transcriptomic makers for normal endochondral ossification suggesting that the Idh1-mutant specific populations cells may fail to undergo normal chondrocyte differentiation and may be important in tumorigenesis.

Conclusion: Mutant *Idh1* chondrocytes have distinct cell populations which lacks the expression of chondrocyte differentiation markers suggesting that these cell populations may play a role in tumorigenesis. This data will allow us to further characterize the molecular and cellular changes that occur in IDH1 mutated enchondroma and chondrosarcoma patients and will aid in developing new therapeutic inventions.



Number of cells for each cluster

Cluster	control	mutant
0	761	40
1	6	565
2	420	136
3	291	213
4	324	124
5	291	80
6	14	346
7	149	167
8	217	89
9	5	232
10	159	45
11	119	79
12	8	70
13	0	164
14	14	133
15	37	109
16	106	20
17	53	55
18	0	76
19	32	20
20	0	36
21	0	21
	3006	2820

Poster #035 3254196

IMPACT OF LIMB SALVAGE VERSUS AMPUTATION ON OVERALL SURVIVAL IN PATIENTS WITH OSTEOSARCOMA OF THE EXTREMITIES

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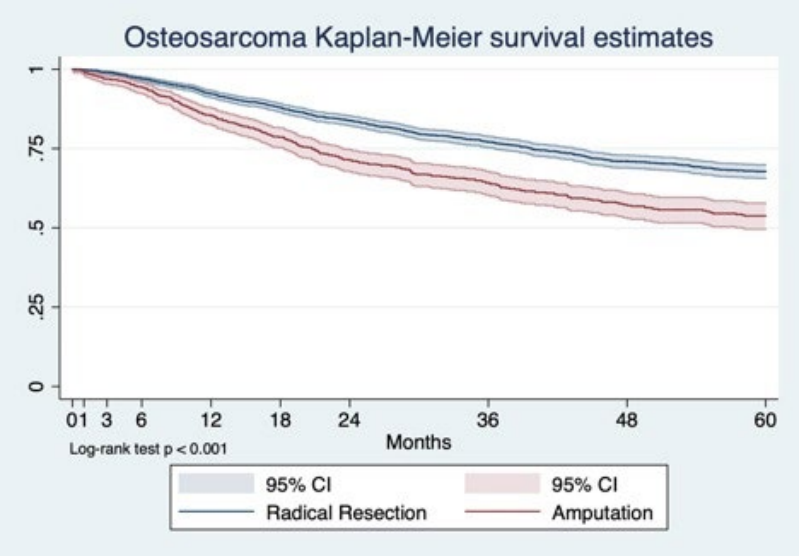
Objective: For decades, amputation was the mainstay of surgical treatment for osteosarcoma of the extremities. With advances in surgical technique and the advent of an osteosarcoma chemotherapy regimen, limb salvage replaced amputation as the dominant treatment paradigm. However, as the disease is uncommon, study sizes have been limited and there have been no large scale, broadly multi-institutional studies presenting the impact of type of surgical resection on overall survival in osteosarcoma. We investigated the largest registry of primary localized osteosarcoma, the national cancer database (NCDB). Our goal was to identify the impact of amputation versus limb salvage on overall survival in a large database of OS patients in the United States.

Methods: We retrospectively analyzed patients in the NCDB from 2004 through 2015. Patients were included who had localized high grade osteosarcoma; we defined two cohorts characterized by patients receiving radical resection vs. amputation. Unadjusted overall survival (OS) was estimated using the Kaplan Meier method, with statistical comparisons based on the log-rank test. A Cox proportional hazard model was used to estimate the association between demographic, pathologic, and treatment variables and OS after adjustment for known covariates. A propensity matched analysis was then performed to control for significant differences between the study cohorts.

Results: We identified 3421 patients presenting with primary localized high-grade osteosarcoma. The patient cohort had a median age of 17 (IQR 13 -30); 2,046 (59.8%) of the patients were males. Average tumor size was reported as 11.48 cm (11.11 – 11.84cm) with metastases present in 489 (14.3%) of the patients. Of these patients, 2634 patients underwent a radical resection while 787 patients underwent an amputation. In a univariate analysis, there were six significant differences between the two cohorts with respect to patient demographics. With respect to tumor and treatment characteristics, there were seven significant differences. Demographic factors predictive of receiving limb salvage were: being younger, female, insured, or being from a higher SES zip code. Pathological factors associated with receiving limb salvage were having smaller tumor sizes, no metastases, upper limb, long bone, or lower AJCC stage osteosarcoma. The hazard ratio of 5 year survival when comparing amputation to radical resection was 1.67 ($p<0.001$). After controlling for potentially confounding factors, limb salvage still conferred a significant survival benefit over amputation (HR: 0.70; $p<0.001$). This survival benefit remained significant after propensity matched analysis of all significantly different demographic, pathologic, and treatment variables (HR: 0.72; $p=0.002$).

Conclusion: This is the largest patient cohort to date examining the impact of limb salvage compared to amputation in osteosarcoma. Limb salvage confers a significant survival benefit over amputation, even when controlling for potentially confounding variables and differences between cohorts. Age, sex, insurance status, SES, tumor size, metastases, location, and stage were predictive of receiving limb salvage surgery; sex, age, tumor size, metastases, comorbidities, surgical margins, stage, chemotherapy, and order of treatment sequence were predictive of a poorer outcome with limb salvage. Further studies are necessary to help define appropriate use of limb salvage.



5 year survival of limb salvage surgery vs. amputation for patients undergoing resection of high grade osteosarcoma of the extremities

Poster #036 3254674

FEASABILITY AND PREDICTIVE VALUE OF FUNCTIONAL PRECISION MEDICINE APPROACH FOR BONE SARCOMAS

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Objective: Bone sarcomas represent a rare and heterogenous group of tumours including osteosarcoma (OS), Ewing sarcoma (EW) and chondrosarcoma. Extensive chemotherapy combined with surgery and radiotherapy are used for most bone sarcomas but once spread the diagnosis is diasmal and there is great need of more individualized therapies for this disease mainly affecting young individuals.

Methods: To meet this medical need we set up a functional precision medicine approach in which potential treatments can be identified based on drug sensitivity testing and genomic profile on sarcoma cells derived from patients with refractiry sarcomas. We recently reported that this system approach can predict patient response to treatment and we identified cSrc inhibitors as active drugs in translocation-sarcomas.

Results: We have now investigated 12 bone sarcomas, 6 psteosarcomas, 5 Ewing sarcomas and 1 grade 3 chondrosarcoma. Patient derived bone sarcomas were curlutred and screened against a library of 525 drugs (both approved and non-approved).

Most patients, some heavily treated, had metastatic disease at the time of drug testing. in general, these patients presented poor total responses to cenventional treatment. However, in vitro we could identify cSrc (such as Dasatinib), ALK inhibitors and tyrosine kinase inhibitors (such as Pazopanib) as potentially active drugs in some of the patients with OS.

Conclusion: Conventional chemotherapy agents like taxanes, vincristine and vinorelbine were found to be active in both OS and ES cells, mirroring current treatment approach for these tumors. Moreover, in 3 cases of ES, the PARP-inhibitor Talazoparib showed activity on tumor cells.

Our study shows that functional assays on patient-derived bone sarcoma cells cultured in vitro are feasible models with potential predictive value and a tool to identify effective drugs in bone sarcoma patients with otherwise few treatment options

Poster #037 3256261

PHASE II TRIAL OF GEMCITABINE AND NAB-PACLITAXEL IN PATIENTS WITH RECURRENT EWING SARCOMA: A REPORT FROM THE NATIONAL PEDIATRIC CANCER FOUNDAITON

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Objective: The combination of gemcitabine and docetaxel has shown modest response rates in patients with recurrent bone sarcoma. Nab-paclitaxel may have less myelosuppression than docetaxel, and preclinical studies in pediatric sarcoma models have demonstrated activity as a single agent or in combination with gemcitabine. Therefore, we performed a phase II trial of gemctiabine and nab-paclitaxel in patients with recurrent Ewing sarcoma, using a single-arm, two-stage design to identify a response rate of $\geq$ 35%. An initial cohort would be expanded to 18 if confirmed responses were seen in at least 2 of the first 11 patients.

Methods: Patients received nab-paclitaxel 125 mg/m^2 over 30 minutes followed by gemcitabine 1000 mg/m^2 over 90 minutes on days 1, 8, and 15 of a 4-week cycle, according to the schedule approved for pancreatic cancer. Myeloid growth factor was used in 8 patients. Responses were assessed by RECIST version 1.1 and required confirmation on follow-up studies.

Results: Eleven patients with measurable disease were enrolled, with median age of 22 years (range 14-27). The median number of prior chemotherapy regimens was 3 (range 1-7). Thirty-five cycles were administered (median 2, range 1-8). Only one patient had a confirmed partial response on subsequent imaging, while two others initially had partial responses but subsequently withdrew because of hematologic toxicity or further progression before confirmation. The prominent toxicity was myelosuppression. Four (36%) of the 11 patients were removed from protocol therapy when significant neutropenia and/or thrombocytopenia occurred despite using myeloid growth factor and reducing doses of gemcitabine and nab-paclitaxel to 675 mg/m^2 and 100 mg/m^2, respectively. Immunohistochemical assessment of putative biomarkers for response to gemcitabine (hEENT-1) and nab-paclitaxel (SPARC, CAV-1) in archival tumor tissue was not predictive of clinical benefit in this small study.

Conclusion: In this heavily pretreated group of patients with recurrent Ewing sarcoma, the combination of gemcitabine and nab-paclitaxel had considerable hematologic toxicity and did not meet the primary objective of achieveing a 35% objective response rate. The confirmed response rate of 9% was similar to previous multi-institutional studies of gemcitabine and docetaxel. Additional radiomic and circulating tumor correlates are being analyzed. Further study of this combination is ongoing for patients with relapsed/refractory osteosarcoma and soft tissue sarcoma.

Poster #038 3256472

REDUCED BARD1 EXPRESSION ENHANCES PARP INHIBITOR-MEDIATED INCREASES IN PD-L1 EXPRESSION IN EWING SARCOMA

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Objective: Ewing sarcoma is a pediatric bone tumor predominately affecting adolescents. Relapsed Ewing sarcoma is nearly uniformly fatal and new treatment options are needed. We recently identified a Ewing sarcoma patient with a pathogenic, paternally inherited germline mutation in *BARD1*(BRCA1-associated RING domain-1). BARD1 is a homologous DNA repair protein recruited to double stranded breaks via its BRCT domain in a poly(ADP-ribose) polymerase (PARP)-dependent manner. BARD1 can complex with the Ewing fusion oncoprotein EWS-FLI1. We hypothesized that Ewing tumor cells with deficient BARD1 would display increased sensitivity to PARP inhibition. As single agent PARP inhibition has not demonstrated significant clinical benefit in relapsed Ewing sarcoma to date, we also questioned whether reduced BARD1 expression could enhance Ewing tumor cell response to treatment with combinatorial PARP/immunotherapy treatment approaches.

Methods: Patient-derived tumor organoids and monolayers (PSaRC-318) were established from a viably cryofrozen metastatic lung lesion from a patient with Ewing sarcoma and a germline*BARD1*mutation. Sensitivity of PSaRC-318 to the PARP inhibitors olaparib and talazoparib was established by performing IncuCyte apoptosis assays. The role of BARD1 in PARP sensitivity was tested in multiple Ewing cells lines using *BARD1*siRNA. PD-L1 expression was examined using RT-PCR, western and flow cytometry. T-cell/tumor cell co-cultures and tumor-primed T-cells were established. T-cell induced tumor cell apoptosis was monitored in real-time using IncuCyte caspase and annexin assays.

Results: PSaRC-318 organoids demonstrate sensitivity to PARP inhibitors olaparib and talazoparib. Treatment of PARP inhibitor-resistant Ewing cell lines with *BARD1*siRNA rendered cells sensitive to PARP inhibition. Ewing tumor cells that are sensitive to PARP inhibition were found to upregulate tumor cell surface expression of the checkpoint protein PD-L1 in response to treatment with PARP inhibitors. Ewing tumor cells were pre-treated with PARP inhibitors and then co-cultured with tumor-primed T-cells. PD-1 blocking antibody added to T-cell/tumor cell co-cultures resulted in an increase in early tumor cell death compared to IgG controls.

Conclusion: Reduced BARD1 expression enhances Ewing tumor cell sensitivity to PARP inhibitors and subsequently results in increased cell surface PD-L1 expression. PD-1 blocking antibody enhanced T-cell mediated apoptosis in Ewing cells pre-treated with PARP inhibitors. Ewing tumors with germline mutations in DNA-damage repair proteins, such as *BARD1*, may be susceptible to PARP inhibitor/anti-PD-1 combinatorial therapy.

Poster #039 3254462

AOST1321, A PHASE 2 TRIAL OF RANKL ANTIBODY, DENOSUMAB, IN 2 COHORTS OF PATIENTS WITH RECURRENT OR REFRACTORY OSTEOSARCOMA: A REPORT FROM THE CHILDREN'S ONCOLOGY GROUP

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Objective: The Children's Oncology Group (COG) Bone Tumor Committee has prioritized phase 2 trials of new agents in recurrent osteosarcoma in order to identify novel therapies with potential activity. These trials have osteosarcoma-specific endpoints based on benchmarks for event free survival (EFS) derived from historical COG clinical trial data for both measureable and completely resected disease. Denosumab is a fully human monoclonal antibody to the receptor activator of nuclearfactor-κB ligand (RANKL). Orthotopic and genetically engineered mouse models demonstrate a role for RANK-RANKL signaling in osteosarcoma. The primary objective of this phase 2 trial was to determine if EFS in patients with recurrent osteosarcoma treated with denosumab exceeded the historical COG benchmarks.

Methods: This was a prospective single arm, open-label, phase 2 trial of RANKL antibody, denosumab, in recurrent osteosarcoma. Skeletally mature patients age 11-49 years old with recurrent osteosarcoma were eligible. Patients with measurable disease according to RECIST 1.1 were eligible for cohort 1 and patients who had undergone complete surgical resection of all sites of recurrent disease were eligible for cohort 2. All patients received denosumab 120 mg subcutaneously every 4 weeks with additional loading doses on days 8 and 15 of cycle 1. Up to 26 cycles were administered along with calcium and vitamin D. The primary endpoint was complete or partial response by RECIST or remaining event-free for 4 months after enrollment for cohort 1. The primary endpoint for cohort 2 was event-free rate at 12 months. In both cohorts, the historical COG experience was utilized as a benchmark for the event-free rate. Secondary objectives included EFS, objective response rate, pharmacokinetics, pharmacodynamics and tolerability of denosumab.

Results: 59 patients enrolled between 11/2015 and 7/2017. One patient withdrew prior to the start of protocol therapy and was inevaluable and two patients were determined to be ineligible. 16 patients in cohort 1 and 40 in cohort 2 were eligible and evaluable for response. The most common grade 3 or greater adverse events were hypocalcemia and hypophosphatemia, and these were most frequently seen in cycle 1 (8% and 11% respectively). One patient experienced delayed hypercalcemia 7 months after discontinuing denosumab. In cohort 1 (measurable), 1 of 15 eligible patients was event-free at 4 months and there were no confirmed objective responses. In cohort 2 (resected), 10 of 38 eligible patients were event-free at 12 months. In neither cohort did the event-free rate exceed the historical COG experience to meet the study defined efficacy criteria.

Conclusion: Accrual of patients with recurrent / refractory osteosarcoma to this single arm phase 2 trial conducted by the COG was brisk. Denosumab was well tolerated with expected side effects but had insufficient activity for further development in recurrent / refractory osteosarcoma. The relationship between RANK and RANKL expression and disease control is being explored. Additional pharmacokinetic and pharmacodynamic data are being analyzed.

Poster #040 3242742

EWS-FLI1 MODULATED ALTERNATIVE SPLICING OF ARID1A REVEALS NOVEL ONCOGENIC FUNCTION THROUGH THE BAF COMPLEX

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Objective: Connections between epigenetic reprogramming and transcription or splicing create novel mechanistic connections that can be targeted with tailored therapies. Multiple subunits of the chromatin remodeling BAF complex, including ARID1A, play a role in oncogenesis, either as tumor suppressors or oncogenes. Recent work demonstrated that EWS-FLI1, the oncogenic driver of Ewing sarcoma (ES), plays a role in chromatin regulation through interactions with the BAF complex. However, the specific BAF subunits that interact with EWS-FLI1 and the precise role of the BAF complex in ES oncogenesis remain unknown. In addition to regulating transcription, EWS-FLI1 also alters the splicing of many mRNA isoforms, but the role of splicing modulation in ES oncogenesis is not well understood. We report a novel feed-forward mechanism describing how EWS-FLI1 – BAF complex interactions contribute to ES oncogenesis and growth.

Methods: Our methods include mass spectroscopy identification of proteins that interact with EWS-FLI1. We also use RNA-seq splicing analysis. We have applied a novel and functional ATPase assay to measure the hydrolysis to ADP in protein complexes. In vitro transcription/translation allows us to determine specific binding regions of ARID1A to EWS-FLI1. Oncogenesis assays are performed in native human mesenchymal stem cells. Transcription profiles were determined using RT-PCR.

Results: Our data indicates that EWS-FLI1 modulates the splicing of the BAF complex protein ARID1A to produce the ARID1A-L isoform in ES cells. We also show that EWS-FLI1 directly binds to the region of ARID1A-L protein that is maintained in the oncogenic isoform. We find that BRG1 ATPase activity is maintained in this complex, indicating that the EWS-FLI1-induced ARID1A isoform remains functional in the BAF complex. We identify ARID1A-L as an EWS-FLI1 regulated isoform required for ES growth that integrates EWS-FLI1 into a functional BAF complex. We also show a novel dependence of EWS-FLI1 on ARID1A-L for mutual protein presence in ES and human mesenchymal stem cells. We also show that the presence of ARID1A-L enhances the transcriptional profile as well as oncogenic transformation by EWS-FLI1.

Conclusion: Our results provide new insights into EWS-FLI1 mechanism that utilizes alternative splicing leading to BAF complex involvement in ES oncogenesis and growth.This mechanism involves both the role of EWS-FLI1 in alternative splicing and interactions with the BAF complex that lead to ES maintenance. We have identified a direct connection between the EWS-FLI1 protein and a splice variant of *ARID1A*, *ARID1A-L*. We demonstrate here that *ARID1A-L* is critical for ES maintenance and supports oncogenic transformation. We further report a novel feed-forward cycle where EWS-FLI1 leads to preferential splicing of *ARID1A-L* and *ARID1A-L* then facilitates ES growth as well as EWS-FLI1 protein stability. Dissecting this interaction may lead to improved cancer-specific drug targeting.

Poster #041 3253291

THE ROLE OF R0 RESECTION IN INTERMEDIATE AND HIGH-GRADE OSTEOSARCOMA OF THE PELVIS

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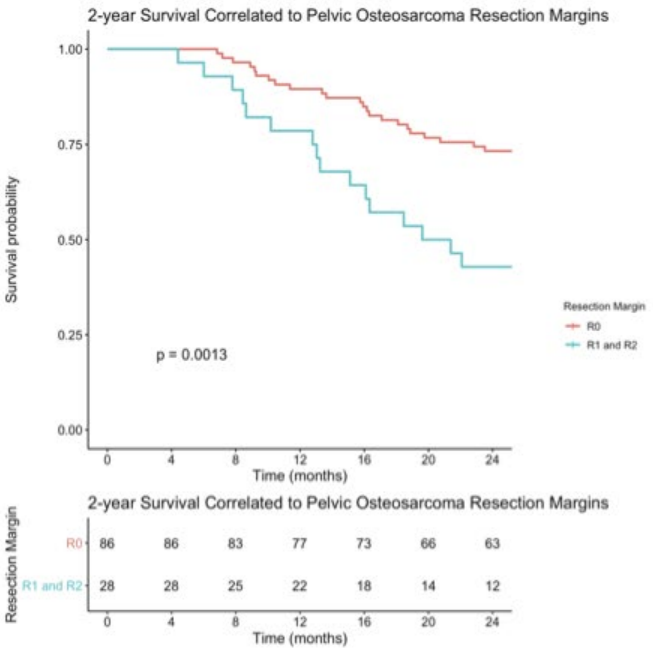
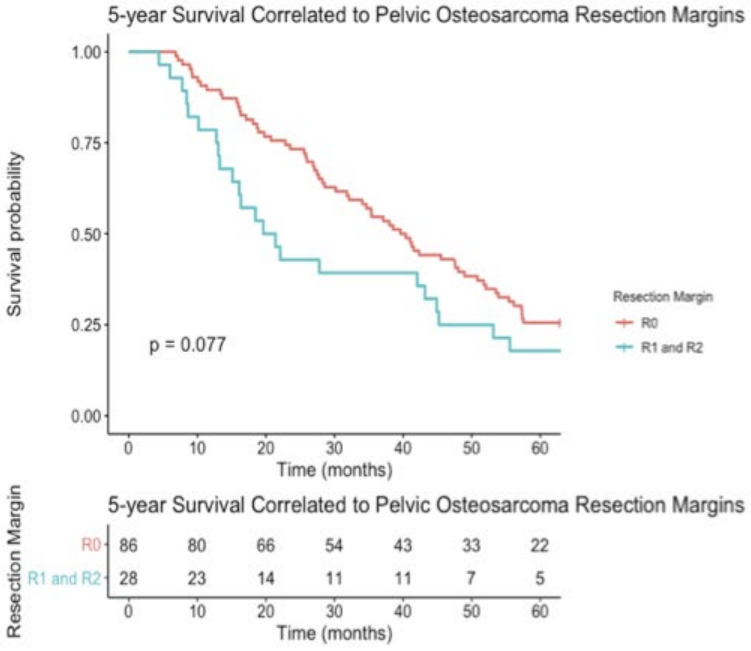
Objective: We aimed to investigate the role of margin resection in survival for intermediate and high-grade osteosarcoma of the pelvis. We also analyzed patient and tumor variables that can impact margin status and survival outcomes.

Methods: Using the American Cancer Society National Cancer Data Base, we retrospectively queried 114 patients who received an initial diagnosis of a grade II or higher osteosarcoma located in the pelvis from 2004 to 2016. Patients who were metastatic at diagnosis and did not receive chemotherapy were excluded from the study. Survival analysis was completed using the Kaplan-Meier method. Multivariable logistic regression analysis was used to evaluate patient and tumor characteristics.

Results: The two-year survival rate for negative margin resections (n=86) compared to positive margins (n=28) were 73.3% (95% CI 64.5-83.2) and 42.9% (95% CI 27.9-65.7) (p=0.0013), respectively. At five years, the survival rates were 25.6% (95% CI 17.8-37.7%) and 17.9% (95% CI 8.1-39.5%) (p=0.077), respectively. Race (p=0.0387) and Charlson Comorbidity Index (p=0.0447) were independently associated with resection status. However, tumor characteristics such as grade, size, and histology, did not correlate with resection margins. Private payor patients also had increased odds of survival (OR 6.7005, p=0.0218).

Conclusion: Our study shows that negative margin resections for patients with intermediate or high-grade pelvic osteosarcomas may improve two-year survival rates. Regardless of the margin status of a resection, however, five-year survival for all patients are poor. Thus, based on our data, the role of surgical margins for intermediate or high-grade pelvic osteosarcoma in survival is unclear. Additionally, patient demographics may correlate more than tumor characteristics to resection status.





Poster #042 3254086

INTRACELLULAR CHOLESTEROL BIOSYNTHESIS IN ENCHONDROMA AND CHONDROSARCOMA

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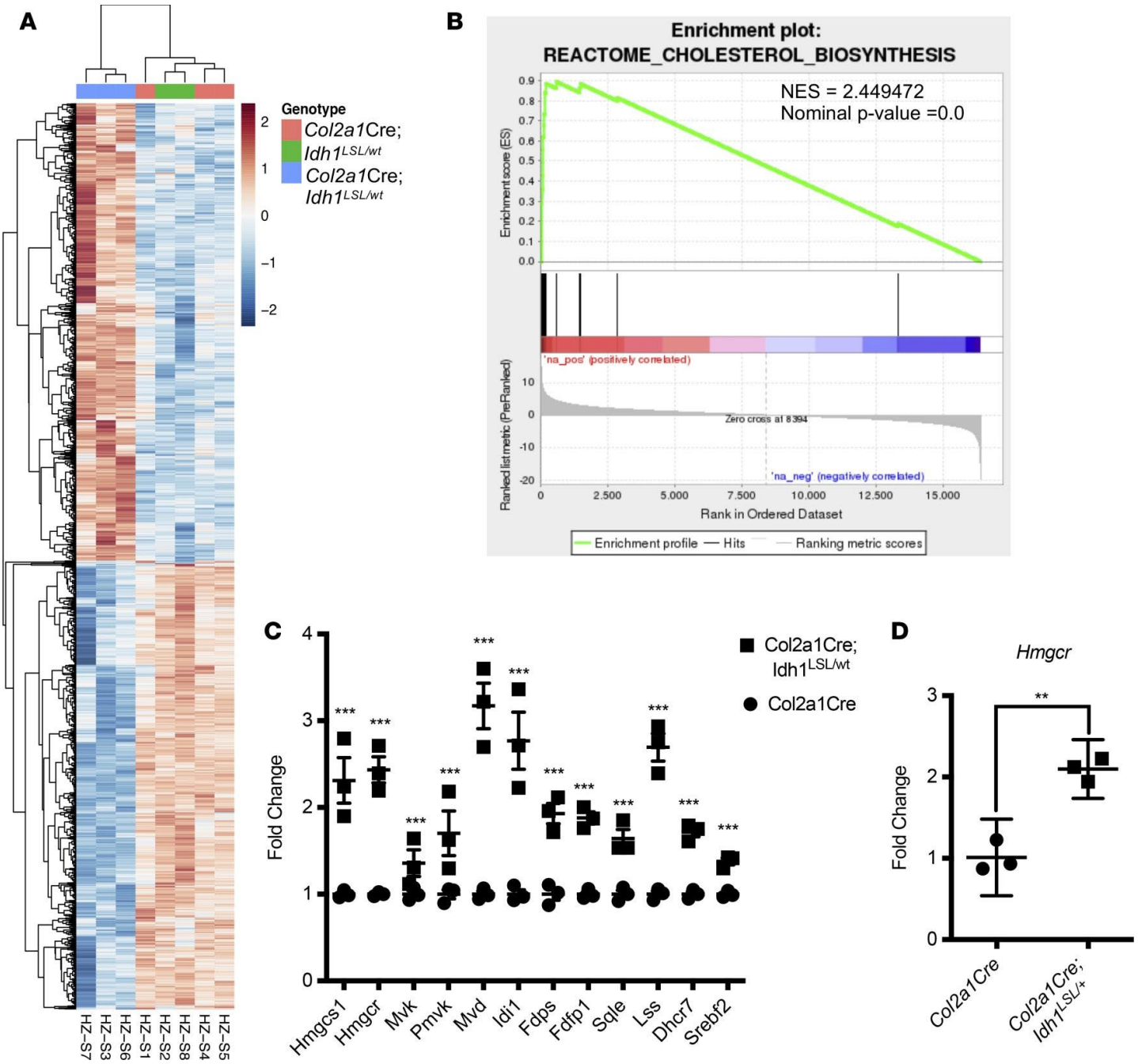
Objective: To examine the role of intracellular cholesteroy biosynthesis in cartilage tumors enchondroma and chondrosarcoma and examine whehter the process could be a potential therapeutic target for these conditions.

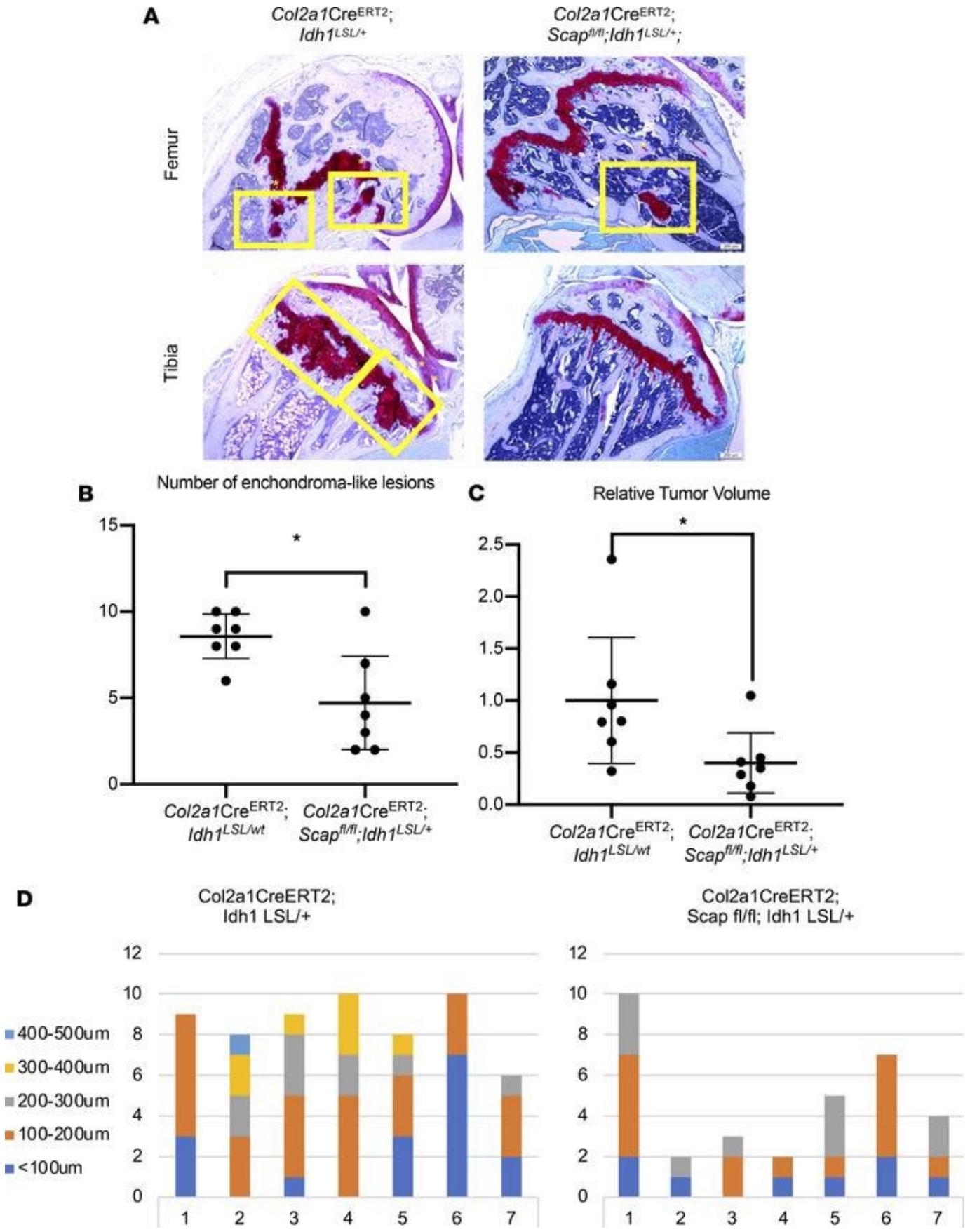
Methods: Genetic mouse models were used to study the role of cholesterol biosynthesis during enchondroma formation in vivo. Expression of mutant Idh1 and deletion of Scap in chondrocytes were induced by tamoxifen at 4 weeks. Cholesterol was analyzed by filipin staining in vitro. Growth-plate chondrocytes were analyzed by Safranin O staining and immunohistochemistry of type X collagen. In the study of chondrosarcoma, human tumors were obtained after surgery. Chondrosarcoma cells from different patients were treated with lovastatin in vitro and then examined by immunohistochemistry of Ki67 and cleaved caspase 3. Patient-derived-xenograft model was used to evaluate tumor growth in vivo. Mice bearing chondrosarcoma cells were treated with lovastatin for 28 days via intraperitoneal injection. Tumor sections were stained for Ki67 and cleaved caspase 3 to examine proliferation and apoptosis. P values were determined by unpaired two-tailed t tests.

Results: RNA-sequencing analysis in Idh1 mutant chondrocytes revealed increase in genes regulating cholesterol biosynthesis. Along with changes in gene expression, filipin staining showed increased cholesterol levels in chondrocytes with Idh1 mutation. Deleting Scap in chondrocytes did not alter growth plate chondrocytes under physiological condition. However, deleting Scap in Idh1 mutant chondrocytes reduced the number of enchondroma-like lesions in those animals. We also examined the role of cholesterol biosynthesis in chondrosaroma where we found inhibiting of cholesterol synthesis by lovastatin significantly reduced cell viability in vitro. In our patient-derived-xenograft models we found that lovastatin treatment suppressed tumor growth in vivo by inhibiting cell proliferation and inducing apoptosis.

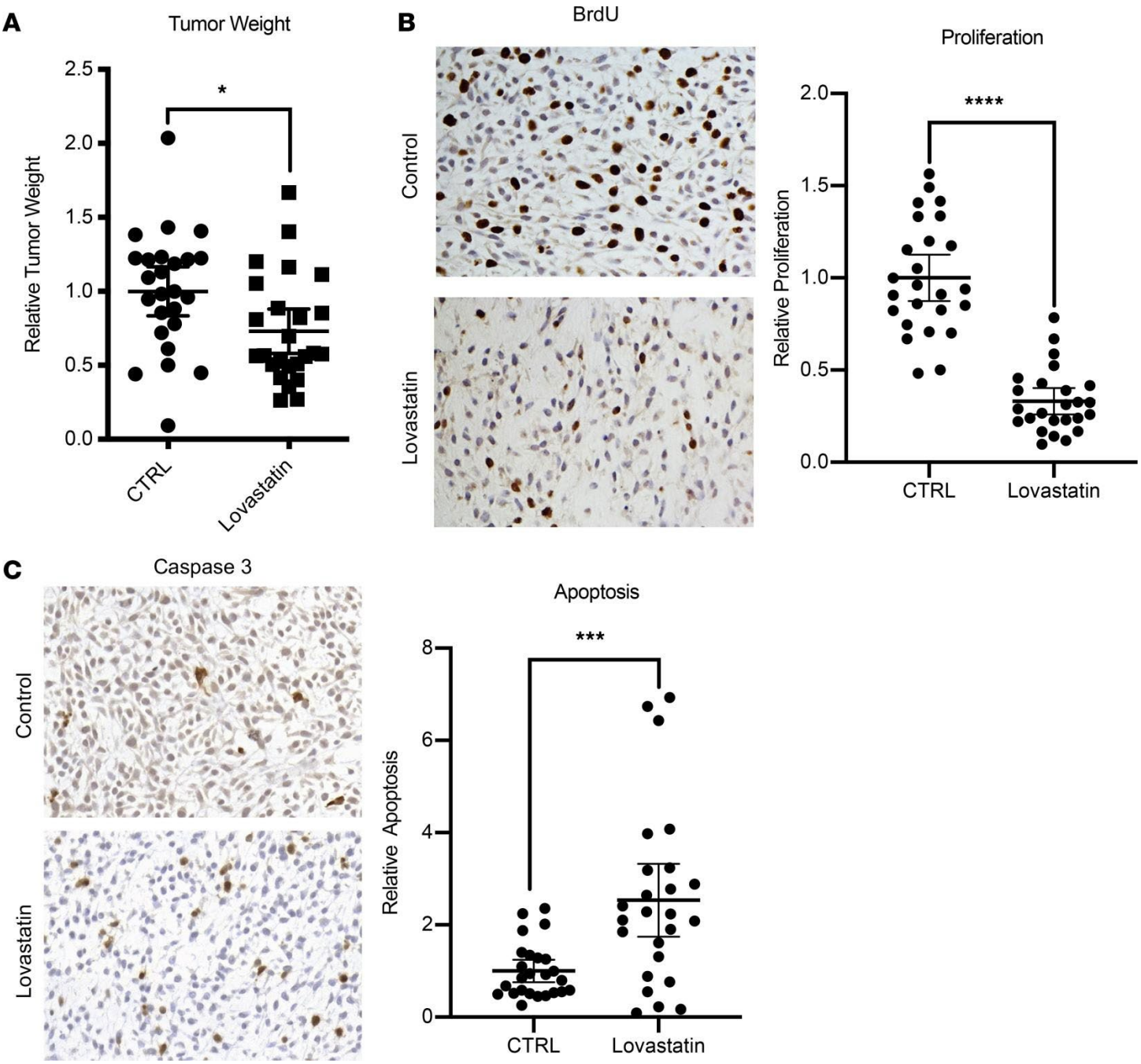
Conclusion: Our study showed that Idh1 mutation caused upregulation in cholesterol synthesis pathway. We found that cholesterol synthesis is important for the tumor growth of enchondroma and chondrosarcoma as inhibiting cholesterol biosynthesis by genetic and pharmaceutical approaches both led to suppressed tumor growth.



(A) Heatmap of RNA-seq on sternal chondrocytes from Col2a1Cre;Idh1$^{LSL/+}$ (n = 3), Idh1$^{LSL/+}$ (n = 2), and Col2a1Cre (n = 3) mice at E18.5. Littermates were used for the analysis. (B) Gene set enrichment analysis for the cholesterol biosynthesis pathway. (C) Relative fold change of gene expression in the cholesterol synthesis pathway (n = 3). ***P < 0.001. The false discovery rate was calculated to control for multiple hypothesis testing. (D) qPCR of Hmgcr of sternal chondrocytes isolated from Col2a1Cre and Col2a1Cre;Idh1$^{LSL/+}$ animals at E18.5 (n = 3). **P < 0.01, unpaired, 2-tailed Student's t test. Mean ± 95% confidence intervals are shown.



(A) Representative Safranin O staining of Col2a1Cre^{ERT2};Idh1$^{LSL/+}$ and Col2a1Cre^{ERT2};Scap$^{fl/f}$;Idh1$^{LSL/+}$ mice. (B) Number of enchondroma-like lesions. (C) Relative tumor volume of enchondroma-like lesions. (D) Distribution of the width of enchondroma-like lesions. Scale bars: 200 μm. Each data point represents 1 animal. n = 7. *P < 0.05, unpaired, 2-tailed Student's t test. Mean ± 95% confidence intervals are shown.



(A) Relative tumor weight of chondrosarcoma xenografts after vehicle or lovastatin treatment. (B) Representative images of BrdU staining on xenografted tumors and quantification of BrdU-positive cells in relative values (original magnification, ×200). (C) Immunohistochemistry of cleaved caspase-3 on xenografted tumors and quantification of cleaved caspase-3–positive cells in relative values (original magnification, ×200). Each data point represents the relative tumor weight, relative percentage of BrdU-positive cells, or relative percentage of cleaved caspase-3–positive cells of each xenograft tumor. n = 25. *$P < 0.05$, ***$P < 0.001$, ****$P < 0.0001$, unpaired, 2-tailed Student's t test. Mean ± 95% confidence intervals are shown.

Poster #043 3254151

GROWTH PATTERN HETEROGENEITY IN EWING SARCOMA PATIENT-DERIVED CELLS REVEALS DIFFERENTIAL SENSITIVITY TO ANTICANCER AGENTS

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Objective: At the Sarcoma Centre at Karolinska University Hospital a functional precision medicine project has been launched where cultured patient-derived sarcoma cells (PDC) from patients are used for drug sensitivity screen and gene panel sequencing as means for investigating possibilities for personalizing treatment. Both soft tissue and bone sarcomas are included and hereby we report results from PDC from patients with Ewing sarcoma with morphologically different cell populations grown *ex-vivo* and distinct sensitivity to oncology drugs.

Methods: Ewing sarcoma cells were obtained either through fine needle aspiration from metastatic sites or from the primary tumor during operation. The cells were grown and expanded *in vitro* and are hereby referred to as Ewing Sarcoma-Patient-Derived Cells (ES-PDC). The content of Ewing cells in the ES-PDC was examined by the expression of the EWS-FLI1 fusion protein using Proximity Ligation Assay (PLA). Drug sensitivity testing was performed using a library of 525 anti-cancer agents at five different concentrations. Drug sensitivity was evaluated using a customized program and expressed as drug sensitivity score (DSS). Sequencing of a custom panel of 16 sarcoma-associated genes was performed using the Haloplex target enrichment system and Next Seq (Illumina). Expression of 180 cancer genes was evaluated using Q-RT-PCR arrays.

Results: Whereas ES-PDCs usually grow as monolayers, two ES-PDCs derived from patients with refractory ES displayed both adherent and spheroid growth pattern. EWS-FLI1 protein was expressed in nearly all cells regardless growth pattern. Drug sensitivity to anti-cancer agents was similar between the two populations but differences were observed in the classes of drugs targeting differentiation and/or epigenetic markers. A closer analysis of the later group of agents showed that spheroid growing ES-PDC are more sensitive to differentiating drugs and epigenetic modifiers than ES-PDCs growing as adherent cells. The expression of cancer-driver genes was also different within both populations.

Conclusion: Distinct growth patterns of PDCs ex vivo seem to be related to distinct tumor biology and clinical course within the same diagnosis. In accordance to previous observations, our material also suggests intratumor heterogeneity in ES. This is a first step in a translational direction based on gene expressions analysis and drug ex vivo drug screening to individualise treatment, identify potential vulnerabilities and opportunities for drug re-purposing in ES. Preliminary results from one case were presented at the 39th meeting of the Scandinavian Sarcoma Group in May 2019.

Poster #044 3254873

DIFFERENTIAL REGULATION OF GLYCOGEN METABOLISM IN MUTANT IDH CHONDROSARCOMAS AND CHONDROCYTES

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Objective: 38-70% of chondrosarcomas (CSAs) harbor somatic mutations in the isocitrate dehydrogenase genes (*IDH1* and *IDH2*). *In vivo,* mutant *IDH1* and its gain of function metabolite, D-2HG, were found to inhibit growth-plate chondrocyte differentiation, driving enchondromatosis, the benign precursor to malignant chondrosarcomas. For these reasons mutant *IDH* has been identified as a driver mutation of CSAs. Upon our characterization of metabolomic activity in CSAs, electron microscopical examination of patient CSA cells revealed glycogen deposition exclusively in mutant *IDH* cells. Thus, we plan to uncover why this phenomenon is present in *IDH* mutant cells and how mutant *IDH* may regulate glycogen metabolism in CSAs to drive tumor growth.

Aims:
1) Examine glycogen deposition in CSAs and characterize how mutant IDH regulates metabolism in CSAs.
2) Modulate glycogen deposition through target enzymes and/or drugs to evalute effects on CSA growth.

Methods: With institutional review board (IRB) approval, human CSA 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. Patient derived xenograft (PDX) CSA tumors were dissociated for usage in *in vitro* experiments. PDX tumors were pulverized and glycogen was quantified by Abcam's Glycogen Assay Kit II. To examine the effects of mutant *Idh* in glycogen metabolism and its role in the development of cartilaginous neoplasia, *Col2a1-Cre, Idh1* R132Q-KI, and $Hif1a^{fl/fl}$; $Hif2a^{fl/fl}$ mice were used.

Results: Significant elevation of glycogen in mutant *IDH* CSAs was confirmed using patient derived xenograft (PDX) tissues in a quantitative glycogen assay, Periodic acid-Schiff (PAS) staining, and PAS diastase stain (PASD). Immunoblot experiments suggest greater glycogen breakdown in wildtype CSAs and greater glycogen synthesis in mutant *IDH* CSAs. *Col2Cre; Idh1*-KI mouse growth plates display positive PAS staining for glycogen accumulation in the hypertrophic and resting zones; however, this phenotype is absent in wildtype growth plates. Immunoblot experiments of $Idh1^{LSL/+}$ E18.5 growth plate chondrocytes show that glycogen breakdown is slightly elevated in $Idh1^{LSL/+}$ Cre^{+} chondrocytes however GFP^{+} chondrocytes do not display activation of glycogen metabolism pathway. RT-qPCR experiments show that mutant *Idh* is a regulator of glycogen metabolism via *HIF* and D-2HG functions via *HIF*.

Conclusion: Mutant *IDH* CSA tumors display enhanced glycogen synthesis as confirmed by glycogen quantification, PAS staining, and immunoblot experiments. Glycogen metabolism's role in CSA tumorigenesis is currently being investigated by CRISPR/Cas9 gene editing to knockout glycogen metabolism enzymes to assess its effects in cell proliferation, apoptosis, and viability. *Idh1* R132Q-KI mouse growth plates also display glycogen deposition, suggesting that mutant *Idh* is a regulator of glycogen metabolism via *HIF*. Targeting glycogen metabolism in CSAs holds as a promising therapeutic for a disease resistant to chemotherapy and radiation.

Poster #045 3255255

METASTATIC BONE DISEASE AT DIAGNOSIS IN EXTREMITY SOFT-TISSUE SARCOMAS: RISK FACTORS AND SURVIVAL ANALYSIS USING THE SEER REGISTRY

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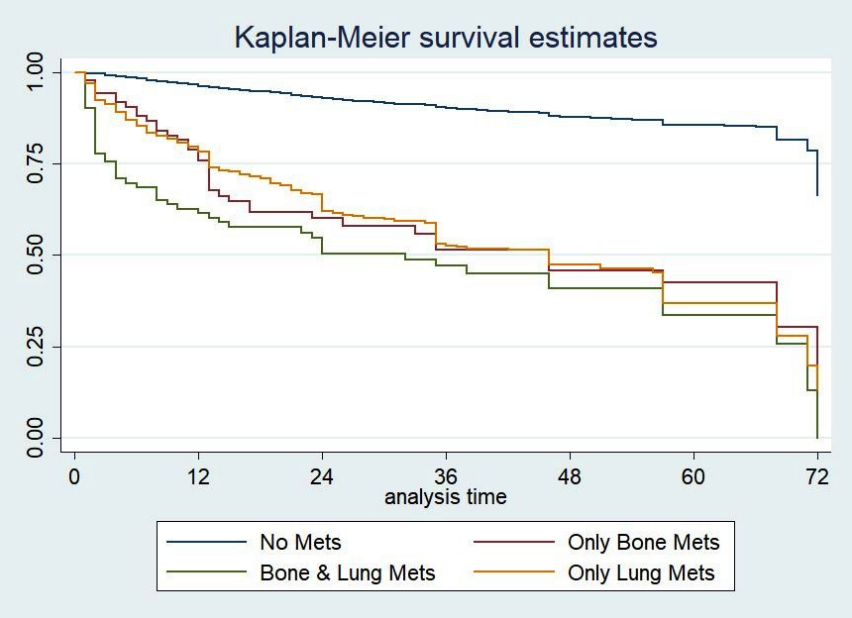
Objective: While lung is the most common site of metastasis from soft tissue sarcoma (STS), skeletal metastasis is a part of the natural history affecting the quality of life and prognosis of these patients. Although a few studies have reported on the incidence of skeletal metastasis, they are single-institution, retrospective reviews making them susceptible to the inherent limitations of these study types. Understanding the tumor and patient characteristics associated with skeletal metastasis, as well as the effect that metastasis has on patient survival, may influence imaging, surveillance and treatment decisions.

(1) What histologic STS subtypes are associated with increased risk of skeletal metastasis? (2) What patient and tumor-specific characteristics are associated with increased risk of skeletal metastasis? (3) What is the impact of skeletal metastasis on patient survival when compared to lung metastasis? (4) Does resection of the primary sarcoma improve survival in the setting of skeletal metastasis?

Methods: Patients were identified from the Surveillance, Epidemiology and End Results (SEER) database with extremity soft tissue sarcoma between January 2010 and December 2015. Risk factors for bone metastasis were investigated using univariate and multinomial logistic regression. Survival based on different sites of metastases was evaluated with Kaplan-Meier analysis. Cox proportional hazard models were performed to identify prognostic factors of survival for patients with bone metastasis. Variables were included in the final model if p-value on the univariate analysis was < 0.25.

Results: Among 8,234 soft tissue sarcomas, 2.2% (n=180) presented with detectable skeletal metastatic disease, of which 50% had simultaneous pulmonary metastasis. The most common STS subtypes to metastasize to bone were identified. Female sex and having health insurance are associated with decreased odds for bone and lung metastases (OR =0.229 and 0.475, respectively; p<.05). Higher tumor grade (II or III), deep tumor location, and positive lymph node involvement are associated with increased odds for bone and lung metastasis (OR=5.1, 3.6, 4.5, 12.3, respectively; p<.05). The 5-year overall survival rate was 41.2% (26.9%-54.9%) for isolated bone metastasis and 32.9% (21.2% – 45.1%) for patients with bone and lung metastasis (**Figure 1**). In survival analysis of cases with bone metastasis, radical resection at the site of sarcoma was the only significant predictor of survival (HR=0.44, p=0.021)

Conclusion: We identified the most common histologic STS subtypes to metastasize to bone. High tumor grade, deep location to fascia and regional lymph node metastasis are significant risk factors for having skeletal metastasis at the time of diagnosis of an extremity STS. While neither systemic chemotherapy nor radiotherapy of the primary sarcoma has a significant influence on survival in the presence of bone metastasis, radical resection of the primary soft tissue sarcoma is associated with increased survival in these patients.



Poster #046 3255261

TEMPORAL HETEROGENEITY OF *IDH1* AND *IDH2* MOLECULAR STATUS IN CONVENTIONAL CHONDROSARCOMA

Anne G. Brouchet[1]*; Anne-Charlotte Bissainthe*[1]*; Elodie Martin*[2]*; Aurore Siegfried*[1]*; Gonzague de Pinieux*[3]*; Pierre Brousset*[1]

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Objective: Cartilaginous tumors have been shown to frequently harbor gene mutations in the metabolic enzymes isocitrate dehydrogenase 1 (IDH1) and 2. From a morphological point of view, conventionnal chondrosarcomas are heterogeneous and characterized by the juxtaposition of areas of different grade. The aim of this study, was to determine the *IDH* mutational status in 141 cases of conventional cartilaginous tumors from different locations and in chondrosarcoma cases for which material was available from both primary sites, and local recurrences and/or metastases, allowing better insights into spatial and temporal tumor heterogeneity.

Methods: Our study included 168 specimens (n=149 paraffin-embedded tumor tissues; n=18 fresh frozen tumor tissues) from 141 patients between 2000 and 2018. IDH1 and IDH2 was studied by Pyrosequencing. Only positions c.394 and c.395 of codon 132 of IDH1 and positions c.514, c.515 and c.516 of codon 172 of IDH2 were explored. We looked for mutations R132H IDH1 (c.395 G>A), R132L IDH1 (c.395 G>T), R132C IDH1 (c.394 C>T), R132S IDH1 (c.394 C>A), R132G IDH1 (c.394 C>G), R172G IDH2 (c.514 A>G), R172W IDH2 (c.514 A>T), R172K IDH2 (c.515 G>A), R172M IDH2 (c.515 G>T), R172S IDH2 (c.516 G>C), and (c.516 G>T). IDH1 and IDH2 status analysis could be determined in only 75 out of 141 patients of the cohort. Mutation analysis failed for 65 patients due to poor quality of the DNA derived from decalcified samples.

Results: We showed that the prevalence of *IDH* mutations was 54.7% (41 out of 75 cases), with the *IDH*R132C mutation being the most common. In two primary tumor samples, we found, the former contained a mixture of cells with different *IDH* mutations (R132S/R132L), while the latter contained a mixture of non-mutated cells (Wt) and mutated cells with various mutations (R172G/R172K). In eight cases, the *IDH* status was different between the primary tumor and the local or metastatic recurrences regardless of bone location: in six cases, *IDH* mutation was undetectable in local recurrences and metastases (IDH => Wt), and in two cases, we observed the appearance of secondary mutations (Wt => IDH). Grading had a significant correlation with both OS and DFS ($p<0.001$), which was not the case for *IDH* mutational status.

Conclusion: This study confirmed the spatial heterogeneity of *IDH* status in conventional CS and demonstrated, for the first time, its temporal heterogeneity between primary and local recurrences/metastatic sites. The temporal heterogeneity of chondrosarcomas could be associated with a disappearance of IDH mutations likely due to the spatial heterogeneity of the primary tumor. This supports the idea that the role of IDH alone (unlike grade) could be irrelevant to the progression of CS, and could partially explain the resistance to IDH inhibitors in nonmutated patients in who other tumorigenesis pathways must be activated.

Poster #047 3255308

MITOCHONDRIAL OXIDATIVE PHOSPHORYLATION MARKERS IN CHONDROSARCOMA: EVIDENCE OF HIGH METABOLIC ACTIVITY

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[2]*Orthopedics, Rothman orthopedic Institute, Philadelphia, PA, USA*

Objective: Chondrosarcoma is the third most common primary bone tumor after multiple myeloma and osteosarcoma. There are no known effective systemic therapies for this disease. Somatic mutations in isocitrate dehydrogenase (IDH1 and IDH2) have been described in chondrosarcoma. These are key enzymes in the mitochondrial tricarboxylic acid cycle and impact intermediary and oxidative phosphorylation metabolism. The oxidative phosphorylation profile of chondrosarcoma is unknown and identifying highly active metabolic pathways may provide the rationale to investigate whether targeting these deregulated pathways has anticancer activity.

Monocarboxylate transporter 1 (MCT1) is an importer of catabolites such as lactate, which are substrates for mitochondrial oxidative phosphorylation. TP53 Induced Glycolysis and Apoptosis Regulator (TIGAR) is a bisphosphatase of Fructose 2,6 P2, which inhibits phosphofructokinase 1 activity and induces oxidative phosphorylation. Transporter of the Outer Mitochondrial Membrane subunit 20 (TOMM20) is essential for import of nuclear encoded mitochondrial subunits of oxidative phosphorylation. Cytochrome C oxidase core IV (COX) is a metabolically labile oxidative phosphorylation subunit. All of these proteins are markers of oxidative phosphorylation metabolism. The mitochondrial metabolic profile of chondrosarcomas is unknown and hence we studied the expression of these four markers in chondrosarcoma and non-malignant cartilage to determine pathway deregulation.

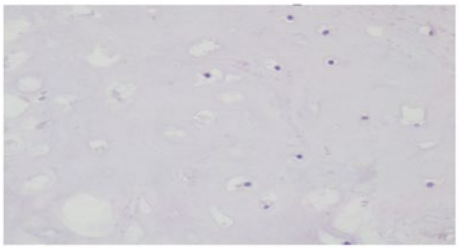
Methods: MCT1, TIGAR, TOMM20 and COX expression was evaluated in IDC by immunohistochemistry on FFPE tissue in chondrosarcomas (12) and non-neoplastic cartilage (3). Human tissues slides were obtained from the tumor bank of the Department of Pathology under a protocol approved by the IRB. Staining patterns defined as positive or negative based on strong staining in greater than 50% of cells. Head and neck squamous cell carcinoma samples were used as positive controls. Chi-square test of independence was performed to compare staining patterns in chondrosarcoma and non-malignant cartilage and a $p<0.05$ was considered statistically significant.

Results: MCT1, TIGAR, TOMM20 and COX expression was positive in the cancer cells of all chondrosarcoma samples and was negative in all non-malignant chondrocytes in non-neoplastic cartilage samples ($p<0.05$).

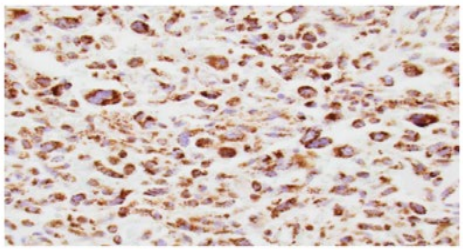
Conclusion: MCT1, TIGAR, TOMM20 and COX, which are markers of high catabolite uptake and mitochondrial oxidative phosphorylation metabolism, are highly expressed in chondrosarcoma compared with non-neoplastic cartilage. The hyper-metabolic status of the chondrosarcoma may contribute to their aggressive behavior and their chemo-resistance. The expression of these proteins may be useful to design clinical trials using specific inhibitors.

TOMM20

Non-neoplastic



Chondrosarcoma



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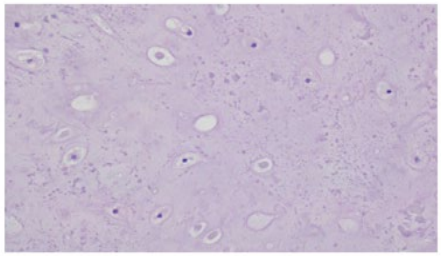
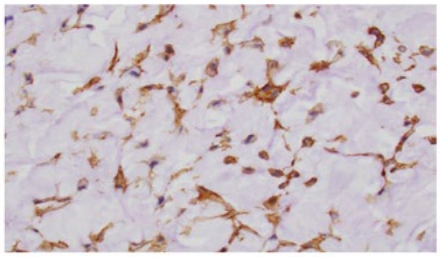
MCT1

Non-neoplastic



Chondrosarcoma



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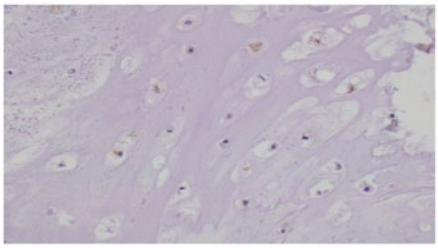
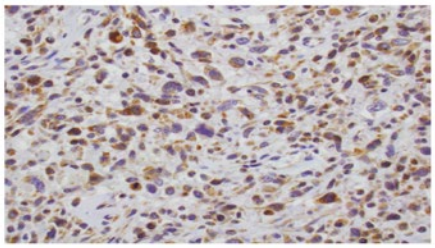
TIGAR

Non-neoplastic



Chondrosarcoma



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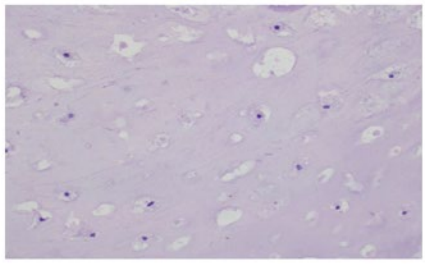
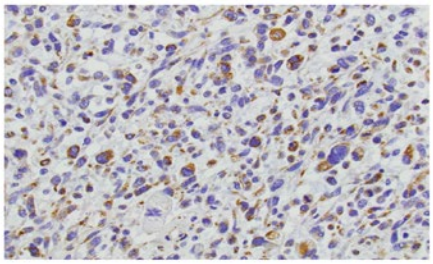
COX

Non-neoplastic



Chondrosarcoma



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Poster #048 3255665

DNA DAMAGE RESPONSE DEFICIENCY IN OSTEOSARCOMA

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Objective: Osteosarcoma is the most common primary bone sarcoma and harbors a host of complex genomic alterations resulting from a variety of mechanisms including chromothripsis. We investigated pathways which can further promote genomic instability in these tumors via loss of DNA damage response (DDR) by whole genome sequencing and by ATRX and ATM loss, both of which can be detected by immunochemistry. *ATRX* is located in Xq21.2 and loss has described in variety of cancers including sarcomas, particularly those with complex karyotypes. *ATM* (ataxia telangiectasia mutated) is located on 11q22 and is a tumor suppressor regulating pathways critical for DNA repair.

Methods: Whole genome sequencing database of 39 osteosarcomas (recurrent and metastatic tumor samples) were queried for mutations in DDR related genes. Unstained slides were prepared from tissue microarrays consisting of decalcified formalin-fixed paraffin-embedded osteosarcoma samples from 260 patients and included 184 primary samples and 94 metastatic samples. Immunohistochemical studies were performed using anti-ATRX (Sigma-Aldrich, HPA001906) and anti-ATM (Abcam, Y170) with an autostainer (Leica Bond III). Loss of staining was defined as complete loss with positive internal control (normal stromal cells or lymphocytes).

Results: Eight of 39 (21%) samples harbored deleterious mutations in DDR related genes including 3 cases involving *ATRX*, and a single case each involving *BRAC2*, *CHEK2*, *CDK12*, *CHEK1*, and *ARID1A*. In addition, rearrangement of *ATRX* was detected in five cases, while a single case each involved rearrangement of *ATM*, *BRCA1*, *MSH2*, and *ARID1A*. Immunohistochemical studies reveal ATRX was lost in 17% (38/225) of analyzable osteosarcoma samples while ATM was lost in in 6% (8/144). Additional clinical correlations are ongoing.

Conclusion: Subsets of osteosarcomas harbor multiple defects which promote genomic instability through compromise of DNA damage repair including ATRX loss and loss of the ATM tumor suppressor pathway. Such alterations could render tumors sensitive to ATR inhibitors, PARP inhibitors, or other strategies to target DNA damage response deficiency.

Poster #049 3256060

COMBINATION THERAPY OF MTOR INHIBITOR AND VEGFR INHIBITOR REGRESS A DOXORUBICIN-RESISTANT OSTEOSARCOMA IN A PATIENT-DERIVED ORTHOTOPIC XENOGRAFT MODEL AND IN VIVO ANGIOGENESIS ASSAY MODEL

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Objective: The efficacy of the combination therapy consisting of mammalian target of rapamycin (mTOR) inhibitor and vascular endothelial growth factor receptor (VEGFR) inhibitor for advanced renal cell cancer has been reported in clinical settings. This combination therapy is expected to be more effective for anti-angiogenesis compared to monotherapy. However, none of the reports have been published regarding osteosarcoma. We established a patient-derived orthotopic xenograft (PDOX) model of the osteosarcoma tumor previously. We reported that the tumor was resistant to doxorubicin (DOX) in the previous study as well as in clinical setting. To confirm angiogenesis *in vivo*model, we previously developed in vivo angiogenesis assay model using Gelfoam and nestin-GFP transfected nude mouse. In the present study, we evaluated the efficacy of the combination therapy of everolimus (EVE), which is mTOR inhibitor, and pazopanib (PAZ), which is VEGFR inhibitor, on the DOX resistant osteosarcoma PDOX model and *in vivo*angiogenesis assay model.

Methods: The osteosarcoma PDOX model were randomized into five groups of seven mice, respectively and *in vivo*angiogenesis assay model were randomized into five groups of 8 fields, respectively. Group 1, Control treated with PBS, i.p., weekly; Group 2, treated with DOX, 2.4 mg/kg, i.p., weekly; Group 3, treated with EVE, 5 mg/kg, oral gavage, daily; Group 4, treated with PAZ, 50 mg/kg, oral gavage, daily; Group 5, treated with EVE and PAZ, oral gavage, daily. Treatment was performed for 2 weeks in each model. In the osteosarcoma PDOX model, treatment efficacy was evaluated on tumor volume ratio and histopathology. Adverse event was evaluated based on body weight ratio. In the *in vivo*angiogenesis assay model, treatment efficacy was evaluated on vascular length ratio.

Results: Combination therapy of EVE and PAZ group suppressed tumor volume ratio compared to all groups significantly in the osteosarcoma PDOX model ($p<0.05$, respectively). Combination therapy of EVE and PAZ group had necrosis of tumor histopathologically. No significant differences of body weight ratio were observed among all groups. Combination therapy of EVE and PAZ group suppressed vascular length ratio compared to all groups significantly in in vivo angiogenesis assay model ($p<0.05$, respectively).

Conclusion: The combination therapy of EVE and PAZ was the most effective in the osteosarcoma PDOX mouse model and suppressed angiogenesis in *in vivo*angiogenesis assay model. This study demonstrates that the combination therapy of mTOR inhibitor and VEGFR inhibitor has possibility to be therapeutic strategy for DOX-resistant osteosarcoma as second-line therapy.

Poster #050 3256334

LOCAL CONTROL WITH INTRALESIONAL CURETTAGE AND ADJUVANT CRYOPABLATION IN EWING'S SARCOMA OF THE APPENDICULAR SKELETON

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Objective: Localized Ewing's Sarcoma of bone is treated with systemic chemotherapy and local control is usually achieved by wide resection. Tumor volume, necrosis rate and resection margins play a role in the decision to add radiation in the adjuvant setting. We have been utilizing localized cryoablation in the setting of benign and malignant bone tumors for limb sparing surgery with good functional and oncological results over the last 25 years. Our protocol in the setting of localized Ewing's Sarcoma of the appendicular skeleton that are small in volume and are staged (Enneking staging) as IIa or minimal IIb, i.e minimal extra skeletal tumor expansion, is intralesional curettage/ geographical resection and cryoablation.

Aim - The aim of this study is to summarize our experience with local cryoablation and curettage/geographical resection in the setting of Ewing's Sarcoma of the appendicular skeleton

Methods: Our departmental database includes approximately 200 patients under the age of 18 that were treated for Ewing's Sarcoma between the years 1993 and 2018. Eight patients were treated by curettage/geographical resection and cryoablation with or without adjuvant radiotherapy and those were included in the study. Their charts were reviewed for demographic, clinical and functional outcomes.

Results: The average age of the patients was 12.6 yrs (range 2-17 yrs) at time of surgery, all were staged as IIa or minimal IIB, six underwent intralesional curettage and two underwent a geographical resection with negative bur close margins. All underwent adjuvant cryo ablation during surgery. Tumor necrosis rate was reported as 100% in all patients. At an average follow-up of 102 months (range 10-227 mos), all patients, but one, are alive. One patient developed a local recurrence and lung metastasis and died of his disease. Two patients received post-operative radiation. Overall functional outcome, as measured by the MSTS 93 score, averaged 27 (range 24-30)

Conclusion: We believe that low volume Ewing's Sarcoma of the appendicular skeleton with minimal extra skeletal involvement can be safely treated by systemic chemotherapy and intralesional curettage or a geographical resection with adjuvant cryoablation without adjuvant radiation. This approach allows for a good oncological and functional outcome.

Poster #051 3256389

THE TEMPORAL DEREGULATION OF THE BALANCE BETWEEN THE ACTION OF MACROPHAGES AND OSTEOCLASTS IS ESSENTIAL FOR THE EFFECTIVENESS OF TREATMENT IN OSTEOSARCOMAS

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Objective: The pivotal role played by the bone microenvironment has been suggested for many years in osteosarcomas. The so called « vicious cycle » described between tumor cells and host cells, is known to promote both tumor proliferation and bone destruction through osteoclast activation. However, the role of osteoclasts in osteosarcoma genesis is still poorly understood. Previous data have shown the beneficial role of macrophage infiltration in osteosarcomas.Macrophages (Mph) and osteoclasts (OCs) share the same cellular origin. Colony-stimulating factor-1 receptor (CSF-1R) activation allows the differentiation of monocytes into macrophages and the CSF-1R blockade inhibits tumor growth by altering Mph polarization. M-CSF (CSF-1) and RANKL are key factors in the differentiation of pre-monocytes into osteoclastic cells.

The objective of this study was to explore the relationship between macrophages and osteoclasts in the OS 2006 cohort to better understand their roles on osteosarcomas behavior.

Methods: The therapeutic protocol of the OS2006 trial combined Zoledronate, an inhibitor of the OCs activity, with chemotherapy and surgery. Patients in the zoledronate group (Z+) received six preoperatively injections of zoledronate. OCs, associated with bone resorption were defined as CD68 positive cells that express TRAP activity. CSF-1R and TRAP levels were measured in the serum of OS2006 patients at different times: biopsy, surgery (time 2), and end of the protocol (time 3) and one year after the end of the treatment. A two-way repeated ANOVA test was run to determine if there were differences in TRAP and CSF-1R concentrations over time. CSF-1R and TRAP levels in the serum were correlated with CSF-1R, Mph, OCs immunostaining in 95 biopsies, then with the response to chemotherapy and prognosis.

Results: The median of CSF-1R and TRAP levels in OS serum patient at biopsy was respectively of 596.7 ng/ml and 9.7 ng/ml. TRAP levels decreased between biopsy and time 2 and 3, while CSF-1R levels increased. There were statistically significant differences in mean TRAP and CSF1-R concentration over time, $F(3,156)=29.49$, $p<0.005$ and $F(3,162)=10.51$, $p<0.005$ respectively. The interaction term between treatment and time was significantly associated with TRAP only, $F(3,156)=7.22$, $p<0.005$. TRAP levels were significantly lower in the group of Z+ patients compared to Z- patients at surgery and at the end of treatment ($p<0.0001$ and 0.0018). No difference was observed for CSF-1R between Z+ and Z- patients. CSF-1R was highly expressed in 58.9% of OS biopsies with an IRS>2. No correlation was found between CSF-1R serum levels and immunostaining. A high serum TRAP level at biopsy was significantly associated ($p=0.0309$) with a better response to chemotherapy in the group of Z+ patients,and conversely a high CSF-1R expression at biopsy ($p=0.0365$) and a high level in serum ($p=0.0583$) were associated with a worse response to chemotherapy.

Conclusion: These results show that osteoclasts play a pejorative role in the response to treatment and that presumably, other cells such as macrophages play a variable role. The deregulation of the balance between the action of macrophages and osteoclasts seems to be essential for the efficiency of treatment and depends on a time window during which the stimulating immune signals are acting.

Poster #052 3256509

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

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[1]*Pediatrics, Baylor College of Medicine, Houston, TX, USA;* [2]*University of Nebraska Medical Center, Omaha, NE, USA*

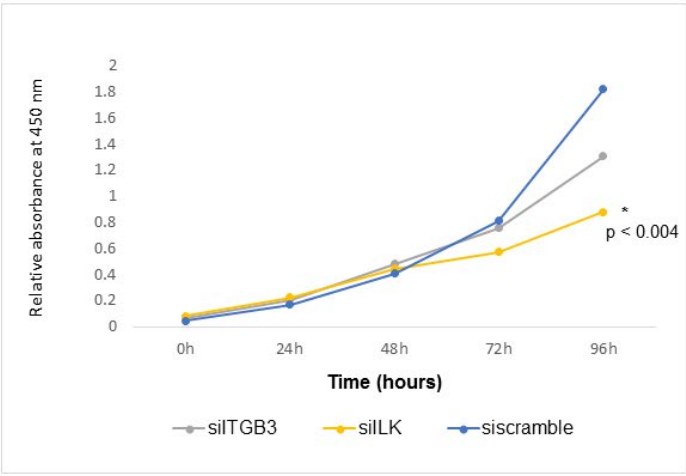
Objective: To investigate the role of the ITGB3-ILK pathway and its downstream signaling events in ES metastasis and to investigate this pathway as a potential therapeutic target.

Methods: To begin to investigate the role of the ITGB3-ILK pathway, we used siRNA to knock down ITGB3 and ILK expression in ES cell lines and then performed functional assays *in vitro*, including cell proliferation and invasion/migration assays. We also tested inhibition of this pathway using small molecule inhibitors targeting ITGB3, ILK and the downstream target activator protein-1 (AP-1), using Cilengitide, Compound 22 and SR11302, respectively. We are currently using these small molecule inhibitors as treatment *in vivo* and assessing rates of metastatic tumor formation in our mouse model compared to controls. We generated stable ITGB3 and ILK overexpression (OE) and knockdown (KD) cell lines, which we are using for similar *in vitro* and *in vivo* investigations.

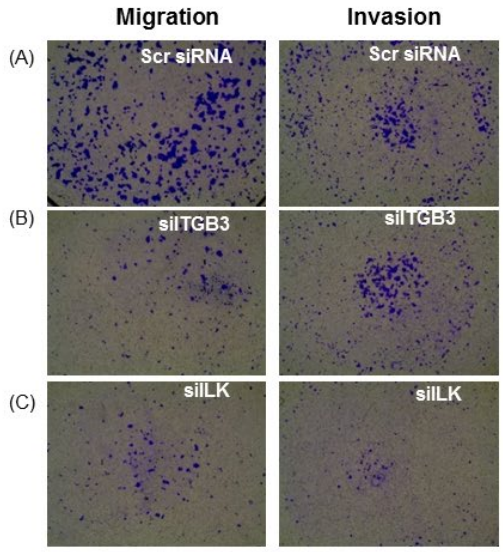
Results: Knockdown of ITGB3 and ILK in our siRNA ES cell lines resulted in decreased tumor cell proliferation and decreased invasion and migration compared to controls (Image 1). We also found significantly decreased ES tumor cell proliferation using each of the small molecule inhibitors *in vitro*. Our preliminary studies using Compound 22 *in vivo* using our mouse model suggest inhibition of primary tumor development and inhibition of metastasis (Image 2). Similarly, preliminary *in vivo* studies of ILK KD lines suggest inhibition, and ITGB3 OE conversely suggests enhancement, of primary tumor development (Image 3) and studies are ongoing to assess rates of metastasis.

Conclusion: These results support our hypothesis that the ITGB3-ILK pathway and its downstream signaling events play a key role in ES metastasis and may serve as a potential therapeutic target. Therefore, we continue testing the effects of inhibition of this pathway on metastatic tumor development *in vivo* using our mouse model. We are currently investigating our ITGB3 and ILK overexpression and knockdown cell lines *in vivo* as well as several small molecule inhibitors. We are also testing ITGB3 and ILK expression in human ES primary and metastatic tumor samples from COG to provide a direct patient correlation.

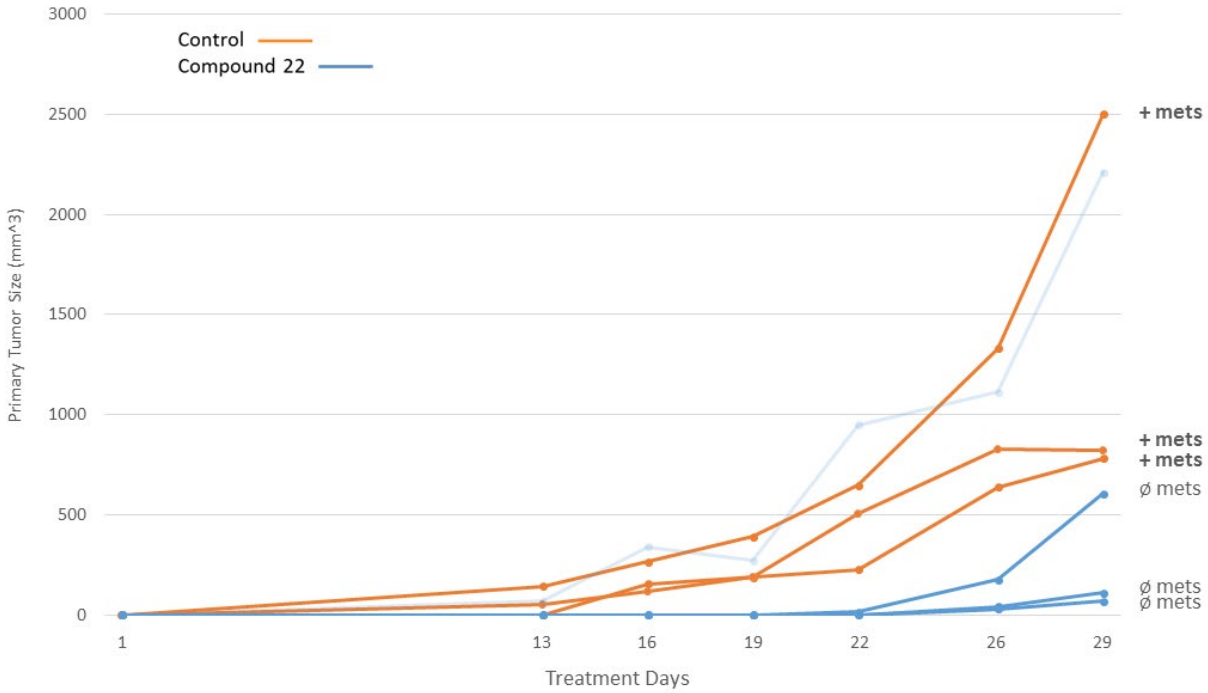
Cell proliferation assay:
Knockdown of ITGB3 or ILK decreases ES cell proliferation



Invasion/migration assay:
Knockdown of ITGB3 or ILK decreases ES invasive and migratory phenotypes



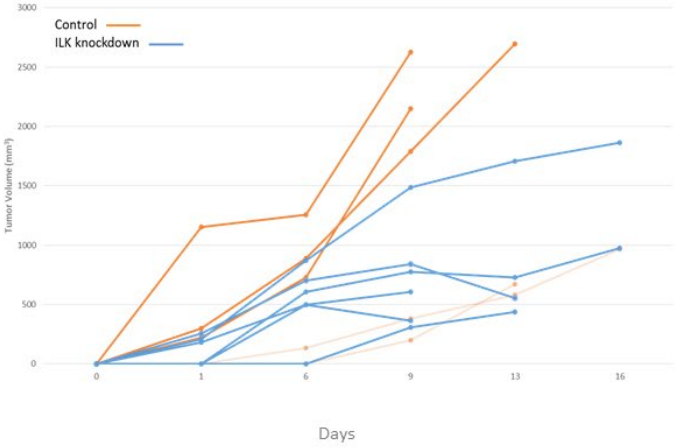
Knockdown of ITGB3 or ILK decreases Ewing sarcoma tumor cell proliferation, invasion and migration compared to controls.

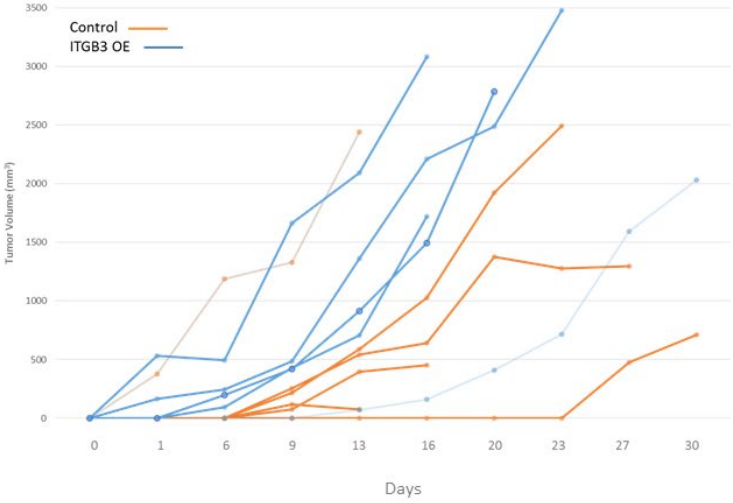


Inhibition of ILK via treatment with the small molecule inhibitor, Compound 22, inhibits primary tumor development and metastasis *in vivo* compared to controls.

Inhibition of ILK via molecular knockdown using shRNA inhibits primary tumor growth *in vivo*.

Overexpression of ITGB3 in ES tumor cell lines promotes primary tumor growth in NSG mice *in vivo*.





ILK knockdown Ewing sarcoma cell lines inhibit, and ITGB3 overexpression cell lines enhance, primary tumor development *in vivo* compared to controls.

Poster #053 3256519

SAFETY OF DISCHARGE AT HIGHER SERUM METHOTREXATE LEVELS IN PEDIATRIC OSTEOSARCOMA PATIENTS

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Objective: Our goal is to study the effect of MTX level at the time of discharge on delay in treatment, acute toxicity, and change of kidney function. Pediatric Osteosarcoma patients are treated with HD-MTX (dose of 12 g/m^2 with a max dose of 20 g/m^2), doxorubicin, and cis-platinum. The most serious acute toxicities from methotrexate include renal and liver impairment. The most common are mucositis and nausea. The current recommended serum level of methotrexate for discharge is less than or equal to 0.1 mM. Increasing the discharge level to <0.15 will allow the patients to be discharged sooner. However, it is not known if this level is safe. We wished to study if the MTX toxicity induced treatment delay, mucositis, and impaired kidney function was more common at a higher than standard discharge level. It is well established that a delay in treatment is correlated with lower survival. Extended time in the hospital is detrimental to both a patients mental and physical health so discharging them sooner would shorten the hospital stay.

Methods: We performed retrospective review of all pediatric osteosarcoma patients, from January 1st 2014 to the present, who were treated with HD-MTX. We defined a discharge level of <0.10 as "standard discharge" and a level of 0.15 to 0.10 as "early discharge".

Results: We reviewed the cases of ten pediatric osteosarcoma patients and separated them into a cohort of five patients who were "standard discharge" and five that were "early discharged". In the five patients (4 males and 1 female median age of 16.6 years old) (70 cycles of HD-MTX treatment) in which the patient was discharged at a level between 0.15 and 0.1. There were four instances of a delay of treatment (5.7% of the cycles) in the early discharge group. The delay was caused by thrombocytopenia, mucositis, and sinusitis. The average stay at the hospital following administration of MTX was 62.5 hours. Average serum creatinine level at diagnosis was 0.88 mg/dL and at discharge was 1.01 mg/dL. There were two recorded cases of mucositis in the early discharge group. We reviewed five patients (2 males and 3 females median age of 14.8 years old) (46 cycles of HD-MTX) where the patient was discharged at a serum methotrexate level of <0.1. There were six instances of delay of treatment (13.0% of the cycles) in the standard discharge group. The delay was caused by mucositis, infection, and acute kidney injury. The average stay at the hospital following administration of MTX was 69 hours. Average serum creatinine level at diagnosis was 0.67 mg/dL and at discharge was 1.01 mg/dL. There were five recorded cases of mucositis in the standard discharge group. The average extra time spend in the hospital after a registered serum methotrexate level of below 0.15 was 53.6 hours per patient.

Conclusion: In our retrospective review of ten cases at our medical center, it appeared that when discharging patients at a serum methotrexate of 0.15 to 0.1 there was no significant increase in delays of treatment or cases of mucositis, with the added benefit of having the patient be able to be discharged sooner. An earlier discharge would help the patient financially, mentally and physically. We plan to gather more information and look at more cases to improve our study going forward.

Results

	Early Discharge Group ≤0.15 to 0.1	Standard Discharge Group <0.1
Patients	5 (4 males 1 female)	5 (2 males 3 females)
Average Age	16.6 Years old	14.8 Years old
MTX Treatments	70 Cycles	46 Cycles
Delays in Treatment	4 (5.7%)	6 (16%)
Cause of Delay	Thrombocytopenia, Mucositis, and Sinusitis	Mucositis, Infection, and Acute Kidney Injury
Average Hours spend in Hospital following MTX dose	62.5 Hours	69 Hours
Average Serum Creatinine at Diagnosis	0.88 mg/dL	0.67 mg/dL
Average Serum Creatinine at Discharge	1.012 mg/dL	1.008 mg/dL
Difference between Diagnosis and Discharge	0.132 mg/dL 15% increase	0.338 mg/dL 50% increase
Number of Reports of Mucositis	2 Cases	5 Cases

Poster #054 3229328

ATR EXPRESSION AS A PROGNOSTIC BIOMARKER AND POTENTIAL THERAPEUTIC TARGET IN OSTEOSARCOMA

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Objective: The ataxia telangiectasia mutated and Rad3 related (ATR) signaling pathway is a well-known regulator of the DNA damage response in cancer. However, the expression and significance of ATR in osteosarcoma remains unknown. We investigated the expression, mechanism, and prognostic value of ATR in osteosarcoma, with subsequent analysis of targeted ATR therapy on osteosarcoma pathogenicity.

Methods: Immunohistochemistry was performed on a unique osteosarcoma tissue microarray composed of 70 patient specimens in order to quantify ATR and phosphorylated ATR (pATR) expression and its association with clinical outcomes. In addition, ATR and pATR expression in osteosarcoma cell lines and patient tissues was evaluated by Western blot and immunofluorescence assay. ATR-specific siRNA and the ATR-selective inhibitor VE822 were applied to reveal the effect ATR inhibition on osteosarcoma cell growth, proliferation, and apoptosis. The underlying mechanism of ATR mediated DNA repair was characterized following siRNA transfection and VE822 treatment. The effect of ATR inhibition on clonogenicity and cell motility were examined using 2D clonogenic and wound healing migration assays. An ex vivo 3D cell culture model was performed to mimic the *in vivo* osteosarcoma environment, and to assess how ATR inhibition affects the capacity of osteosarcoma cells to form characteristic spheroids.

Results: Immunohistochemistry revealed elevated ATR and pATR-expression correlates with shorter patient survival and decreased tumor necrosis following neoadjuvant chemotherapy. Knockdown of ATR with siRNA and attenuation of ATR signaling with the ATR inhibitor VE822 decreased osteosarcoma cell growth and proliferation, while also inducing cell death in a time- and dose-dependent manner. Inhibition of ATR suppressed Chk1 activation and increased expression of gH_2AX in osteosarcoma cells.

Conclusion: Elevated ATR expression is an independent predictor of poor prognosis in osteosarcoma patients. Our results support ATR as a novel prognostic biomarker and promising therapeutic target in osteosarcoma therapy.

Poster #055 3240352

TARGETING SPINDLE ASSEMBLY CHECKPOINT AS A NOVEL THERAPEUTIC STRATEGY IN EWING SARCOMA

Shunya Ohmura[1]*; Martin Orth*[1]*; Aruna Marchetto*[1]*; Stein Stefanie*[1]*; Julia Gerke*[1]*; Julian Musa*[1]*; Maximilian Knott*[1]*; Fabienne Wehweck*[4]*; Tanja Paul*[4]*; Tilman Hölting*[1]*; Laura Romero-Pérez*[1]*; Florencia Cidre-Aranaz*[1]*; Merve Kasan*[1]*; Wolfgang Hartmann*[2]*; Uta Dirksen*[3]*; Thomas Kirchner*[5]*; Thomas Grünewald*[6]

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Objective: Ewing sarcoma (EwS) is the second most common bone-associated cancer in children, adolescents and young adults. Reciprocal chromosomal translocations which cause chimeric fusions of the *EWSR1* gene with variable members of the *ETS* family of transcription factors (most commonly *FLI1*; 85% of cases) are considered to be the major drivers of this disease.

Despite significant therapeutic improvements for patients with localized disease in past decades, outcome for patients with metastatic or recurrent disease remains unacceptably poor. In addition, current therapeutic options are associated with acute and chronic adverse effects, which may impair quality of life. Hence, the development of more effective and in particular less toxic therapies is mandatory.

In the search for novel therapeutic targets specific for EwS, we screened for genes, which are highly overexpressed in EwS compared to normal tissues and upregulated by EWSR1-FLI1. This process identified *TTK* (alias *MPS1*) as a new candidate drug target for EwS. Herein, we investigated its potential oncogenic role and therapeutic utility in EwS.

Methods: To obtain first insights into potential oncogenic roles of TTK in EwS, we analyzed biological effects by *TTK* expression silencing on proliferation, clonogenicity and cell viability using RNA interference (RNAi). Moreover, we assessed potential anti-neoplastic effects by pharmacological TTK inhibition with a specific TTK inhibitor. With the aim of discovering synergistic effects through combination of the TTK inhibitor with other drugs, combination efficiency was analyzed using the Chou-Talalay method. To assess the clinical relevance of TTK we carried out Kaplan-Meier survival analysis in a patient cohort stratified by TTK expression levels.

Results: *TTK* silencing by RNAi significantly reduced cell proliferation and clonogenic growth of EwS cell lines. Pharmacological TTK inhibition by a specific inhibitor also caused a significant reduction of cell viability of EwS cells, while osteosarcoma cell lines and non-transformed mesenchymal stem cells derived from EwS patients showed relative resistance toward pharmacological TTK inhibition, suggesting a relative specificity of TTK inhibition for EwS. Because we observed a plateau in efficacy for short-term cell viability assays in higher concentration levels, we performed long-term assays and found that clonogenic growth could be fully inhibited in a dose-dependent manner. Interestingly, clonogenic growth inhibition was durably maintained after three-day application of the TTK inhibitor followed by drug wash-out. We assume that once aneuploidy is induced by TTK inhibition, EwS cells cannot recover in the absence of the inhibitor, but instead deteriorate in subsequent cell division cycles. Next, we explored potential synergy of the TTK inhibitor with other drugs. So far, we have not observed any prominent synergistic effect with chemotherapeutics or small-molecule inhibitors, when concomitantly applied with the TTK inhibitor. Finally, we found high TTK expression is significantly associated with poor outcome of EwS patients. Importantly, we could confirm this association in patients with localized disease, suggesting its potential biomarker independent of the metastatic status.

Conclusion: We identified TTK as a previously undocumented therapeutic target in EwS. Based on our *in vitro* results, we conclude that TTK contributes to cell proliferation and clonogenic growth of EwS cells and its inhibition could be implemented as a therapeutic strategy in EwS. Furthermore, *TTK* high expression is associated with poor patient outcome independent of the metastatic status, suggesting its potential role as a prognostic biomarker. Currently we are searching for potential synergistic partners by analyzing transcriptome changes upon *TTK* silencing and conducting further *in vitro* and *in vivo* mechanistic experiments to consolidate our observation on its oncogenic role and therapeutic potential in EwS.

Poster #056 3253293

A CROSS SPECIES PERSONALIZED MEDICINE PIPELINE IDENTIFIES THE CRM1 EXPORT PATHWAY AS A POTENTIALLY NOVEL TREATMENT FOR OSTEOSARCOMA

Alexander L. Lazarides, MD[1]*; Jason Somarelli*[1]*; Erdem Altunel*[1]*; Sneha Rao*[1]*; Sarah M. Hoskinson*[1]*; Maya O. Sheth*[1]*; Serene Cheng*[1]*; So Young Kim*[1]*; Kathryn Ware*[1]*; Laura Selmic*[2]*; Cindy Eward*[1]*; David Hsu*[1]*; William Eward*[1]
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Objective: Osteosarcoma (OSA) is a rare, but disproportionately lethal cancer that predominantly affects children. Sadly, discovery of new therapies for OSA has largely been unsuccessful in the past 30 years; there is an urgent need to identify new treatments for OSA. Pet dogs with naturally-occurring OSA represent a unique comparative "model" to discover new treatments for OSA. Unlike humans, in which fewer than 1,000 cases of OSA occur each year, there are nearly 50,000 new cases each year of OSA in dogs. In addition, dogs have an intact immune system, a shared environment with humans, and more rapid progression of disease. Together these factors make dogs an important comparative model for new therapies for OSA

Methods: We developed patient-derived cell lines and xenografts of OSA from both dogs and humans and applied these models to identify new therapies for OSA using high-throughput drug screens *in vitro* followed by *in vivo* validation. Whole exome sequencing was performed on the patient-derived models and original tumors to identify potential driver mutations.

Results: A high-throughput screen in both dog and human OSA identified CRM1 inhibitors as effective at killing dog and human OSA patient-derived cell lines *in vitro*. *In vivo*, CRM1 inhibition led to significant tumor growth inhibition in patient-derived xenografts from dogs and humans. Western blotting demonstrated increased levels of CRM1 protein expression across nine different dog and human OSA cell lines compared to non-transformed human osteoblasts. CRM1 upregulation in OSA cells was further verified by immunofluorescence staining. Increased CRM1 expression was prognostic for poorer metastasis-free survival and poorer overall survival.

Conclusion: Our cross-species personalized medicine pipeline identified CRM1 as a potential therapeutic target to treat OSA in both dogs and humans. Future studies are focused on testing CRM1 inhibitors in canine clinical trials.

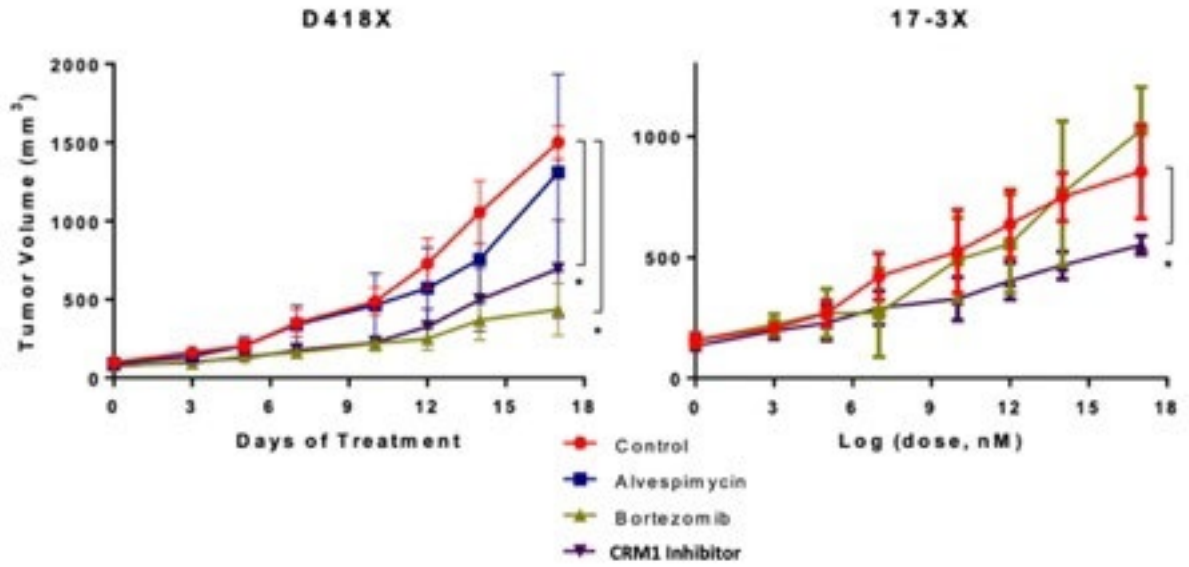

Figure 1. *In vivo*, CRM1 inhibition led to significant tumor growth inhibition in patient-derived xenografts from dogs (D418X) and humans (17-3X)

Poster #057 3253294

THE ROLE OF SURGICAL RESECTIONS FOR INTERMEDIATE AND HIGH-GRADE PELVIC CHONDROSARCOMA

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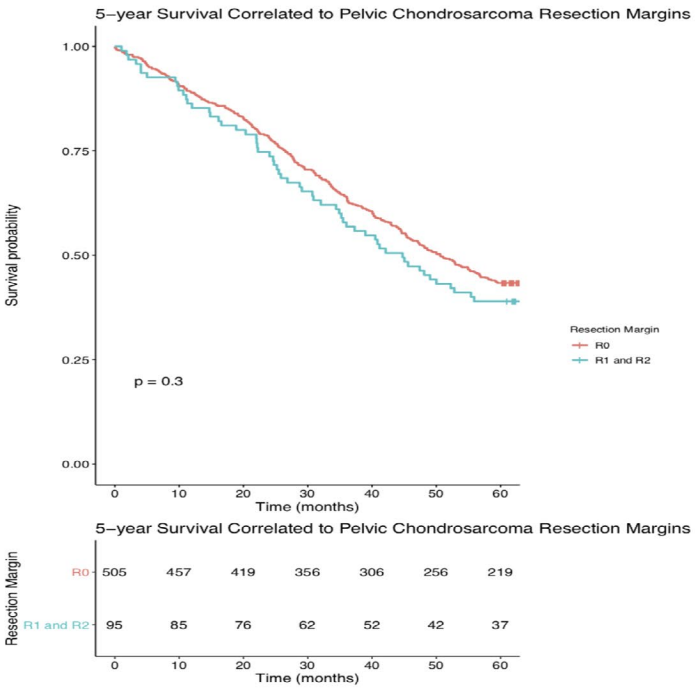
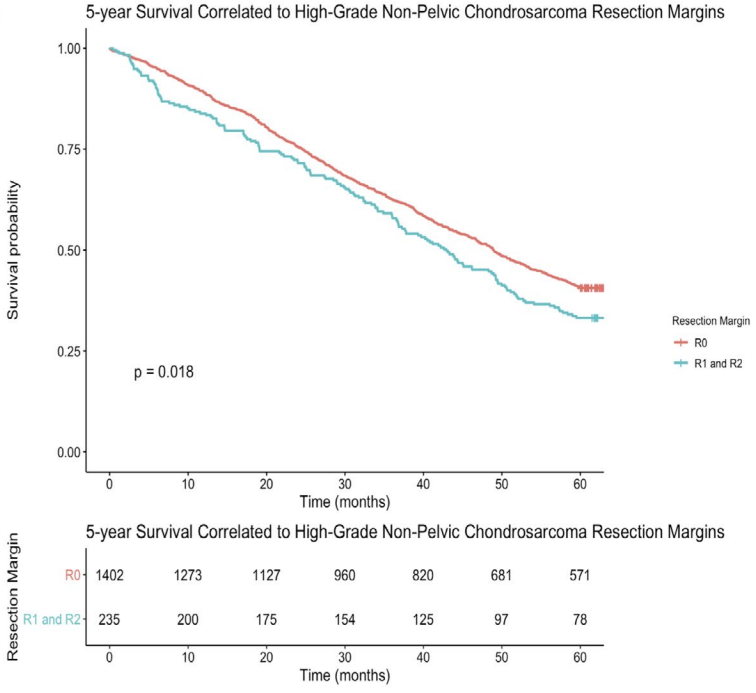
Objective: We investigated the impact of surgical margins on outcomes in patients with chondrosarcoma of the pelvis. Patient demographics and tumor characteristics were also studied in order to determine potential independent predictive variables.

Methods: We retrospectively queried 600 patients who received an initial diagnosis of a Grade II or higher chondrosarcoma located in the pelvis using the American Cancer Society National Cancer Data Base from 2004 to 2016. Patients who were metastatic at diagnosis and were excluded from the study. Survival analysis was completed using the Kaplan-Meier method. Multivariable regression analysis was used to assess resection status, patient and tumor characteristics.

Results: Five hundred five patients had negative surgical margins of their intermediate or high-grade pelvic chondrosarcoma and 95 patients had positive margins. There was not a significant difference in 5-year survival between those with negative margins (43.4%; 95% CI 2.2-47.9%) and positive margins (38.9%; 95% CI 30.3-50.1) (p=0.3). However, patients with intermediate or high-grade non-pelvic chondrosarcoma who had negative surgical margins (n=1402) had an increased 5-year survival rate compared to those with positive margins (n=235) (p=0.018). Patients who received a negative margin resection were more likely to be older than 30 years of age (OR 2.7162, p=0.0365) and typically received no radiation (OR 3.4725, p=0.0173) in a multivariable analysis. Lower grade tumors (p=0.0056) and privately insured patients (p=0.0153) had increased independent odds of five-year survival.

Conclusion: Although surgical margins have a stronger correlation with five-year survival of non-pelvic intermediate or high-grade chondrosarcoma, it may not cause a significant difference in patients with pelvic high-grade chondrosarcoma. Additionally, factors such as the tumor grade and a patient's socioeconomic status may play a role in influencing overall survival.





Poster #058 3253859

PRIMARY SOLITARY FIBROUS TUMORS OF BONE: A MONOCENTRIC RETROSPECTIVE ANALYSIS OF 22 PATIENTS

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Istituto Ortopedico Rizzoli, Bologna, Italy

Objective: Primary solitary fibrous tumor (SFT) of the bone is exceedingly rare with only few cases described in the literature. Objective of the study is to investigate the clinical relevance of criteria of malignancy developed for SFT of soft tissues; we reviewed all cases of primary bone solitary fibrous tumor treated at our institution. All cases were assessed morphologically immunohistochemically (CD34 and STAT6) and molecularly (*NAB2-STAT6* gene rearrangements by RT-PCR). Survival analysis was carried out using log-rank tests.

Methods: Twenty-two cases of primary SFTs of bone were retrieved. Age ranged from 8 to 84 years (median: 50 years), with a slight female prevalence (12 female and 10 male). Most lesions were located in the axial skeleton (4 sacrum, 4 pubis, 2 scapula and 1 lumbar vertebra), followed by the lower extremities (5 femur and 3 tibia) and upper extremities (4 humerus). Radiologically, all cases were all lytic, with areas of sclerosis in 2 cases. Mean tumor size was 10.4 cm (range, 5-20 cm).

Results: Nineteen patients underwent segmental resection or amputation with wide/radical margins in 15, intralesional margins in 3 and with marginal margins in one patient. In 3 patients only a biopsy was done, followed by radiation therapy. Thirteen cases showed more than 4 mitotic figures/10 HPF and were associated with high cellularity, cytologic atypia and foci of necrosis. CD34 and STAT6 immunopositivity was observed in 91% and in 95% of cases respectively. RT-PCR analysis was feasible in only two cases that confirmed the presence of *NAB2-STAT6* chimeric transcripts. Five and 10-year disease-free rates were 59% and 28%, respectively. Twelve out of 22 patients died of disease with multiple distant metastasis with a mean of 60 months from diagnosis; 3 patients died of other diseases; one patient was alive with multicentric diseases and the remaining 6 patients were disease-free at last follow-up (mean 255 months). Statistical analysis showed no correlation between disease free-survival and overall survival and all the clinicopathological parameters evaluated (age, gender, tumor size, tumor site, presence of necrosis, pleomorphism, mitosis, margin status and stage).

Conclusion: Criteria of malignancy devised for SFT of soft tissues failed to predict outcome in primary SFT of bone. Aggressive behavior seems to be independent from mitotic count or any other clinical and morphologic feature.

Poster #059 3254498

TARGETING BIG3-PHB2 PROTEIN INTERACTION TO SUPRESS OSTEOSARCOMA PROGRESSION

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[2]*Division of Orthopedic Surgery, Tokushima University, Tokushima, Japan*

Objective: It is the most urgent issue to develop the novel therapeutic drug for relapsed osteosarcoma due to its poor clinical outcome. We recently demonstrated that Brefeldin A-inhibited guanine nucleotide-exchange protein 3 (BIG3) plays a critical role in breast cancer cell growth and progression through its inhibiting tumor suppressive activity of Prohibitin 2 (PHB2). Currently, the development of BIG3-PHB2 interaction inhibitory peptide, stERAP utilizing PHB2 tumor suppressive activity is ongoing. However, although the public database analysis reveals the high expression of BIG3 in osteosarcoma cells, the pathophysiological role of BIG3 in osteosarcoma cells is unclear. The aim of this study is to clarify the critical role of BIG3-PHB2 complex and the possibility of stERAP as a therapeutic drug in osteosarcoma cells.

Methods: We investigated the expression of BIG3 in osteosarcoma cell lines, Saos-2, U-2 OS, MG-63 and HOS in comparison with normal osteoblast, HOB using qPCR and Western blotting analyses. The anti-tumoral effects were analyzed by knockdown of BIG3 by siRNA and inhibition of BIG3-PHB2 complex by stERAP treatment in means of WST-8 and wound healing assay.

Results: BIG3 was significantly upregulated in osteosarcoma cell lines. Importantly, the knockdown of BIG3 by siRNA led to significant inhibition of cell growth of osteosarcoma cell lines. Importantly, stERAP treatment resulted in significant suppression of the cell proliferation in a dose-dependent manner in Saos-2, MG-63, and HOS, in which IC50 was 99nM, 116nM and 131nM, respectively. Interestingly, immunocytochemistry revealed that BIG3-PHB2 complex localized in mitochondria in osteosarcoma cells.

Conclusion: Our findings suggest that BIG3-PHB2 complex in mitochondria plays a critical role in the tumor growth and malignant progression of osteosarcoma and stERAP is might be a promising anti-tumor drug for osteosarcoma therapy.

Poster #060 3254783

SIGNALING CROSS-TALK BETWEEN HUMAN OSTEOSARCOMA AND MESENCHYMAL STEM CELLS VIA INTERLEUKIN-8 IN THE TUMOR MICROENVIRONMENT

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Objective: Osteosarcoma (OS) is the most common primary malignant bone tumor in children and adolescents. Traditional therapeutic approaches include local control of the primary lesion by surgery and/or chemotherapy, and treatment of disseminated disease with multiagent cytotoxic chemotherapy. However, over the last three decades, there have been no noticeable improvements in patient survival, especially for the subgroup having shown metastasis at diagnosis. It is known that malignant phenotypes of OS, such as proliferation, invasion, and metastasis, are significantly influenced not only by characteristics of the tumor itself, but also by the surrounding microenvironment. It has been reported that normal cells can be influenced by humoral factors from tumors, which lead to the normal cells acquiring a function to support the tumor cells. In the present study, our data revealed that both MG63 cells and hMSCs released IL-8 and influenced each other via an IL-8 signaling loop, which caused possible changes in the ecology of tumors. We believe that the results would contribute towards elucidation of the molecular mechanisms of tumor progression that occur in the microenvironment.

Methods: We developed a new co-culture model, using OS cells and mesenchymal stem cells (MSCs) without cellular contact, and found that both cell types expressed IL-8 at a high level, and focal adhesion factor (FAK) in OS cells was phosphorylated leading to an increase in the metastatic potential of the tumor in the co-culture condition.

Results: The results of cDNA array analyses demonstrated that IL-8 mRNA expression was significantly increased in MG63 co-cultured with hMSCs. We also analyzed the paracrine action of IL-8 between MG63 and hMSCs in the co-cultured condition. The potential of invasion and proliferation of OS cells might increase through IL-8-induced activation of FAK and Akt signaling. We confirmed significantly higher IL-8 release and FAK phosphorylation in metastatic lesions in the lung in vivo as well as in vitro. Administration of anti-IL-8 antibody resulted in the inhibition of FAK expression, its downstream signaling, and the invasive potential of the OS cells, resulting in decrease in metastatic lesions.

Conclusion: We ascertained that IL-8 plays an extremely important role as a humoral factor in the progression of osteosarcoma. That is, therapeutic strategies targeting IL-8 may enable establishment of a different therapeutic approach for cases resistant to current anti-cancer drugs. To the best of our knowledge, our study is the first report to show that IL-8 could be a therapeutic target of human OS using a co-culture system with OS cells and hMSCs. Although our notions will require further investigation, the cytokines induced by OS may coordinate with cells in the vicinity and contribute to potentiating the invasion and angiogenesis required in the tumor microenvironment. Taken altogether, the present study provides evidence of cross-talk by IL-8 between hMSCs and OS cells.

Poster #061 3255251

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

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Objective: Ewing sarcoma (EwS) represents a group of translocation positive, highly malignant sarcoma that occurs in children, adolescents and young adults. Characteristic for EwS is a disease-specific chromosomal translocation encoding for aberrant transcription factors, EWS-FLI1 in most cases. EWS-FLI1 drives malignant transformation, progression, proliferation and forces expression of tumor-cell specific molecular targets. Therapeutic inhibition of EWS-FLI1 could to date not translate into clinic practice. As a result, EWS-FLI1 cooperating pathways have received more scrutiny. Conduction of a kinome-wide shRNA screen in EwS and control cell line, lead us to investigate BUB1B as a potential target in EwS. BUB1B is an essential element of spindle checkpoint assembly (SAC). Dysfunction of BUB1B is leading to genetic disorders which are associated with the development of Rhabdomyosarcoma in early childhood. Furthermore, spindle checkpoint incompetence can lead to chromosomal instability and aneuploidy, a hallmark of cancer. Complete loss of this checkpoint leads to mitotic catastrophe and apoptosis. We observed an association between higher BUB1B expression levels and lower patient survival rates. We hypothesize a potential link between EWS-FLI1 - FOXM1 - BUB1B and that a pharmacologically interference within this pathway make EwS cells more sensitive to agents—such as vinca alkaloids—that act at the mitotic and spindle level.

Methods: *In silico* expression data as well as capturing of BUB1B mutation in A673 EwS cell line was conducted. We achieved BUB1B RNA expression in tumor samples and distinct cell lines. Furthermore BUB1B protein expression and activation via colcemid exposure was investigated and detected. The role of BUB1B in EwS was investigated using a functional shRNA-based approach with subsequent flow cytometry and cell viability analyses.

Results: shRNA-mediated loss of BUB1B severely affected colony formation and to a lesser extend cell viability, but this was not specific to EWS-FLI1 bearing cell lines. The A673 EwS cell line shows after treatment with spindle formation inhibitor colcemid functional checkpoint competence indicated by M-phase arrest in flow cytometric analysis. Checkpoint competence was lost after BUB1B knockdown, indicating BUB1B contribution to SAC in EwS. Consistent with our hypothesis, EWS-FLI1 modulation resulted in concomitant BUB1B expression changes. Furthermore, we observed a decrease in protein and RNA levels of BUB1B as a result of proteasome inhibition of FOXM1 by Siomycin A in EwS cell lines—indicating a potential interaction between those two proteins.

Conclusion: We illustrate the first steps towards characterization, functionality and therapeutic options of a signaling axis between EWS-FLI1- FOXM1- BUB1B in EwS. Our preliminary results support this hypothesis, warranting further investigation. Furthermore, we could assume that BUB1B contributes to SAC in EwS and governed by EWS-FLI1 contributes to speedy cell cycle progression and tumor proliferation – underlining EWS-FLI1's pro-tumorigenic exploitation of cell cycle regulation mechanism.

Poster #062 3255313

COPPER LEVELS AND ALDH1A1 EXPRESSION VARIES BETWEEN LOW AND HIGHLY METASTATIC OSTEOSARCOMA CELL LINES AND HUMAN SAMPLES

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Objective: Osteosarcoma (OS) is the most common primary malignancy of bone. OS undergoes metastasis preferentially to the lungs and is often chemo-resistant. We previously have observed significant differences in both intracellular copper (Cu) levels and expression of *ALDH1A1* between low and highly metastatic murine OS cell lines. Disulfiram, an FDA-approved ALDH inhibitor and Cu chelator, showed effectiveness against murine OS cells in vitro and in our in vivo mouse model of metastatic OS. This study was designed to determine endogenous intracellular Cu levels and *ALDH1A1* expression levels in SaOS-2, LM2, and LM7 human OS cell lines. 2-Determine patient tumor and blood serum levels of Cu between metastatic and non-metastatic sarcoma patients.

Methods: SaOS-2, LM2, and LM7 human OS cell lines were generously provided by Dr. Eugenie S. Kleinerman (University of Texas MD Anderson Cancer Center) and cultured with 10% FBS in DMEM. OS patient tumors and serum were obtained from our clinical sarcoma registry and tissue bank. Protein was quantified using a protein assay (Bio-Rad) following the manufacturer's instructions. Cu concentrations were determined using a Perkin Elmer AAnalyst 600 atomic absorption spectrophotometer adjusted to detect Cu (324.8 nm). mRNA was collected from human OS cell lines as well as primary OS tumors using the RNeasy Kit (Qiagen), and cDNA was obtained using a Reverse Transcriptase Kit (Bio-Rad). qPCR for ALDH was performed using SYBR Green Supermix (Bio-Rad).

Results: As previously demonstrated in murine OS cells, we also observed that intracellular Cu is inversely proportional to metastatic potential in human OS cell lines (SaOS-2>LM2>LM7). Cu levels were significantly higher in less metastatic SaOS-2 compared with its highly metastatic variant LM7. qPCR showed that LM2 and LM7 have significantly increased *ALDH1A1* expression compared with SaOS-2 using an ordinary one-way ANOVA. Tumor samples from OS patients without detectable metastatic disease at the time of primary tumor resection demonstrated increased intratumoral Cu levels compared with patients with known metastatic disease. Conversely, serum Cu levels from OS patients with metastases demonstrated increased blood Cu levels compared with non-metastatic patients (n=6). ALDH expression levels were significantly increased in the tumors of metastatic sarcoma patients compared with non- metastatic patients (n=4) using an unpaired t-test.

Conclusion: We have demonstrated that human OS cells and tumors of varying metastatic potentials display significant differences in Cu metabolism and *ALDH1A1* expression. Consistent with our observations in murine OS cells, highly metastatic human OS cell lines display decreased intracellular Cu levels and increased *ALDH1A1* expression compared with less metastatic OS cells. Our work additionally shows that metastatic patients display decreased intratumoral Cu levels, increased blood levels of Cu, and higher tumor *ALDH1A1* expression compared to non-metastatic patients.

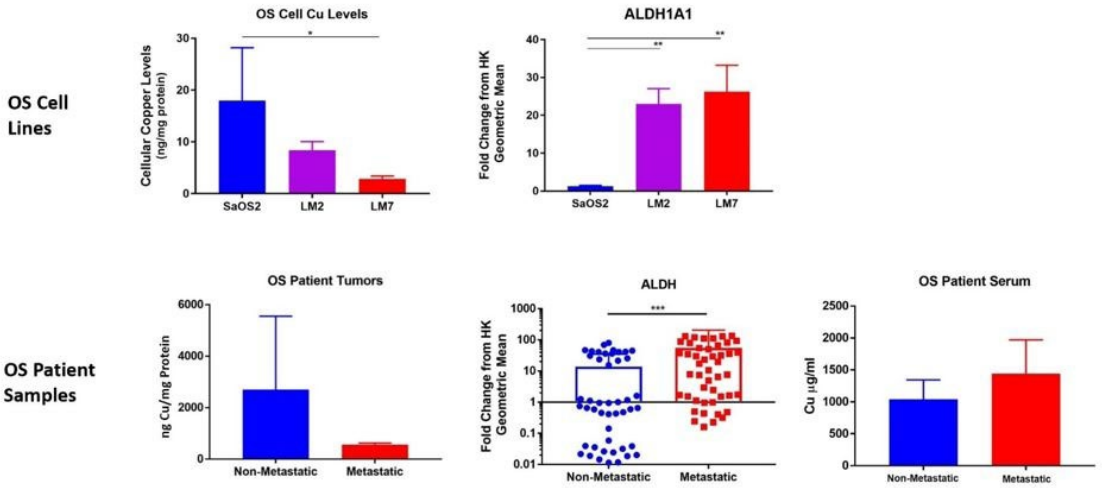

Figure 1. OS Cell Lines- Intracellular Cu levels were significantly decreased in highly metastatic LM7 compared to SaOS2 using an ordinary one-way ANOVA (n= 9). qPCR showed that highly metastatic human OS cell lines LM2 and LM7 expressed significantly higher levels of ALDH1A1 mRNA transcripts compared to related SaOS2.

Figure 2. OS Patient Samples- Intracellular Cu levels were decreased in metastatic OS tumors (n= 4). qPCR showed that tumors from patients with highly metastatic OS expressed significantly higher levels of ALDH1A1 mRNA transcripts compared to tumors from patients without metastatic disease using an unpaired t-test (n= 6). Blood serum samples from patients with metastatic OS display increased Cu levels compared to patients without metastatic disease (n=5).

Poster #063 3255608

EPIGENETIC MODULATING DRUGS ON CARTILAGE AND CHONDROSARCOMA DIFFERENTIATION AND VIABILITY

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Objective: Chondrosarcoma is a malignant form of cartilage which has limited response to radiation and traditional chemotherapy. Given that chondrosarcoma tissues may have epigenetic changes that may be a target of therapy, we sought to investigate the response of adult cartilage primary cells, a chondrosarcoma cell line, and enchondroma tissue to epigenetic-modifying drugs. Our hypothesis was that there would be a differential response to phenotype change, proliferative ability, and possibly viability between malignant and nonmalignant cartilage cells. The goal of this study is to help us better understand the pathophysiology of chondrosarcomas as well as potentially identify therapeutic targets.

Methods: We have used a previously described model for manipulating adult cartilage primary cells taken from discarded arthroplasty patients tissue, enchondroma specimens, and chondrosarcoma cell lines in 2-dimensional and 3-dimensional cultures with the application of epigenetic modifying drugs including Trichostatin A, 5-Azacytidine, and Sodium Valproate to modify epigenetic mechanisms to evaluate the effect of these drugs on phenotype, viability, and proliferative ability. Phenotypic assessment was performed by using RT/PCR to measure the expression of Collagen I and Collagen II. Viability was assessed with MTT assays. Proliferative ability was monitored by growing the cells in culture and cell counting with hemocytometers.

Results: With primary chondrocytes, we are able to demonstrate de-differentiation of the cells in two-dimensional culture with loss of collagen II and increase of collagen I expression over the course of multiple cell passages. By culturing the cells in a pellet we could restore differentiation. Contrary to previous reports with other types of cartilage tissues, there was no block to differentiation with Trichostatin or 5-azacytidine. We showed that these drugs can induce re-differentiation in the 2-dimensional culture conditions similar to the 3-dimensional cultures. When these same medications are applied to chondrosarcoma cells, we see no appreciable effect on collagen I expression, but we do see an increase in collagen II expression with sodium valproate and 5-azacytidine. With these medications, there was no significant loss of viability, but with the Trichostatin A, we saw a significant reduction of viability when comparing chondrosarcoma to primary cartilage cells as well as enchondroma cells.

Conclusion: Epigenetic-modifying drugs have differential effects on primary cartilage and chondrosarcoma cells. There is a significant effect on chondrosarcoma viability with Trichostatin A. This data supports the investigation of these types of medications in possible future therapeutics for chondrosarcoma.

Poster #064 3255652

DIABETES-ASSOCIATED ADVANCED GLYCATION END-PRODUCTS Nε-CARBOXYMETHYLLYSINE AND PENTOSIDINE EXERT MALIGNANCY ON BONE TUMORS VIA THE ACTIVATION OF SKELETAL CANCER STEMNESS

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Objective: Diabetes mellitus and cancers are common diseases with high critical impacts on human health worldwide. The association between an increased cancer risk and diabetes mellitus have been recently demonstrated from growing evidence of numerous epidemiological studies (from 0.84-fold to 2.01-fold increased risk). In addition, diabetes-associated advanced glycation end-products (AGEs), an etiology of diabetic complications, have been investigated to exhibit as a positive modulator in prostate tumor progression. Despite convincing evidence of positive correlation between diabetes mellitus and cancer risk, much less attention is paid to the link between diabetes mellitus/AGEs and bone cancer/metastatic bone cancer. Therefore, there has been a great deal of concern about the interaction of diabetes mellitus/AGEs and bone cancer or its malignancy due to a lower percentage of 5-year survival rates. Here, we investigated the cancerous or malignant role of AGEs in bone cancer progression, including osteosarcoma cells and chondrosarcoma cells.

Methods: Human osteosarcoma cells MG63 and human chondrosarcoma cells JJ012 were cultured and used to investigate the role of Nε-carboxymethyllysine (CML) and pentosidine (PT), two major components of AGEs, in cancer stemness characteristics contributing tumorigenicity and malignancy. Sarcosphere formation assay was used to determine the stemness ability of MG63 cells and JJ012 cells under CML treatment (0-25 μM) and PT treatment (0-25 μM) for 14 days. The protein expressions of cancer stemness-related signals (aldehyde dehydrogenase 1 family member A1 (ALDH1A1) and CD44) and sirtuin 6 (SIRT6) under CML and PT treatment (0-25 μM) in MG63 cells and JJ012 cells for 3 days were determined by Western blotting.

Results: Both of CML and PT (10 and 25 μM) significantly promoted sarcosphere formation in MG63 cells (CML: 10 μM: a 3.7-fold increase, $p<0.01$; 25 μM: a 2.5-fold increase, $p=0.01$; Figure 1A) (PT: 10 μM: a 3.7-fold increase, $p<0.01$; 25 μM: a 4.3-fold increase, $p<0.01$; Figure 1B) in a dose-dependent manner. Similarly, both of CML and PT modestly increased sarcosphere formation in JJ012 cells (CML: 10 μM: a 1.5-fold increase, $p=0.38$; 25 μM: a 1.3-fold increase, $p=0.60$; Figure 1A) (PT: 10 μM: a 1.8-fold increase, $p=0.37$; 25 μM: a 1.9-fold increase, $p=0.27$; Figure 1B). Besides, CML dose-dependently induced protein expressions of cancer stemness markers (ALDH1A1 and CD44) in both MG63 osteosarcoma cells and JJ012 chondrosarcoma cells (Figure 1C; $p<0.05$, quantification by densitometry), accompany with an upregulation of SIRT6 protein expressions (data not shown; $p<0.05$, quantification by densitometry). Moreover, PT exhibited the similar effect as CML on inducing protein expressions of ALDH1A1, CD44 and SIRT6 (data not shown; $p<0.05$, quantification by densitometry).

Conclusion: Cancer stem cells (CSCs) function as a nest of self-renewal tumor cells to promote tumor growth and malignancy including remedial relapse and metastasis. CSCs in bone tumors exert the malignant functional role, including self-renewability, tumorigenicity, sphere formation, drug-resistance with activation of pluripotent signals (ALDH1, CD133, CD44, c-kit, Nanog, Stro-1, Sox2 and Oct3/4). In addition, SIRT6, a sirtuin family member of NAD^+-dependent deacetylase, has been investigated to contribute to migration and invasion of Saos-2 and U2OS osteosarcoma cells. Moreover, overexpression of receptor for AGEs (RAGEs) markedly induced cell proliferation in U-2OS osteosarcoma cell. In this study, we found that major components of AGEs, CML and PT, promoted the malignancy of osteosarcoma cells and chondrosarcoma cells via activation of cancer stemness characteristics accompany with an upregulation of SIRT6 expression. These findings suggest AGEs exert a malignant role in skeletal tumor progression.

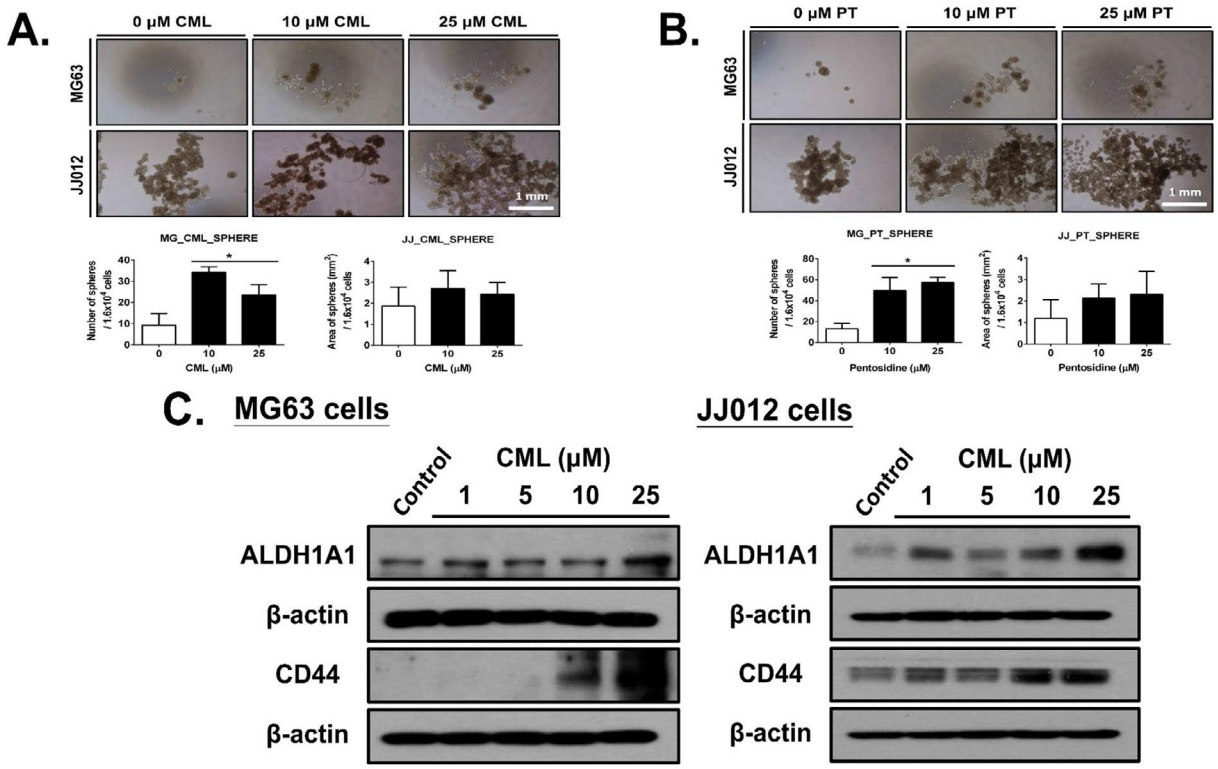

Figure 1. Nε-carboxymethyllysine (CML) and pentosidine (PT) promote the malignancy of MG63 human osteosarcoma cells and JJ012 human chondrosarcoma cells via activation of cancer stemness characteristics. MG63 cells and JJ012 cells were cultured with CML and PT (0-25 μM). Sarcosphere formation of MG63 cells and JJ012 cells under (A) CML and (B) PT treatment were shown. (C) Western blot analysis of protein expressions of ALDH1A1, CD44 and β-actin in MG63 cells and JJ012 cells. Scale bar = 1 mm. All data are present as means±SEM for three independent experiments. *, $p<0.05$ as compared with control group.

Poster #065 3255959

ARE INTRA-ARTICULAR RESECTIONS FOR PROXIMAL FEMUR SARCOMAS WITH INTRA-ARTICULAR DISEASE SAFE?

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Objective: The impact on local recurrence of intra articular hip resection of a proximal femur bone sarcoma in the presence of intra articular disease (intra-capsular, extra-osseous disease) or pathological fracture is concerning.

Methods: We performed a competing risk analysis of actuarial local recurrence free survival with death as a competing event for 82 proximal femur resections stratifying them for presence of intra-capsular disease performed from Jan 2006 to Dec 2016. We recorded type of resection (intra vs extra-articular), pathologic fracture, histology (Ewing's vs Osteosarcoma vs Chondrosarcoma), chemotherapy induced necrosis, and adjuvant radiation that impact local recurrence outcomes in a multivariable Cox proportional hazard model.

Results: At a median follow-up of 43 months (Range 5 - 140 months), 3 were lost to follow up, 45 were free of disease, 2 alive with disease, 32 died of disease. Twenty eight patients without intra-articular disease had intra-articular resections (planned safe margin). Fifty one patients had intra-capsular disease, of which 44 had intra-articular resections (planned close margin), 7 had extra articular resections (planned safe margin). We compared these 44 patients who had planned close margins with 35 (28 without intra-articular disease, 7 with extra articular resections) who had planned safe margins to assess impact on local relapse. We had 5/44(11%) local recurrences in the close margin group at a median follow up of 46 months (2-84months) [2 in chondrosarcoma, 2 in Ewing's sarcoma (both necrosis <90%) in 1 in osteosarcoma (necrosis <90%], three of which had a pathologic fracture at presentation (1 each in osteosarcoma, Ewing's sarcoma and chondrosarcoma) . Four (11%) in the safe margin group had a local recurrence at a median follow up of 31 months [2 in osteosarcoma (both necrosis <90%), 2 in Ewing's sarcoma (1 with necrosis <90%)]. There were no local recurrences in cases with extra-articular resections in the presence of intra-capsular disease. The LRFS for safe and close margins cohort with death as a competing event was 89% and 92% at 3 years and 84% and 87% at 5 years (p=0.74). On univariate cox propotional hazard model, a close margin did not significantly predict a higher risk of LR (p = 0.745). Necrosis <90% [chondrosarcoma excluded (26cases)] significantly predicted local recurrence (hazard ratio of 11 and a LRFS of 50% at 5 years, p = 0.005). Presence of pathologic fracture at presentation did not significantly predict worse LRFS, MFS, OS at 5 years (92% vs 80%, 58% vs 58% and 51% vs 58% respectively at 5 years, p > 0.05).

Conclusion: Local recurrence is not significantly worse when intra- articular resection is performed in the presence of intra-articular disease for proximal femur bone sarcomas. Poor necrosis predicts higher local recurrence irrespective of margins.

number	variable	categories	sub-distribution hazard ratio	robust-std-error	p-value	confidence-interval
1	sex	male	0.92	0.67	0.91	(0.23,3.79)
		female				
2	path fracture	yes	1.06	0.78	0.94	(0.25,4,47)
		no				
3	intra-capsular disease	yes	1.06	0.78	0.94	(0.27,4.59)
		no				
4	final histology	ewing				
		osteosarcoma	1.44	1.17	0.66	(0.29,7.08)
		chondrosarcoma	0.91	0.80	0.91	(0.16,5.12)
5	age			0.27	0.72	(0.94,1.05)
6	margin	safe	0.99			
		close	1.875	1.22	0.337	(0.52,6.75)

Competing risk analysis: death as a competing event for local recurrence

	planned close margin	safe margin	p value
number	44	35	
local recurrences	5 (11%)	4 (11%)	
median follow up in months	46	31	
pathologic fracture with local recurrence	3	0	
LRFS at 3 years with death as competing event	92%	89%	0.74
LRFS at 5 years with death as competing event	87%	84%	

Poster #066 3256013

BASED ON THE POTENTIAL IMMUNOGENIC EFFECT OF TREATED TUMOR TISSUE REIMPLANTATION DOES EXTRA CORPOREAL RADIATION AND RE-IMPLANTATION (ECRT) FOR INTERCALARY OSTEOSARCOMA RESECTION PROVIDE OUTCOME BENEFITS?

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Surgical Oncology, Tata Memorial Centre, Mumbai, Maharashtra, India

Objective: BASED ON THE POTENTIAL IMMUNOGENIC EFFECT OF TREATED TUMOR TISSUE REIMPLANTATION DOES EXTRA CORPOREAL RADIATION AND RE-IMPLANTATION (ECRT) FOR INTERCALARY OSTEOSARCOMA RESECTION PROVIDE OUTCOME BENEFITS ?: matched analysis of a diaphyseal osteosarcoma cohort

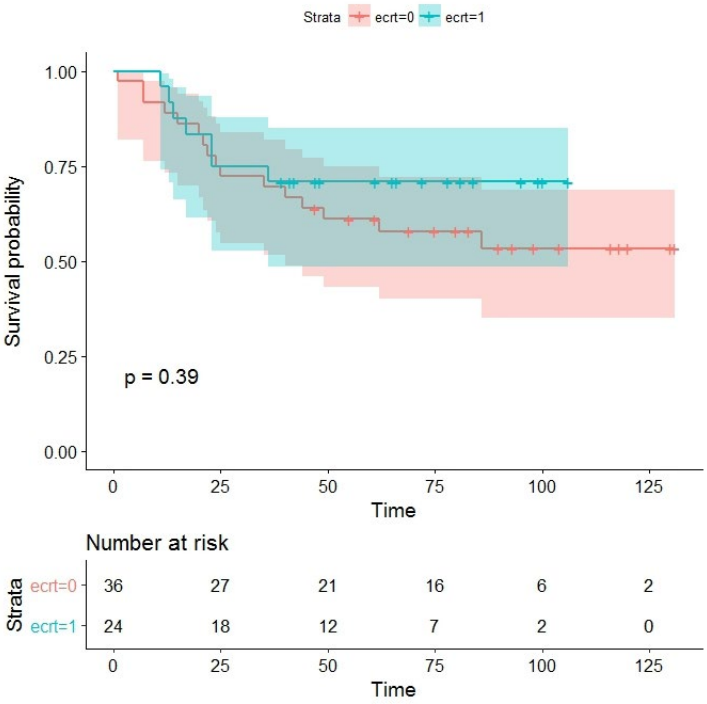
Methods: Of 720 cases of surgically treated high grade osteosarcoma patients treated at our institute from 2006 to 2013, 61 had predominantly diaphyseal disease. All patients were non metastatic at presentation. Patient and tumor characteristics, treatment details, local recurrence-free, metastasis-free and overall survival were compared for 24 patients who had reconstruction with ECRT vs 37 who did not. Both the groups were well matched in terms of baseline characteristics Means were compared with the t-test, proportions with the chi-square test and survival with the log rank test. Kaplan-Meier method was used to construct time to event curves. Cox proportional hazard regression modeling was employed for multivariate time to event analysis.

Results: Twenty two had ECRT with or without vascularised fibula. Fifty gray single dose was used in all cases. Two had pasteurization and re-implantation. Thirty seven had non ECRT reconstructions(including intercalary or osteoarticular endoprosthesis, pedicled bone grafts, rotationplasty and amputations). Five year local recurrence-free survival was 85% for ECRT and 97% for non ECRT groups (p=0.17). Five year metastasis-free survival was 63% and 54%, respectively (p=0.44). Five year overall survival was 70% and 58%, respectively (p=0.39).

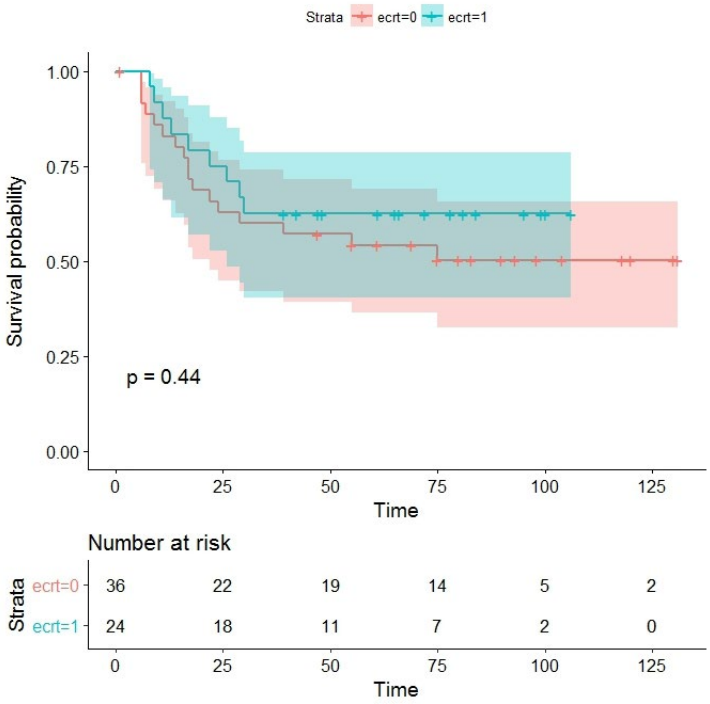
Conclusion: The data from this study did not demonstrate significantly better local recurrence free, distant relapse free or overall survival benefit in the ECRT group.

variable	re-implantation group	non-reimplantation group	p-value
n	24	37	
female sex	1 (4%)	13 (35%)	
median follow up in months	54	62	
mean length of resection in cms	20	22	0.07
proportion of tumor size over 8 cm	80	90	0.3
median age in years (range)	17 (8-35)	17(6-58)	

variable	re-implantation group (n = 24)	non-reimplantation group (n = 37)	p value
local recurrence	1 (4 %)	1 (2.7%)	
metastasis	8 (33%)	18 (48%)	
local recurrence with metastases	2 (8%)	0	
died of disease	7 (29%)	15 (43%)	
died of other causes	0	1	
alive with disease	2 (8%)	3 (8%)	
disease free	15 (62.5%)	18 (48.64%)	
5 yr LRFS	85 % (range 60 - 90)	97 (range 80-95)	0.17
5 yr MFS	63 (range 40 - 78)	54 (range 35-70)	0.44
5 yr OS	70 (range 50-85)	58 (range 40 - 70)	0.39



Kaplan Meier curve for overall survival stratified by reimplantation with numbers at risk



Kaplan Meier curve for metastasis free survival stratified by reimplantation with numbers at risk

Poster #067 3256546

IMPACT OF LOCAL TREATMENT STRATEGY FOR PRIMARY SITE ON OUTCOMES OF EWING SARCOMA

Yen-Lin Chen, MD[1]*; Saveli I. Goldberg*[1]*; Ruoyu Miao*[1]*; Edwin Choy*[2]*; Gregory Cote*[2]*; Kevin Raskin*[3]*; Santiago Lozano-Calderon*[3]*; Joseph Schwab*[3]*; Thomas DeLaney*[1]

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Objective: Local primary tumor treatment for Ewing may involve surgical resection, radiation therapy (RT) or combination. Optimal local strategy remains controversial for different anatomic sites and extent of resection. We assessed the impact of local treatment strategy on non-metastatic Ewing sarcoma patients treated in a high-volume, referral sarcoma center.

Methods: We performed an IRB approved retrospetive review of Ewing sarcoma patients whose primary site was treated with surgery, RT, or both in conjunction with systemic therapy from our institutional sarcoma database. Patient demographics, clinicopathologic characteristics, treatment details, and outcomes were analyzed. Analysis was controlled for propensity scores for receiving different local treatments.

Results: 230 patients with Ewing sarcoma, M0 at diagnosis, treated with local therapy from 1985-2016 were identified. Primary sites included: lower extremity 65 (28.3%), pelvis 50 (21.7%), trunk 32 (13.9%), head/neck 32 (13.9%), upper extremity 26 (11.3%), mobile spine 25 (10.9%)**.** 86 pts (37.4%) underwent surgery, 85 (37%) had surgery and RT (median dose 50.4 Gy), and 59 (25.6%) had RT only (median dose 55.8 Gy). Median follow up was 58 months. Median tumor size was 7 cm (1- 32 cm).

For patients with R1 resection, 90.2% received surgery and RT vs. 9.8% surgery only; for patients with R0 resection 66.9% had surgery only vs. 33.1% +adjuvant RT(Chi-Square < 0.0001). Local modality by anatomic site is listed in table 1.

Overall local control at 5 years was 93.7% (95%CI: 88.9-96.5): with surgery only 96.9% (95%CI: 88.8-99.2), surgery and RT 95.6% (95%CI: 88.6-96.2), and RT only 85.5% (95%CI: 70.3-93.3). Surgery and RT vs. surgery was no statistically different (p=0.447) whereas surgery and RT or surgery only resulted in better local control vs. RT only (p=0.019). However, in patients with positive surgical margins, OS, DFS, and LC were all significantly better with surgery and RT vs. surgery only (p=0.0038, 0.0016, and 0.0108, respectively).

For all appendicular skeleton, OS (p=0.0578), DFS (p=0.0235), and LC (p=0.0007) were all significantly better for surgery and RT or surgery vs. RT. For axial skeleton, there was no difference between the treatment strategies.

Median age of patients was 17 years (range 0-75 years). With no difference in local treatment strategies, local control in patients age <18 was similar to that of patients ≥ 18 at 91.6%(95%CI: 84.0-95.8) vs. 96.6%(95%CI: 89.5-98.9) p=0.453, but patients age ≥18 had a significantly higher rate of distant failures at a rate of 82.9%(95%CI: 74.1-88.9) vs. 68.9%(95%CI: 58.0-77.6) p=0.0097 and worse overall survival (p=0.0048). Later treatment year as a continuous variable was significantly associated with better local control (p=0.051). There was also dose dependent positive association with increasing RT dose (p=0.0405).

Finally, when adjusted by propensity score (for site, age, margin, and chemotherapy), there was no difference in OS, DFS, or LC between surgery and RT versus surgery only; however, when adjusted by propensity score (by site, age, total dose, and chemotherapy), surgery + RT was better than RT for local control (p=0.0275).

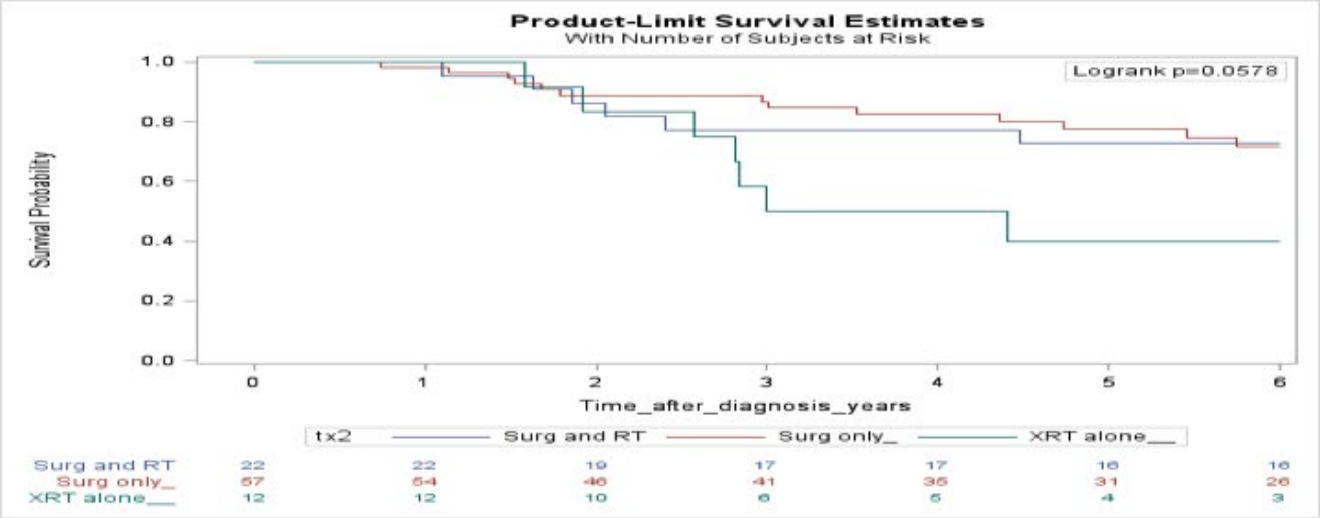
Conclusion: Overall primary local site control for M0 Ewing sarcoma was higher with surgery +/- RT (96.9% and 95.6^) with reasonable control using RT alone (85.5%) if necessary. Combined surgery and RT or RT alone was more likely to be used in axial vs. appendicular sites. For appendicular sites surgery and RT or surgery appear to be better than RT alone; however, for axial sites all local therapy modalities had equivalent outcomes. Patients with positive margin resection benefited from surgery and adjuvant RT vs. surgery only. While local control appears to be equal across age groups, patients 18 and older had higher rate of distant metastases and more needs to be done to improve survival in older patients.

TABLE 1: LOCAL TREATMENT MODALITY BY SITE

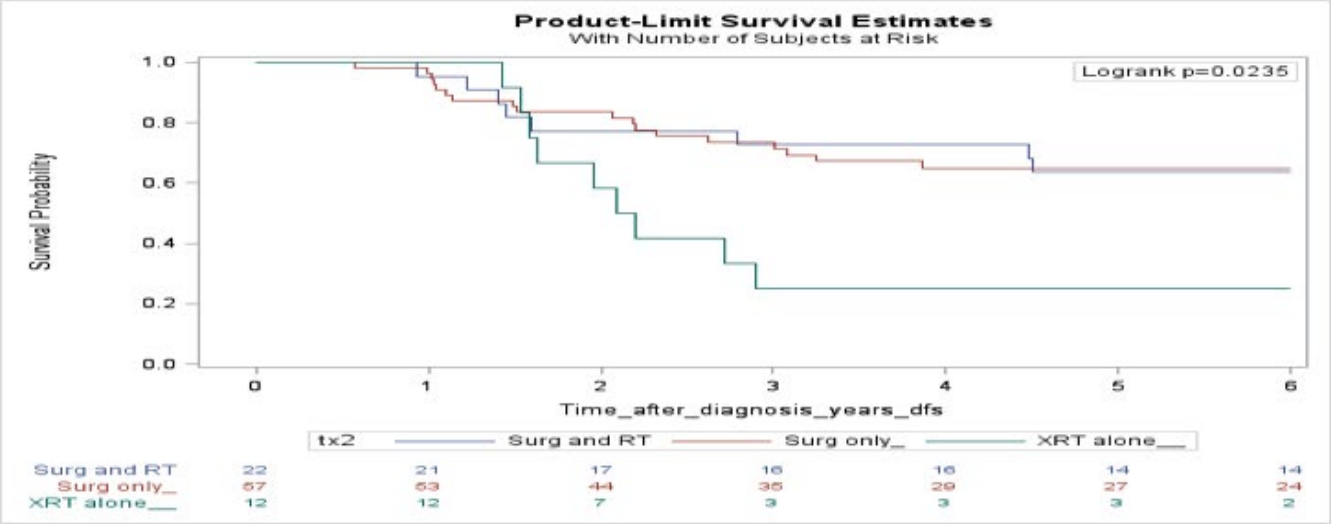
	Extremities	*Head/Neck*	*Spine*	*Trunk_*	*Pelvis*	*Total*
Sorgery+RT	22	14	17	15	18	86
	(24.18%)	(43.75%)	(68.00%)	(46.88%)	(36.00%)	
Surgery_alone	57	3	1	13	11	85
	(62.64%)	(9.38%)	(4.00%)	(40.63%)	(22.00%)	
XRT_alone	12	15	7	4	21	59
	(13.19%)	(46.88%)	(28.00%)	(12.5%)	(42.00%)	
Total n	***91***	***32***	***25***	***32***	***50***	***230***

Statistic	**DF**	**Value**	**Prob**
Chi-Square	10	64.7776	<.0001

Extremity (Upper Extremity, Low Extremity). Overall Survival p=0.0578



DFS p=0.0235



Local Control p=0.0007

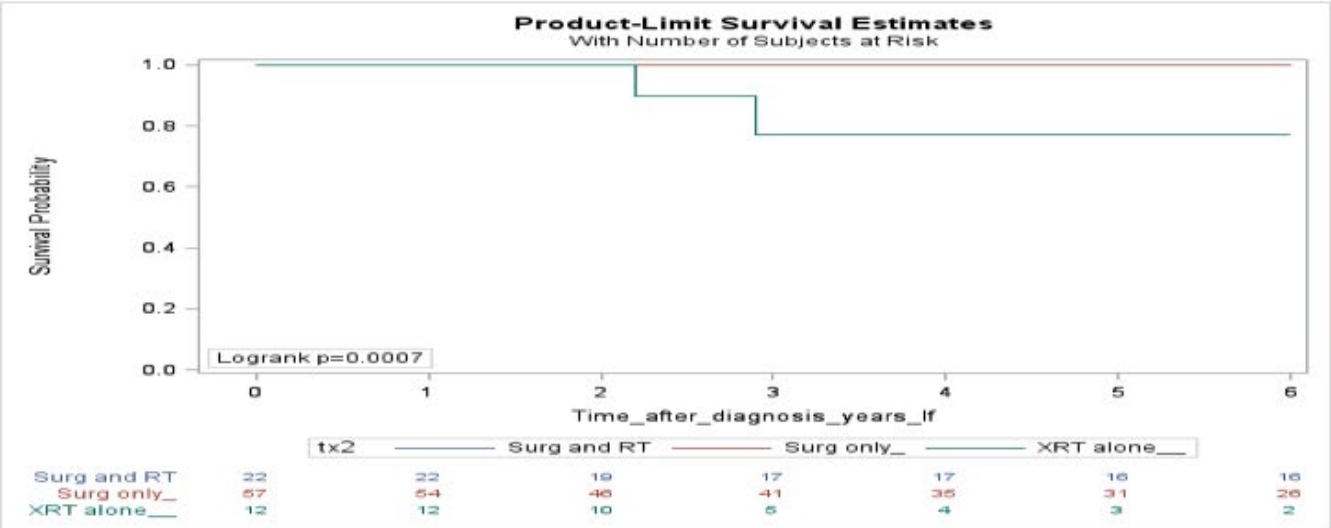
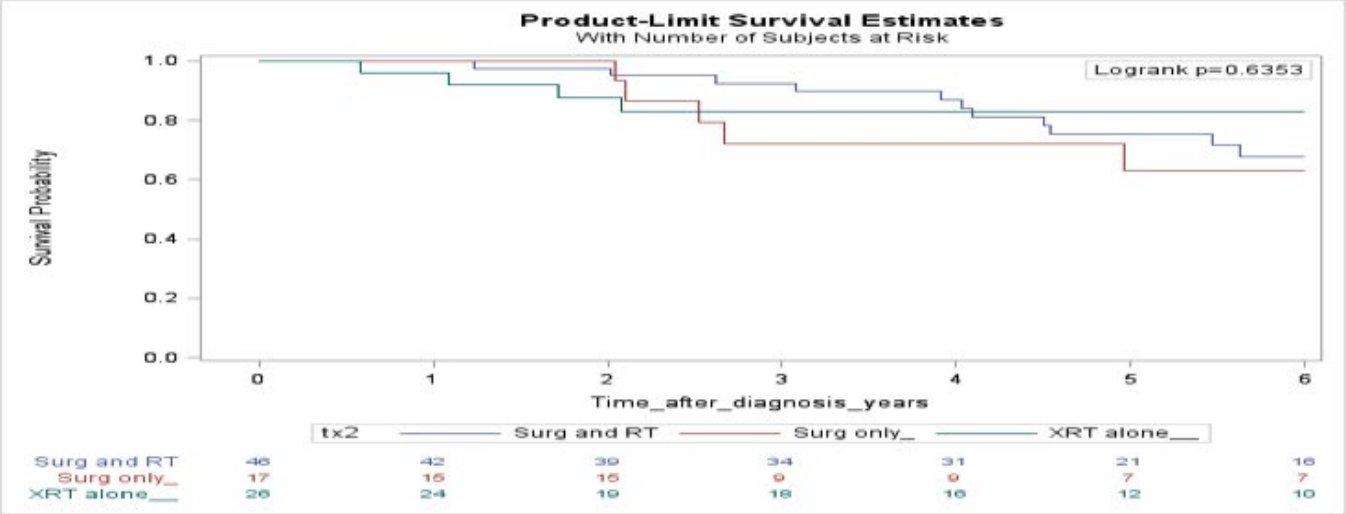
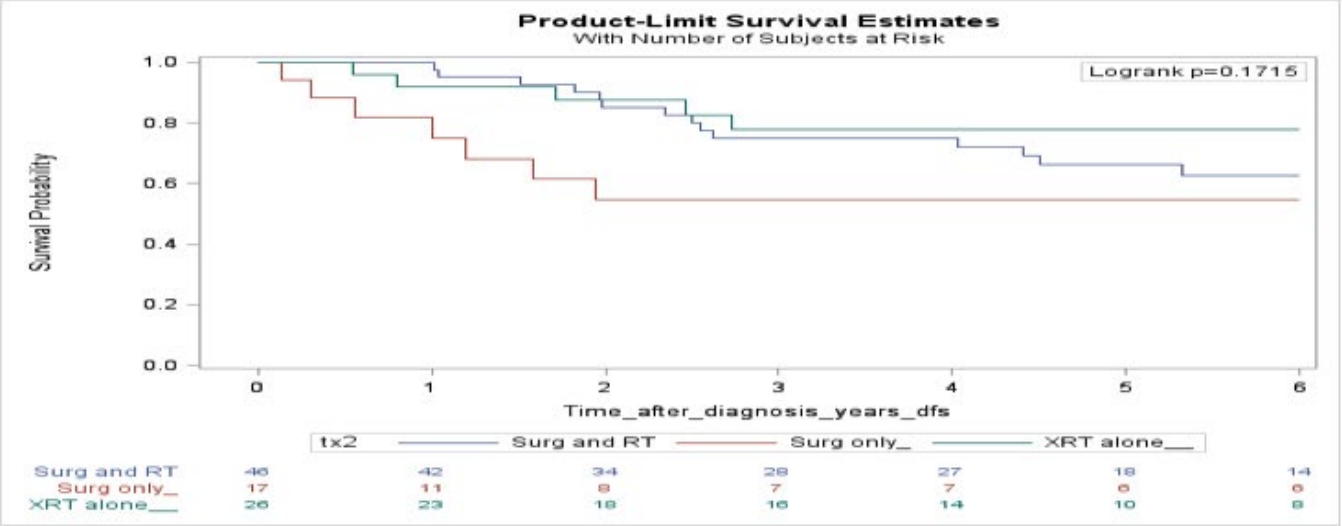


FIGURE 1: For appendicular skeleton, surgery+/- RT was better than RT only, whereas for axial skeleton, surgeyr+/-RT no different than RT only.

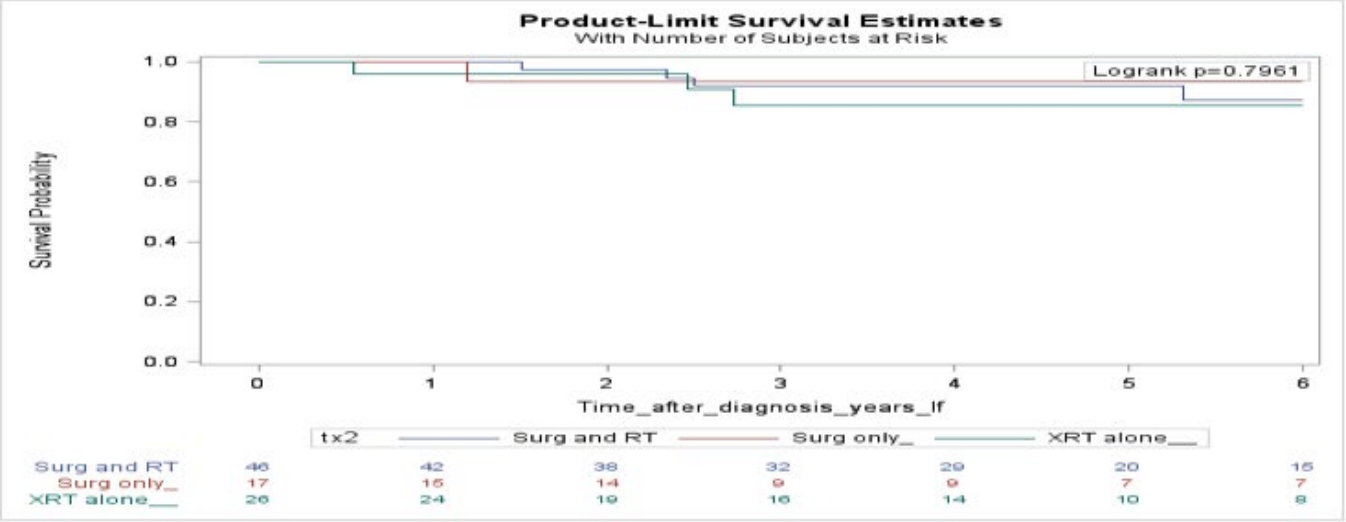
Other Sites (Head/Neck, Trunk, T_C_L spine) : Overall Survival p=0.6353



DFS p=0.1715



Local Control p=0.7961



Poster #068 3222958

GENOMIC ANALYSIS DOES NOT SUPPORT 'MALIGNANT TRANSFORMATION' OF OSTEOBLASTOMA TO OSTEOSARCOMA

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Objective: Although osteoblastomas and osteosarcomas are both bone-forming tumors, they represent different clinical and histologic entities. In a search of the English literature dating back 50 years, only 24 cases of this transformation have been reported. Given the rarity of this clinical phenomenon and lack of objective genetic data, it remains unclear whether this transformation is real or simply coincidental. We have identified a single patient who was initially diagnosed with and treated for a benign osteoblastoma and subsequently presented a few years later with a high-grade osteosarcoma in the same anatomic region. This scenario provides an opportunity to compare and contrast the genomic landscapes of these two tumors within a single patient treated at a single institution.

Methods: Whole genome sequencing was performed on samples obtained from a single patient including each of the two tumors, osteoblastoma (OB) and osteosarcoma (OS), and a matched germline sample. Sequencing and data analysis were performed to evaluate for structural variants, copy number variation, single nucleotide variants and insertions/deletions.

Results: Structural and copy number variation analysis revealed significant alterations in both tumors. In the osteoblastoma there were large chromosomal areas of copy number loss, contrasted to the frequent chromosomal gains observed in the osteosarcoma. Several areas of focal copy number gain were observed in both tumors, though none in an area of a known oncogene. There was near-zero overlap in the somatic small variants, somatic copy number variation pattern, and predicted structural variants in the osteoblastoma as compared to the osteosarcoma. A single pathogenic germline mutation in *BRIP1* R798X was identified with high confidence in all three samples.

Conclusion: Although malignant transformation has historically been accepted, review of the literature has revealed a paucity of convincing evidence and tremendous controversy has persisted. We found the benign and malignant tumors to have distinct genomic profiles with almost complete non-overlap in somatic changes including small variants, structural variants and copy number profile. Findings from this study strongly argue against "malignant transformation" in this case and conversely support two distinct neoplasms with entirely dissimilar genetic makeups.

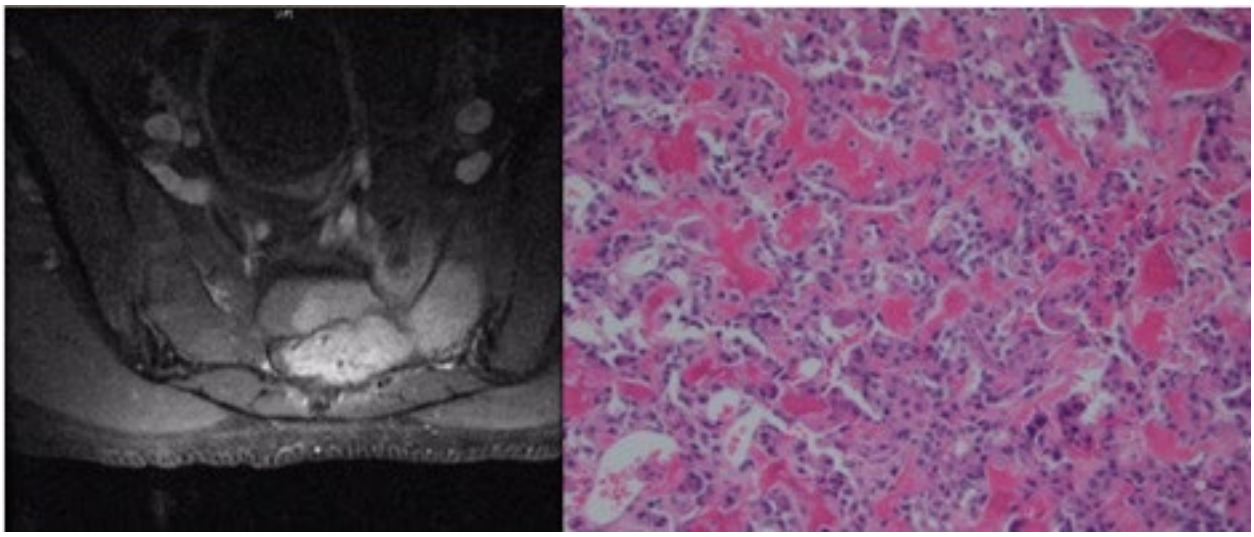

Figure 1: **(A)** 2010 Axial T1 weighted post-contrast, fat suppressed MRI of the lumbar spine demonstrating enhancement following contrast administration and **(B)** low power micrograph demonstrating relatively bland appearing spindle cells with small nuclei and occasional giant cells.

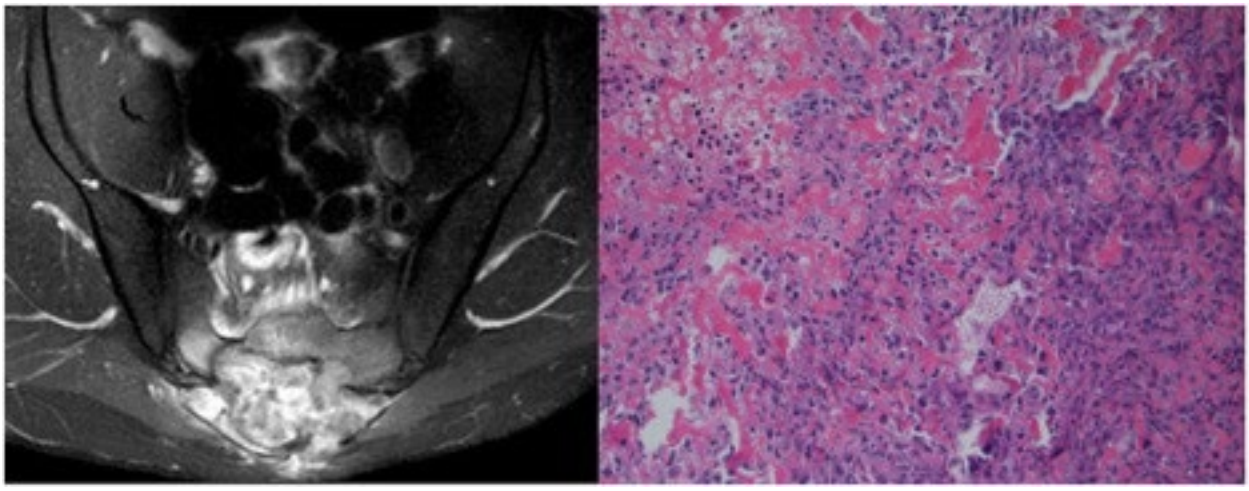

Figure 2: **(A)** 2015 Axial T1 weighted post-contrast, fat suppressed MRI of the pelvis demonstrating extensive enhancement following contrast administration and **(B)** low power micrograph demonstrating increased cellularity and osteoid formation

Poster #069 3231545

GENETIC TRANSPOSITION OF *TP53* REGULATORY ELEMENTS ELICITS ONCOGENE EXPRESSION IN OSTEOSARCOMA

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Objective: Many highly advanced cancers present genetic instability manifested by complex and heterogeneous chromosomal alterations. This is a curious paradox because a cancer cell with an unstable genome risks lethal alterations in every cell division. Genetic instability should therefore hamper rather than promote cancer growth and its competitive advantage has remained an enigma. Genome instability is typically coupled to loss of the *TP53* gene, the master guardian of genome integrity. The presence of *TP53* inactivation usually signals a poor long-term response to therapy and hence a poor outcome. The most common primary malignant tumor of bone, osteosarcoma, has one of the most rearranged genomes of all cancers and a high cell-to-cell variability. In osteosarcoma, *TP53* is commonly inactivated by structural rearrangements. We hypothesized that *TP53* rearrangements in osteosarcoma lead to the induction of cancer-driving genes by gene fusion or promoter swapping events. This novel driver mechanism would directly explain the benefit of a genetically unstable genome, as stimulation of *TP53* promoter elements by repeated DNA breaks would constitutively activate downstream oncogene expression.

Methods: Whole genome mate pair sequencing technology (Nextera Mate Pair, Illumina) was used to detect structural alterations affecting *TP53* in a discovery cohort of 36 chemotherapy-treated resection specimens and a validation cohort of 36 treatment-naïve diagnostic biopsies from pediatric and adult conventional osteosarcoma patients. Whole genome DNA copy number alterations were investigated in 120 osteosarcomas, including the aforementioned cases (Cytoscan HD arrays, Thermo Fischer Scientific). For 70 osteosarcomas and 13 control osteoblastomas, high-quality RNA was obtained, and global gene expression analysis was performed using RNA sequencing (TruSeq, Illumina). To monitor intratumor heterogeneity among individual cells, single cell low-pass whole genome sequencing (0.01x, 100 cells per tumor) was applied to osteosarcoma cells.

Results: There was a statistically significant correlation between structural alterations, detected by mate pair sequencing, affecting *TP53* and young age at diagnosis (two-tailed Mann-Whitney *U* test $P = 0.02$). By integrating array and sequencing data, we identified a subset of cases with copy number loss, or copy number neutral loss of heterozygosity, of whole or parts of the *TP53* coding region and concurrent relative copy number gain of the *TP53* promoter region along with regions of the proximal part of chromosome arm 17p. This was denoted as "*TP53* promoter gain". In perfect alignment with the sequencing data above, *TP53* promoter gain was non-randomly associated with young age of onset (two-tailed Mann-Whitney *U* test $P = 0.009$). Thus, in a subgroup of particularly young osteosarcoma patients, the *TP53* promoter is transposed to novel locations in the genome. This suggests that certain osteosarcomas are driven by a specific tumorigenic mechanism in which ectopic localization of the *TP53* promoter is a key element. In line with this, we show that activation of the *TP53* promoter by ongoing chromosomal damage leads to overexpression of oncogenes translocated into its vicinity.

Conclusion: Our results show how genetic instability can turn the regulatory elements of a tumor suppressor gene to paradoxically promote oncogenesis. More specifically, we demonstrate that *TP53* is not only lost in carcinogenesis, its promoter can be selected for during tumor evolution and elicit oncogene expression. Previous reports on promoter swapping involve promoters that are believed to be constitutively active in the cell-of-origin. In contrast, we show that acquired genetic damage can activate a transferred promoter to drive oncogene expression. This mechanism provides the first plausible explanation for a direct competitive advantage conferred by the complex genome seen in high-grade cancer.

Poster #070 3253039

SURVIVAL IN PATIENTS WITH CARCINOMAS PRESENTING WITH BONE METASTASIS AT DIAGNOSIS: A SEER POPULATION-BASED COHORT STUDY

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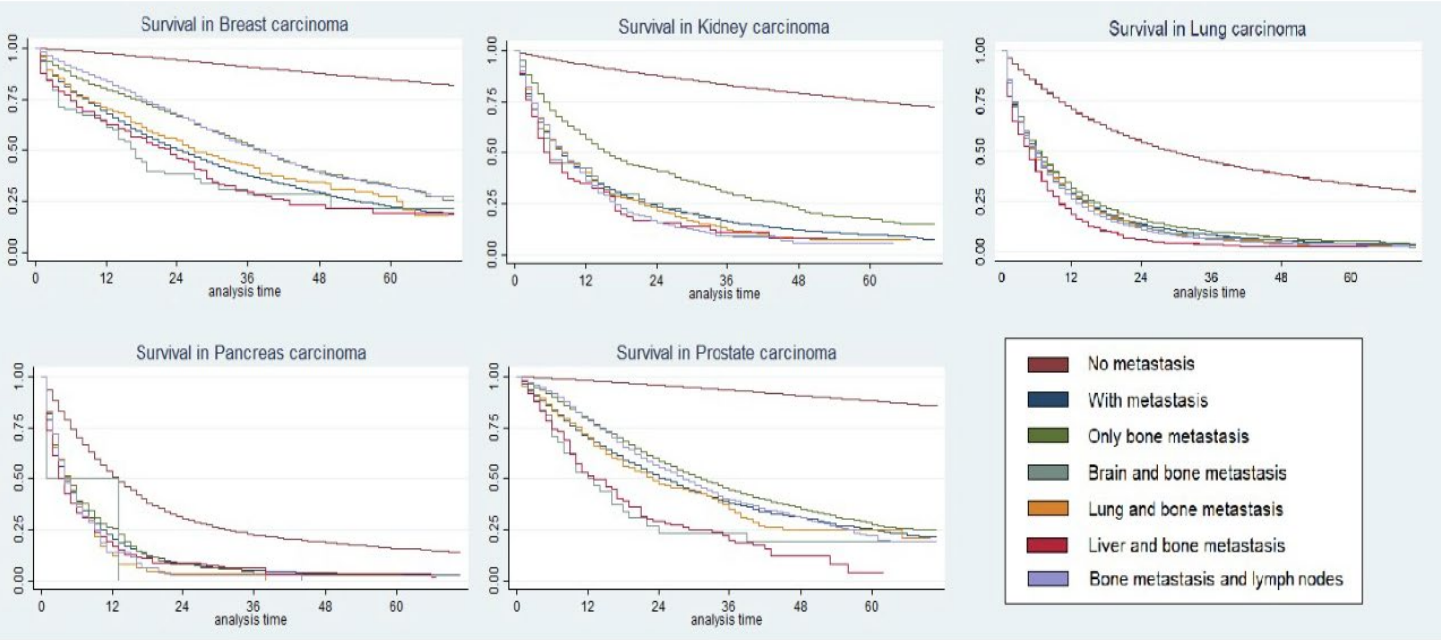
Objective: Bone is the third most common site of metastatic disease in patients with carcinomas, and it's a common reason of consult for musculoskeletal oncologists. The presence of bone metastases (BM) is usually associated with terminal-stage illness. Having other synchronous metastases in addition to bone metastases has been associated with impaired prognosis compared with isolated bone metastasis in patients with primary gynecological or prostate cancer. For other cancer types, this information is not available in a population-based setting. We hypothesize that survival for other carcinomas will follow the same pattern, being better when no synchronous metastases are observed. The purpose of this study was to (1) Identify the most common carcinomas presenting with bone metastasis at diagnosis, and to analyze (2) The survival of patients with carcinomas and BM at diagnosis, and (3) The effect on survival of synchronous metastasis to BM within that population based on a large population analysis.

Methods: Patients diagnosed with carcinoma between January 2010 and December 2015 were identified from the Surveillance, Epidemiology and End Results (SEER) database. The most common carcinomas presenting with BM at diagnosed were identified. Survival based on the presence of BM and synchronous metastases (lung, brain, liver, lymph nodes) was evaluated with Kaplan-Meier analysis. Five-year survival (%) and their corresponding 95% Confidence Intervals (CI) stratified by carcinoma type were calculated. Crude and adjusted Hazard Ratio (HR) and their corresponding 95% CI for mortality comparing isolated BM to other synchronous metastases were performed to identify the effect of synchronous metastases on final survival. The analysis was performed with Stata Statistical Software: Release 15, College Station, TX: StataCorp LLC, 2017.

Results: A total of 2,035,204 patients with carcinoma were identified of which 98,606 (4.85%) presented with BM at diagnosis. The most common carcinoma types with bone metastasis were lung (49.4%), prostate (15%), breast (13.6%), renal (4.7%) and pancreas (2.3%). Five-year survival with isolated BM was lowest in patients with pancreatic carcinoma (5.8%, 95% CI 3.0 to 9.9%), followed by lung carcinoma (8.1%, 95% CI 6.2 to 10.3%), and highest in patients with breast carcinoma (41.1%, 95% CI 38.6 to 43.5%). Synchronous metastases increased significantly the risk of mortality within the majority of carcinomas, except pancreatic carcinoma (with any metastases HR: 0.99, p=0.823; with lung HR:1.2, p=0.167; with brain HR:1.3, p=0.746; with liver HR: 1.14, p=0.208; with lymph nodes HR: 1.18, p=0.232) most likely due to its very poor prognosis.

Conclusion: Patients with carcinomas presenting with BM at diagnosis have a poor prognosis which is worsened if synchronous metastasis such as lung, brain, liver and lymph nodes are present. Knowing the survival of these patients is important information when planning orthopedic interventions.



Poster #071 3253213

PERCUTANEOUS CORE NEEDLE BIOPSY VERSUS OPEN BIOPSY OF MALIGNANT BONE TUMOR IN DIAGNOSTIC ACCURACY, COMPLICATIONS, AND COST-EFFECTIVENESS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Objective: Biopsy is a particularly important step in the appropriate treatment of bone sarcoma. Open biopsy (OB) is considered the gold standard although recent studies showed core needle biopsy (CNB) have the same accuracy and less invasiveness and lower costs. The objective of this systematic review and meta-analysis was to assess the value of open biopsy of bone sarcomas.

Methods: Medline/PubMed, Cochrane and Japan Medical Abstracts Society Web were searched for studies published between 1962 to 2018 providing data on diagnostic accuracy, safely and costs of percutaneous needle biopsy and open biopsy for malignant bone tumor. Two reviewers independently assessed the methodological quality. The Cochrane Collaboration's RevMan 5.1 software was used for the meta-analysis.

Results: Overall, 989 articles were identified articles were identified and 12 were eligible for inclusion. Of these, 1 was intervention study and 11 were observational study. There was no significant difference in the accuracy rate between the OB and CNB groups in observational studies (risk difference (RD), 0,08; 95% confidence interval (CI), 0.00–0.17; *P*=0.06), but OB have slight good accuracy rate. In the data on complications, no significant difference was found when comparing OB and CNB (risk ratio (RR), 1.5 confidence interval (CI), 0.37–6.00; *P*=0.57). CNB has apparent good cost-effectiveness (P<0.00001).

Conclusion: OB and CNB biopsies were equivalent in terms of efficiency and related complications, but OB may have slight higher accuracy rate. CNB was substantially less expensive. CNB could be the first line diagnostic test for malignant bone tumors.

Poster #072 3254536

CLINICAL PROGNOSTIC FACTORS AND TREATMENT OUTCOMES IN ADULT PATIENTS TREATED WITH EWING SARCOMA

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Objective: The data about treatment results of Ewing sarcoma in adult patients are limited due to the rarity of disease. The aim of our study was to analyzed prognostic factors and outcomes of therapy in this group of patients.

Methods: Between 2000 and 2018, 180 patients above 18y old diagnosed with Ewing sarcoma (EWSR1 rearrangement FISH confirmed in up to 50%) were treated in referral center according to current standard multimodal protocols. In 50 patients (28%) treatment was introduced outside our hospital, and 23 of them had started recommended therapy after 3 months since the date of biopsy/whoops operation. We analyzed prognostic factors and overall survival (OS).

Results: The median age of our patients was 28 years (18-67y), primary tumor was localized axially in 114 patients (63%), metastases at presentation were detected in 51 pts (28%). 5-year OS was 65% for patients with localized disease while in metastatic disease it was 15%, the number of metastases was a prognostic factor. 5-year OS was significantly better in patients treated at referral center (or when the patients were admitted to referral center within 3 months from the day of biopsy, which was performed outside referral center), comparing to patients treated outside referral center; and 5-year rates in total population were 28% and 14%, respectively. In terms of OS, unfavorable prognostic factor showing a statistical trend (p=0.098) was lower dose density of neoadjuvant chemotherapy due to toxicity.

Conclusion: In order to improve survival of patients with rare disease such as Ewing Sarcoma the consultation/treatment at the Tertiary Cancer Referral Center is mandatory.

Poster #073 3254945

MICRORNA-451A-CMTM6 NETWORK IS A POTENTIAL METASTASIS REGULATOR OF EWING SARCOMA CELLS

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Objective: Ewing sarcoma (EWS) is a second most common malignant bone tumor in children, and the prognosis of metastatic cases is extremely poor. Recently, microRNAs (miRNAs) play an important role in intracellular networks that occur in the carcinogenic process and it is attracting attention as a novel therapeutic target. In this study, we aimed to identify miRNAs related to the prognosis of EWS and clarify its target gene.

Methods: RNA was extracted from the tumor tissues of 10 EWS patients, and comprehensive miRNA expression analysis was performed using a microarray to identify miRNAs that correlate with prognosis. The identified miRNAs were introduced into EWS cell lines and comprehensive gene expression analysis was carried out by microarray analyses, and integrated analysis with a database (miRWalk) was performed to identify miRNA target genes.

Results: The expression profiles of miRNA in the tumor tissue of 4 patients with good prognosis group and 6 cases with poor prognosis group were compared, and 2 miRNAs (miR-451a, miR-487b) with significantly higher expression in good prognosis group, and one miRNA (miR-4763-3p) with significantly higher expression in the poor prognosis group were found. When these genes were introduced into EWS cell lines, miR-451a did not affect cell proliferation, but significantly suppressed cell migration. By gene expression analysis, CMTM6 and MIF were identified as candidate targets of miR-451a, whose expression was significantly reduced in miR-451a-transfected cells. From reporter assay, it was found that CMTM6 was a direct target gene of miR-451a. Finally, depletion of CMTM6 confirmed that EWS cell migration was significantly reduced.

Conclusion: The present study suggests that the miR-451a-CMTM6 network plays an important role in the metastasis process of EWS. In the future, we will understand the detailed mechanism of the metastasis by the miR-451a-CMTM6 network and verify the usefulness as a therapeutic target.

Poster #074 3255070

IDENTIFICATION OF FSTL1 AS A POSSIBLE THERAPEUTIC TARGET FOR OSTEOSARCOMA

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Objective: Osteosarcoma is the most common primary bone malignancy, which often affects children, adolescents and young adults, treated with surgical resection and intensive adjuvant chemotherapy. However it is very hard to treat relapsed patients or primary advanced patients because of few therapeutic tools after using initial chemotherapy. Follistatin-like1 (FSTL1) is known as an extracellular glycoprotein belonging to bone morphogenetic protein (BMP) protein family, which has a role of organ development like lung, ureter, central nervous system and skeletal system. FSTL1 was also found to be act as a cardioprotective protein after myocardial infarction. We have reported a novel function of FSTL1 regarding bone metastasis of cancer cells by mediating tumor cells' bone tropism and expanding a population of pluripotent mesenchymal stem-like CD45−ALCAM+ cells derived from bone marrow which suppresses antitumor immune responses in vitro and in vivo. Recently, we have found that FSTL1 is highly up-regulated in murine and human osteosarcoma cell lines which pushed us pursuing whether FSTL1 could serve as a possible target for treating osteosarcoma.

Methods: Fifty primary biopsy samples from osteosarcoma patients were collected from archived formalin-fixed paraffin-embedded (FFPE) blocks in our institute. All the patients approved usage of these samples for the research purpose. FSTL1 and DIP2A (major receptor of FSTL1) was stained with monoclonal anti-FSTL1 antibody and monoclonal anti-DIP2A antibody, respectively and detected with immunofluorescence conjugated secondary antibodies. Fifty-five serum samples were collected from 31 osteosarcoma patients out of the 50 primary osteosarcoma patients and each serum sample was analyzed FSTL1 containment with enzyme-linked immuno-sorbent assay (ELISA). We also created anti-FSTL1 blocking monoclonal antibody and examined antitumor effect of this antibody using murine syngenic osteosarcoma model and compared its effect with other immune checkpoint inhibitors.

Results: FSTL1 was highly and frequently up-regulated not only in murine and human OS cell lines but also in tumor tissues. Thirty-five out of 50 FFPE samples were strong or medium positivity for FSTL1 and 31 out of 50 samples showed strong or medium positivity for DIP2A. The expression level of FSTL1 and DIP2A were highly correlated. All the patients with tumor burden were detected FSTL1 in their serum. Moreover, FSTL1 were not detected in the serum from some patients without tumor burden, who were followed long after treatment without any recurrence. In syngenic osteosarcoma models implanted with murine NHOS or LM8 tumor cells, treatment with anti-FSTL1 blocking monoclonal antibody significantly induced anti-tumor effect. These effects seemed to be obtained through the blocking mechanism of FSTL1, which consequently induced several immunoregulatory cells. However, other commercially available immune checkpoint inhibitors (anti-PD1, anti-PDL1 and anti-CTLA4) did not succeed to activate important immunoregulatory cells in the osteosarcoma model, resulting in the moderate anti-tumor effects.

Conclusion: These results suggest that FSTL1 could be a target molecule for the novel treatment of osteosarcoma, particularly in patients with dysfunctional immunity.

Poster #075 3255111

EFFICACY OF IRE1α-XBP1 INHIBITORS IN OSTEOSARCOMAS

***Taisei Kurihara**; Yoshiyuki Suehara; Takuo Hayashi; Tatsuya Takagi; Keisuke Akaike; Kei Sano; Kazuo Kaneko; Tsuyoshi Saito*
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Objective: Bone and soft-tissue sarcoma are rare malignant tumors comprising numerous histological subtypes. Most of them are high-grade malignancy and novel effective therapies are still required. In recent years, endoplasmic reticulum stress (ERs) responses have been suggested to be involved in the aggressive behavior of various cancer types, prompting new studies focused on this area for the development of new therapies. Our previous study, based on comprehensive protein analyses, demonstrated an association between the ERs response and aggressiveness in Ewing sarcomas (ESs). We also found that IRE1α inhibitors exert antitumor activity in ESs. In the present study, to develop novel therapies for osteosarcomas (OSs), we investigated the functional activity of ERs and the antitumor effect induced by inhibitors of ERs in OSs.

Methods: We conducted reverse transcription polymerase chain reaction (RT-PCR) and quantitative (q)-PCR to elucidate the expression of XBP1 and XBP1 splicing (XBP1s) variants in OS cell lines (143B, MG63, KHOS, KHOSR2, U2OS, U2OSR2) and surgical materials. We also performed knockdown of XBP1 by using siRNA and conducted inhibitor assays using several IRE1α-XBP1 inhibitors. Furthermore, we investigated the association of the ERs responses pathway in OS cell lines.

Results: Expression of XBP1 was confirmed in OS cell lines and surgical materials by RT-PCR. The knockdown of XBP1 by siRNA inhibited the cell proliferation of the OS cell lines. Regarding inhibitor assays using IRE1α-XBP1 inhibitors, toyocamycin exerted a strong anti-tumor effect (IC50 <0.07 [0.04 to 0.07] μM) in the OS cell lines. Remarkably, drug resistant cell lines (KHOSR2, U2OSR2) also showed high antitumor effect. In each cell line, expressions of ERs response pathway related proteins (XBP1, ATF4,ATF6, etc) were clarified.

Conclusion: We confirmed the association between the ERs response and the tumor activity in OS. We also found that IRE1α-XBP1 inhibitors suppressed cell growth in OS. In a future study, we plan to verify the antitumor effects and toxicity of IRE1α-XBP1 inhibitors in OS *in vivo*. We believe that our findings may lead to the development of novel therapeutic strategies for OS.

Poster #076 3256081

DETECTION OF PULMONARY METASTASIS USING GFP TRANSFECTED PATIENT-DERIVED OSTEOSARCOMA CELLS IN A PATIENT-DERIVED ORTHOTOPIC XENOGRAFT (PDOX) MODEL

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Objective: Many models of metastases using fluorescent protein transfected cancer cell-line have been reported. However, few reports that metastases were detected by using patient-derived cell (PDC) have been reported. Osteosarcoma often developed lung metastases, causing poor outcome clinically. No reports that osteosarcoma PDC could detect distant metastases using fluorescent protein have been reported yet. In this study, we transfected green fluorescent protein (GFP) into PDC and evaluated metastatic action using GFP transfected osteosarcoma PDC (OS-PDC).

Methods: A 16-year-old girl patient developed the recurrence of osteosarcoma in left distal femur and surgical resection was performed. Primary cell culture was performed using the osteosarcoma tumor fragment. After several passage, OS-PDC could culture stably and the GFP lentiviral vector was transfected into OS-PDC. After the OS-PDC could express GFP stably, the GFP transfected OS-PDC cells were transplanted into tibia of nude mice to make patient-derived orthotopic xenograft (PDOX) model to observe distance metastases (n=3). Six weeks after transplantation, each organ was harvested and observed to detect distance metastasis using Fluorvivo®and OV100®as imaging systems.

Results: In two out of three mice, tumor volume of GFP transfected OS-PDC increased in size of orthotopic site and GFP in tumor could be seen. In one mouse, bilateral lung metastases were detected using Fluorvivo®and OV100®. None of metastases were detected in other organs.

Conclusion: The GFP transfected OS-PDC PDOX model was established to detect distant metastases. Since the patient developed lung metastases in clinical setting, the result of the current study reflected actual clinical behavior of osteosarcoma. Using GFP transfected PDC, the distance metastatic action can be observed under the image, suggesting the possibility of helping the patient to decide the future treatment strategy.

Poster #077 3256400

MIRNA COMPONENTS OF MRNA TRANSCRIPTIONAL PATTERNS DISCOVERED USING DIMENSIONAL REDUCTION ANALYSES OF OSTEOSARCOMA TUMOR RNA-SEQ DATA

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Objective: Osteosarcoma remains a serious problem and targeted therapy has not become a reality due to the sparsity of recurrent driver events. Our approach at the University of Minnesota has been to associate global tumor transcriptional patterns with patient outcomes. In previous work we have defined independent cell cycle, immune related, and 14q32 miRNA based transcriptional patterns that are reproducibly associated with osteosarcoma patient outcomes. However, understanding how mRNA and miRNA transcriptional patterns relate to each other remains unclear.

Methods: In this work we generated mRNA and miRNA profiles using RNA-Seq from individual human osteosarcoma tumors. We identified miRNA and mRNA transcriptional patterns using an unbiased dimensional reduction technique that we have developed, Gene Cluster Expression Summary Scoring (GCESS). miRNA and mRNA transcriptional patterns that correspond with each other were identified using Pearson correlation.

Results: This technique identified previously known associations, e.g. a strong muscle mRNA transcriptional pattern highly correlated with miRNA clusters containing miRNAs such as miR-1 and miR-133 known to be associated with muscle specific regulation. Strong correlations with known cell cycle and immune response mRNA clusters were also identified.

Conclusion: This technique provides an opportunity to identify correlated expression clusters across multiple platforms and could lead to a more complete understanding of the driver events, perhaps leading to novel therapeutic strategies for challenging diseases such as osteosarcoma.

Poster #078 3256446

UNUSUAL SITES OF OSTEOSARCOMA ISOLATED RELAPSE TO THE HEAD AND NECK REGION: PHARYNGEAL TONSIL AND THYROID

***Janay McKnight**; Anna Tamulonis; Paul Kent*
Rush University, Chicago, IL, USA

Objective: Recurrent osteosarcoma (OST) occurs in 30-50% of cases of initial localized disease and 80% of metastatic disease. Common sites of recurrence include lungs and bones (80% respectively). With the introduction of intensive, high-dose chemotherapy for the treatment of osteosarcoma, changes in the pattern of metastases observed at relapse have been reported. The unusual sites of recurrence include the kidney, brain, muscle, subcutaneous tissue, stomach, duodenum, and penis. OST relapse to the head and neck region are rare. Isolated recurrences in the tonsil or thyroid have not been previously reported. We present two cases of what we believe to be the only reported of osteosarcoma relapse isolated in the tonsil or thyroid.

Case Report 1: A 27-year-old male diagnosed with osteosarcoma relapse isolated to the tonsils after an isolated bone relapse and after initial diagnosis. He was originally treated off protocol (COG AOST0031) following the standard neoadjuvant chemotherapy protocol "MAP" (methotrexate, doxorubicin, and cis-platinum) to complete 29 weeks of therapy. He remained disease free, until an isolated condyle relapse was identified by biopsy and treated with an en bloc resection. The second relapse occurred 13 months after to the first recurrence. He presented with an enlarged right tonsil that was thought to be strep throat. The tonsillar swelling persisted which prompted an ENT evaluation and biopsy, identifying it as relapse of osteosarcoma. PET scan, bone scan, CT of head showed no other detectable disease. He was treated with resection, high-dose chemotherapy, and proton beam radiation therapy.

Case Report 2: A 29-year-old male diagnosed with osteosarcoma relapse isolated to the right thyroid after relapses to lung, ischium, and spine and following initial diagnosis. Right thyroid mass was first noted on CT scan performed 10 months after initial diagnosis at which time it measured 3.3 cm. Subsequent CT scan demonstrated interval increase in size to 4.5 cm. Subsequent neck ultrasound on confirmed a 4 x 4 x 5.2 cm mass isolated to the right thryoid. He is receiving chemotherapy—zometa and avastin— which has been held since due to his thoracotomies. He underwent right thoracotomy and right thyroid lobectomy.

Methods: We reviewed PubMed and Google Scholar using the keywords: "Osteosarcoma", "Relapse of Osteosarcoma", "Osteosarcoma relapse in tonsils", "Osteosarcoma relapse in thyroid", "Relapse of Osteosarcoma to head and neck region", "Unusual patterns of relapse in OS", and "Unusual sites of metastatic reoccurrence of osteosarcoma." The search was limited to the English Language.

Results: Osteosarcomas account for approximately 1% or less of all head and neck cancers. The vast majority occur in the mandible and maxilla. Of the 488 reported cases of OST relapse to the head and neck region *(Fig.1)*, this seems to be the only known case of an isolated relapse to the pharyngeal tonsil or thyroid.

Conclusion: Based on our literature review, we believe this is the only reported case of osteosarcoma relapse isolated to the tonsils or thyroid. We want to emphasize the importance of understanding that OST can occur in other parts of the body to avoid misdiagnosis, undertreatment/overtreatment, and/or no treatment at all. There has been an emerging pattern of unusual relapses after wide spread adoption of multiagent chemotherapy. In this case, the recurrence of osteosarcoma to the right pharyngeal tonsil resembled swollen lymph nodes in the neck mimicking strep throat, while the relapse to the thyroid was thought to be a sore throat. Reporting these rare cases of OST relapse can lead to early recognition of this relapse prevented further distant metastasis.

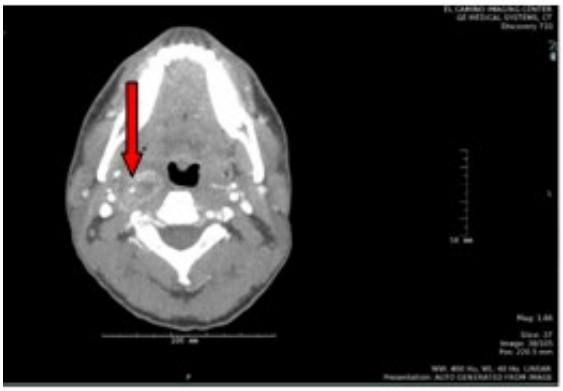
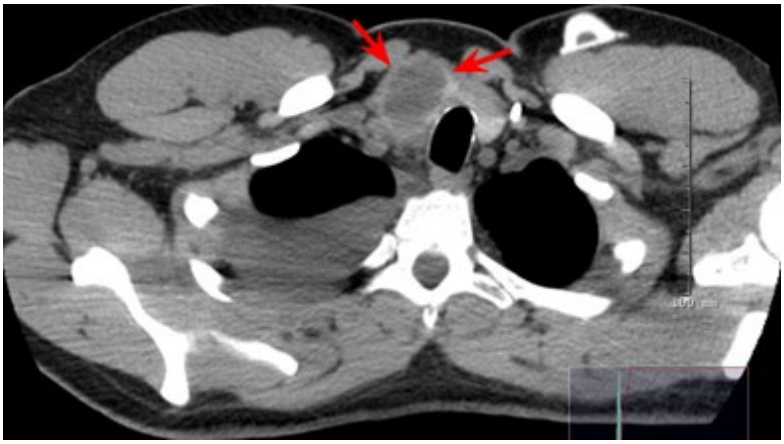


Image shows an axial CT scan acquired before treatment with the appearance of marked osteoid formation to the right pharyngeal tonsil.



CT of the right thyroid showing rapidly increasing palpable right thyroid mass measuring approximately 3.7 x 4.1 x 6.2 cm. It is largely occupied by a very suspicious, lobulated, irregular and heterogeneous mass measuring 4 x 4 x 5.2 cm.

Site	No. of cases (%)
Maxilla	183 (37.5)
Mandible	225 (46.11)
Skull	53 (10.86)
Skull base	9 (1.84)
Orbit	8 (1.64)
Sella	3 (0.61)
Others	7 (1.43)
Total	488 (100)

Figure 1. Case Reports and Data of Osteosarcoma Isolated Relapses to the Head and Neck Regions

Poster #079 3256479

CHANGES IN BODY MASS INDEX AMONG BONE SARCOMA SURVIVORS DURING LONG-TERM FOLLOW-UPS

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Objective: The purpose of this study was to track changes in weight/body mass index (BMI) during long-term follow-ups after treatment for primary bone sarcoma to assess the impact of clinicopathologic features and treatment modalities on weight.

Methods: In an IRB approved protocol, we identified 353 adult patients with bone sarcoma treated at our institution between 1995 and 2013 who were disease free for over five years, and collected information on the weight at baseline and at least one year after completion of treatment for the primary tumor, including surgery, radiotherapy and chemotherapy. 204 patients were excluded due to insufficient data on weight and/or height. Association between maximum weight/BMI gain and clinical parameters were assessed by Student t test or ANOVA. The multivariate logistic regression was used to analyze weight outcomes and risk variables.

Results: Among the 149 patients, the median age was 46 years old (range: 18-78). There are 72 females and 77 males. Primary sites include head and neck (26, 17.4%), upper extremity (9, 6.0%), lower extremity (45, 30.2%), spine and pelvis (63, 42.3%), rib/clavicle/sternum (6, 4.0%). Histology includes osteosarcoma (78, 52.3%), chondrosarcoma (18, 12.1%), chordoma (40, 26.8%) and Ewing sarcoma (13, 8.7%). The average BMI at baseline was 27.4 (standard error: 0.43), and 42 patients (28.2%) had a BMI above 30. 74 patients (49.7%) received chemotherapy, whereas 75 patients (50.3%) had radiotherapy. Along with tumor excision, 8 patients (5.4%) received arthroplasty in hip, 21 (14.1%) in knee, and 4 (2.7%) in shoulder; 27 patients (18.1%) underwent spinal stabilization. Five (3.4%) had lower extremity amputation. The median follow up was 9.5 years. The maximum weight gain was 3.27 kilograms on average, with an average change in maximum BMI gain of 1.11. BMI gain was higher in patients who had spine stabilization, lower extremity amputation, or arthroplasty in knee or hip (average: 1.74 vs 0.67, p=0.011). Multivariate logistic regression identified the surgery type as the only significant risk factor for BMI gain (p=0.011). There was no significant difference in BMI gain among different genders, primary tumor sites, histologies, tumor size, grade, chemotherapy, or radiotherapy.

Conclusion: Bone sarcoma survivors who had spine stabilization, lower extremity amputation, or arthroplasty in knee or hip are at higher risk in weight gain in the long term, most likely due to reduced mobility. Rehabilitation should be an important component of returning to normal daily activities after treatment.

Poster #080 3257333

OSTEONECROSIS OF THE JAW (ONJ) WITH DENOSUMAB (D'MAB) FOR GIANT-CELL TUMOR OF BONE (GCTB)

Noemi Simeone, Medicine[1]*; Anna Maria Frezza*[1]*; Elena Palassini*[1]*; Giacomo G. Baldi*[1]*; Alessandra Raimondi*[1]*; Rocio Lesta Mellid*[1]*; Carlo Morosi*[2]*; Gabriella Greco*[2]*; Massimo Maniezzo*[3]*; Marco Guzzo*[4]*; Paolo Casali*[1]*; Silvia Stacchiotti*[1]
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Objective: D'mab is approved for adults and skeletally mature adolescents with advanced GCTB. ONJ is a major adverse event reported in patients (pts) receiving bisphosphonate (BPs) and RANKL inhibitors such as d'mab. The phase 2 registration study of d'mab in GCTB (Lancet Oncology 2013), at a median follow-up of 13 months, reported 1% ONJ events, occurring roughly 13–20 months after treatment initiation. A more recent update of this study (Ann Oncol 2017), at a median follow-up of 55 months, showed 5.3 % ONJ events. We report herein on the incidence, clinical features and outcome of ONJ in pts affected by GCTB treated with d'mab at our institution.

Methods: All consecutive GCTB treated with d'mab at our institute for a locally advanced/metastatic GCTB from 2008 to 2019 were reviewed, focusing on pts who developed an ONJ. All cases received d'mab, 120 mg, on days 1, 8, 15, 29 and every 4 weeks thereafter, until evidence of progression or limiting toxicity. By institutional protocol, all pts underwent preventive dental screening with a complete oral clinical examination and ortopantomography (OPT) before starting d'mab and then annually while on therapy. All pts was encouraged to maintain good oral hygiene. Oral cavity and oral symptoms were then checked at every visit. In addition, pts were advised to immediately report any oral symptoms and in particular tooth mobility, pain or swelling or mouth sores failing to heal or the presence of secretions. In addition, pts on d'mab were asked to discuss in advance any dental procedure. Risk factors for ONJ (ie: use of dental appliances, denture traumatisms, poor oral hygiene, concurrent disease (e.g. diabetes, peripheral vasculopathy, concomitant use of corticosteroids) were registered.

Results: At a median follow up of 70 months (range 1-125), we observed 5 ONJ events (17.2%) in 29 consecutive cases treated with d'mab. ONJ was detected after 125, 119, 85 and 44 months of treatment, respectively. All pts responded to d'mab and were still responsive at the time on ONJ onset. In all cases, d'mab was stopped at the time of ONJ diagnosis. ONJ was diagnosed based on the presence of exposed bone in the maxillofacial region and confirmed by OPT and CT/MRI evaluation. One patient presented with bone exposure in the right lower region, 2 pts at the left lower region and the other one in the left upper region. A risk factor for ONJ was detected only in one pt, being a dental extraction 26 months before developing ONJ while on d'mab. In 2 cases, the ONJ was cured in 6 months with ozone treatment followed by surgical resection. These 2 pts had an evidence of GCTB progression after 9 and 11 months from d'mab interruption and were rechallenged with d'mab, with a new response. In one of two pts a local relapse of ONJ was evident after 41 months from d'mab rechallange and was treated again with d'mab interruption followed by O_3 gas + surgery with remission of the ONJ, while the second pt is still on d'mab and fine after 32 months from restarting d'mab. The other 2 pts are currently receiving O2 therapy and are scheduled to undergo surgery.

Conclusion: Our retrospective series suggest that ONJ incidence in GCTB pts requiring a prolonged treatment with d'mab for advanced disease might be higher than reported. Notably, all pts in our series developed ONJ after more than 3 years from starting GCTB, thus making a strict dental monitoring of pts receiving a long-term therapy mandatory. In our cases, GCTB progression was observed after d'mab interruption and d'mab, which is currently the only active drug known in the disease, could be rechallenge with a new response. The optimal treatment of ONJ for these pts remains to be defined.

Poster #081 3240850

MUSCULOSKELETAL AND TRANSLATIONAL RESEARCH BIOBANK (MTRB): ESTABLISHMENT, MAINTENANCE AND CHARACTERIZATION OF PATIENT-DERIVED OSTEOSARCOMA CELLS

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Objective: Osteosarcoma (OS) is a malignant bone tumor that affects children and adolescents. Standard therapy for OS comprises neoadjuvant chemotherapy, surgery and adjuvant chemotherapy. Patients who have a poor response to chemotherapy have a substantially worse survival than those with a good response with 5-year overall survival of around 45–55% and 75–80%, respectively. This is mainly due to complexity of intra- and inter-heterogeneity of OS. Musculoskeletal and translational research biobank (MTRB) established in 2012 aims to ensure excellent quality biological specimens to support various research projects in musculoskeletal sciences and translational research center. MTRB provides high-quality biospecimens to support numbers of our translational research including proteomics study, prognostic marker identification and epidemiological study. Therefore, the present study reveals our biobank system as well as internal assessment of patient-derived primary cells to ensure excellent quality biological specimens.

Methods: MTRB has practices and standard operating procedures annually to ensure excellent quality specimens, including
1. Clinical Annotation and Informed consent
2. Biospecimen collection and processing methods
3. Quality Assurance Procedures
4. Storage and retrieval

Results: *Clinical Data and Informed consent obtained*
Examples of the type of data that is valuable to collect: demographic, pathology, treatment and response, surgery data. *Biospecimen Harvesting, collected and Transportation* (Table 1) Preferably, blood collection should be done pre-operation and as close as possible to the time when the tissue is donated to the biobank and at an alternative time appropriate for the research study. Tissues are usually obtained from surgeries immediately after surgery. Keeping the tissue at a cold temperature immediately. No more than 30 minutes should elapse between the time of biopsy/resection and time of freezing of a given sample. Nowadays, MTRB storage 3 types of biological specimens that shown in Table 2

Quality of Primary cell lines
Accumulation of genetic aberrations of cancer cell lines that occurs with increasing passage numbers has limited their clinical correlation. When OS primary cell lines were grown they must be subcultured (passage) to obtain sufficient number of cells to make the characterization analyses and to cryopreserve obtained. In Fig.1 shown the OS primary cell lines morphology between passage 1, 3 and 10 from subcultured, was changed of cell morphological differed significantly in passage 1 and passage 10. The growth of cells proliferation (doubling-time) presented as increased of passages and doubling-time are correlated in Fig.2 The migration-invasion capacity of OS primary cell lines are shown in Fig.3 in passage 3 and 10 are significantly increased compared with passage 1.

Storage and retrieval system
The system can track sample volumes and link daughter aliquots and duplicate samples, and monitor freezing and thawing cycles, as well as disposal of them. Biobanks are intended to manage the safekeeping of clinical data and other sample associated data. MTRB has policies regarding security safeguards to protect data and personal information stored in its database against failure, loss and damage.

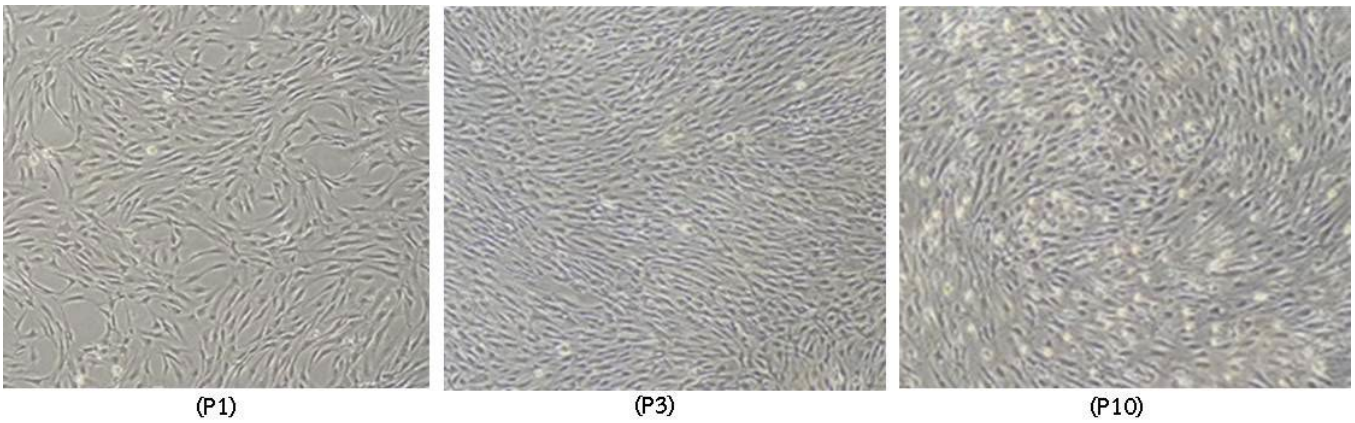
Conclusion: "Quality materials lead to quality results" Operations are standardized to international best practices, with audit systems in place to ensure compliance and regular testing to assure quality. The critical initiative for our future work to find solutions in advances in additional tumor types of samples collection techniques, modernizing our biological collections, deriving new cell lines, and building a clinical data repository for better cancer diagnostics and therapy.

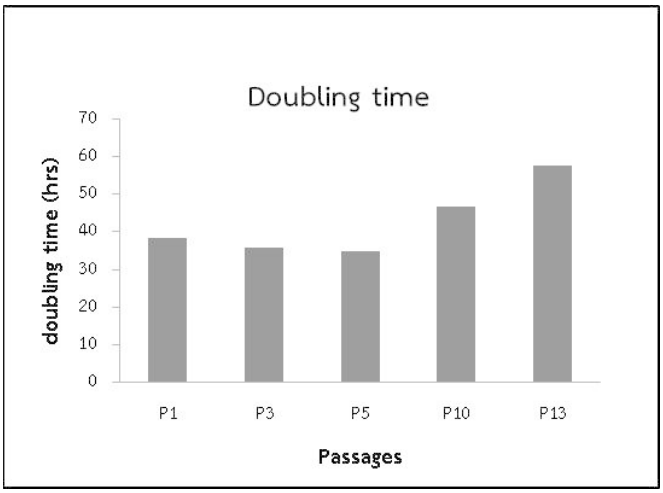
Table 1 Osteosarcoma patients recruited in MTRB from 2012-2018.

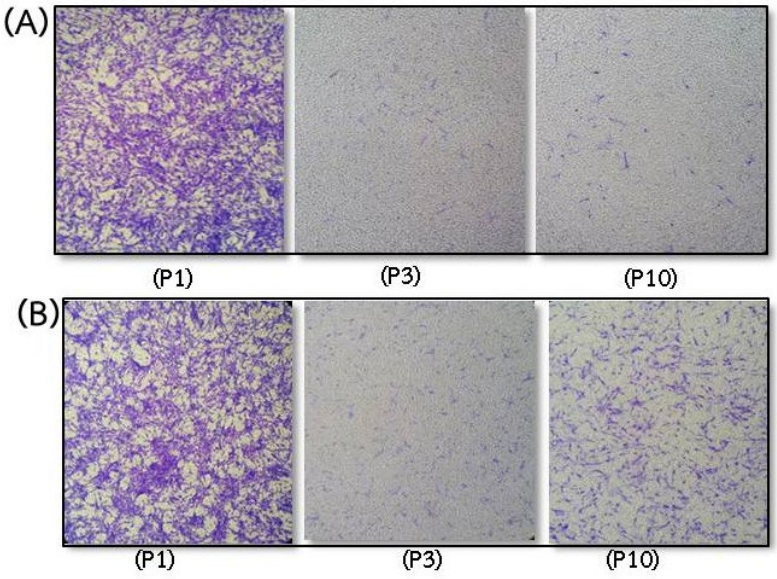
Time	Number of cases	Percentage (%)
2012	9	11
2013	19	23
2014	9	11
2015	12	15
2016	7	9
2017	11	13
2018	15	18
Total	82	100

Table 2 Types and numbers of specimens collected in MTRB

Percentage of biobanks storing specimens of this type	n	Percentage (%)
• Plasma / buffy coat	249	55
• Fresh tissue	113	25
• Primary cell line	94	21







Poster #082 3241715

DEVELOPING A NOVEL SPHEROID MODEL FOR CHONDROSARCOMA RESEARCH AND DRUG SCREENING

Ruichen Ma; *Feiqi Lu; Jonathan Mandell; Margaret L. Hankins; Anette Duensing; Rebecca Watters; Kurt R. Weiss*
University of Pittsburgh, Pittsburgh, PA, USA

Objective: Chondrosarcoma (CS) is a primary sarcoma of the bone whose histology resembles cartilage. CS has demonstrated resistance to both chemotherapy and radiation, and complete surgical removal is the only reliable treatment. In the setting of metastatic CS, survival is unlikely. Therefore, it is of importance that preclinical models mimic the disease with the greatest possible fidelity, in order to reliably develop new treatments. It has been demonstrated that three-dimensional (3D) cancer cell spheroids may recapitulate tumor biology with greater fidelity than traditional 2D techniques. This technology has not been widely reported in chondrosarcoma. We hypothesize that: 1- Development of 3D CS spheroid models will provide a better recapitulation of human disease, and 2- 3D CS cultures will enable more accurate predictions of novel treatments that are likely to be successful against CS.

Methods: Experiments were performed with the commercially-available HT-1080 CS cell line as well as a patient-derived cell population (KSCS). CS patient samples were collected fresh and were digested into single cell suspensions. Primary cells were cultured in flasks, trypsinized, and seeded into 96-well non-treated conical bottom plates with DMEM medium containing 0.5% methylcellulose. With the exception of tissue harvesting, spheroids from HT-1080 CS cells were created in an identical fashion. Images were taken every three days to monitor spheroids after formation. Spheroids were fixed using paraformaldehyde and pre-embedded with 3% agarose. Paraffin-embedded spheroids were sectioned and slides were stained with hematoxylin and eosin. RNA was extracted from 2D cell cultures and from day 14 spheroids. qPCR was performed to detect CS markers of interest including *VEGF*α, *COL2A1* and *COL10A1*. For drug studies, cells were seeded into 96-well plates for 2D culture and 3D culture. Treatments with disulfiram and copper were performed for 48 hours then presto-blue was added to detect cell viability.

Results: Under bright field microscopy, spheroids are round and produce an extracellular matrix. H&E staining reveals that cell-cell attachments are more pronounced at the periphery of the spheroid structure while the core is less dense. Cartilage-like matrix can be observed in the KSCS patient-derived spheroids. In the HT-1080 cell line, *VEGF*α, *COL2A1*, and *COL10A1* gene expression levels are upregulated significantly in spheroids compared to the monolayer cells. Disulfiram/copper has high cytotoxicity on HT-1080 cells grown in 2D monolayer, but 3D spheroids are highly resistant to this treatment.

Conclusion: This study demonstrates that the same CS cells grown in 2D vs. 3D produces different outcomes in gene expression and treatment response. CS spheroids demonstrate superior recapitulation of the primary tumor compared with CS cells grown in monolayer and might enable a more reliable path forward in the development of novel CS treatments. Further work is ongoing to characterize these spheroids and develop novel drug screens to test in this 3D model.

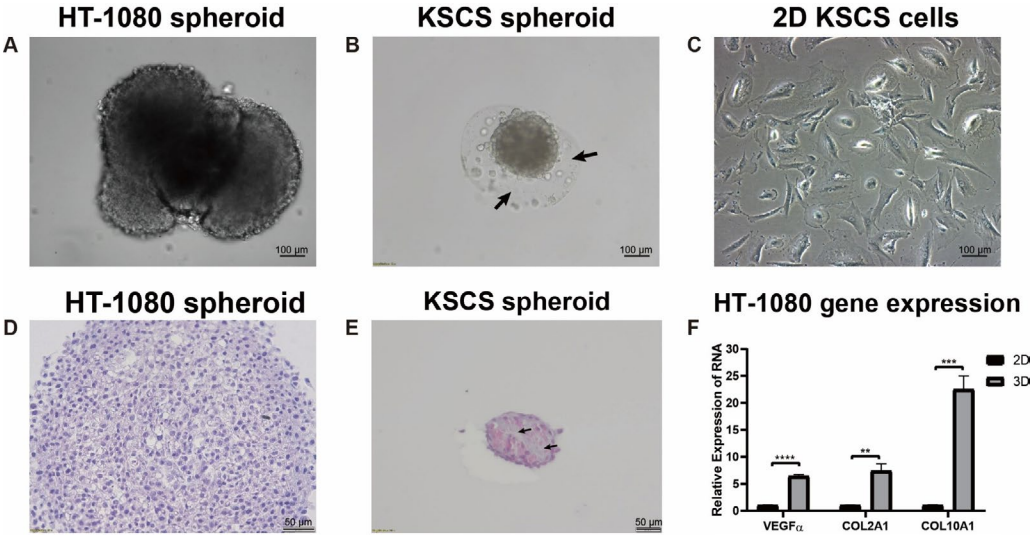


Figure 1. Characterizing 3D CS spheroid cultures in morphological and molecular aspects. A) Day 28 HT-1080 spheroid, 10X. B) Day 11 KSCS spheroid. The spheroid produces a matrix-like substance (arrow) at its periphery, 10X. C) Monolayer KSCS cells, 10X. D-E) H&E staining of HT-1080 and KSCS spheroids. In the KSCS spheroid, extracellular matrix (Arrow) is formed inside, 20X. F) VEGFα expression and CS markers COL2A1, COL10A1 expression are upregulated in the HT-1080 spheroid when compared to HT-1080 2D cultures. **p<0.0001.

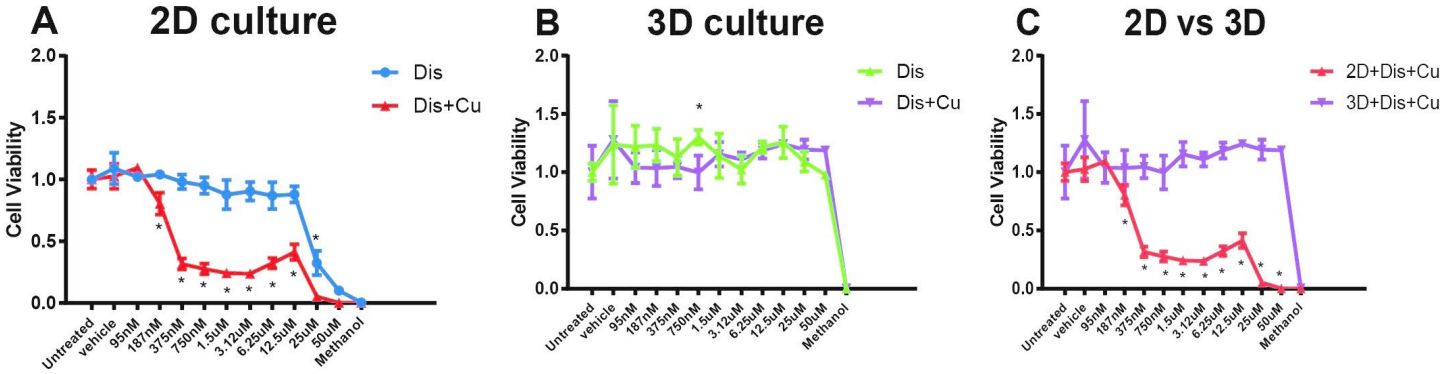


Figure 2. HT-1080 cells grown in spheroids demonstrate greater resistance to chemotherapy than cells grown in monolayer. A) In 2D culture, disulfiram has low cytotoxicity, whereas disulfiram plus 500nM copper decreases the IC50 dramatically. B) Both Disulfiram and Disulfiram/copper have little effect on spheroids. C) Compared to 2D culture, spheroids are highly resistant to Disulfiram/copper. *p<0.05.

Poster #083 3252962

THREE-DIMENSIONAL CULTURE MODEL OF CHONDROSARCOMA FOR CHEMO/RADIOTHERAPEUTIC TREATMENT PREDICTION

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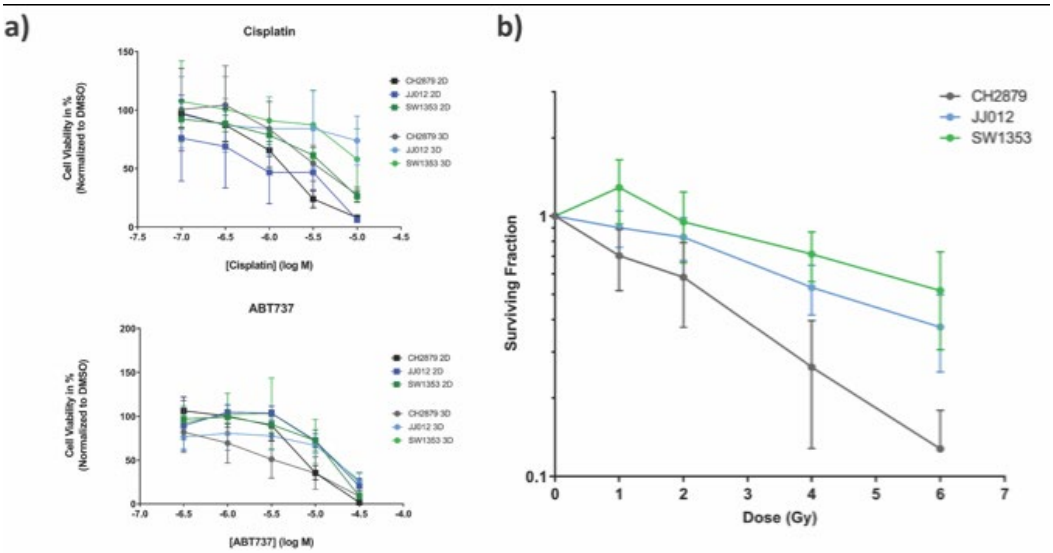
Objective: Chondrosarcomas are a malignant group of cartilaginous neoplasms, which account for around 20% of malignant bone tumors, making them the second most common bone malignancy after osteosarcoma. As chondrosarcoma is highly resistant to conventional chemotherapy and radiotherapy, surgical resection is the only curative treatment option, which is not always possible. The histological grade is so far the best prognosis predictor; grade II and III chondrosarcoma is significantly more aggressive compared to atypical cartilaginous tumour/ grade I chondrosarcoma. Five -year survival for grade II and III chondrosarcoma is low (53%) and novel chemo- and radio-therapeutic treatment options may improve outcome. Alternative chemo- and radio-therapy opportunities have been explored predominantly in cell lines, which are simple to use but lack the complexity encountered *in vivo*, such as the presence of matrix, and differing nutrient access. More representative *in vitro* models can be developed using 3D culture technologies. Here, we develop improved *in vitro* models for discovery of novel treatment options for chondrosarcoma patients.

Methods: Chondrosarcoma cell lines CH2879 (grade III), JJ012 (grade II) and SW1353 (grade II) were either cultured using conventional 2D methods or cultured in alginate scaffolds for up to 17 days. The model was validated using histological and immunohistochemical stains and the cell morphology was assessed by an expert bone tumor pathologist. The 2D and 3D models were then treated with a small panel of 7 compounds, including cisplatin, doxorubicin, temozolomide, mTOR (INK128), mutant-IDH (AGI-5198), BCL2 (ABT-737), and PARP (BMN673) inhibitors, as well as combination treatments, from 3-14 days and the cell viability was assessed using a Presto blue assay. Radiotherapy resistance of the 3D model was additionally assessed by a 3D colony formation assay, counting the amount of clonal spheroids formed after radiation.

Results: All three cell lines formed spheroids within the 3D alginate scaffold. An increase was observed in proteoglycan and collagen II production by the tumor spheroids over time of culture and lower expression of IGF1R was more representative of previously published results in primary tumors, compared to 2D cultures. The 3D cell cultures displayed varied responses compared to 2D culture of the same cell lines. For example, the two IDH mutant cell lines were, in general, more resistant to compounds compared to 2D and all three cell lines were more resistant to cisplatin treatment (e.g. CH2879 IC50- 2D= 1.49μM, 3D= 2.5μM) (Figure 1a). However, higher resistance to chemotherapeutics was not always observed, such as in the cell response to ABT-737 where CH2879 and JJ012 cell lines were more sensitive in 3D culture (Figure 1a). In general 3D cultured chondrosarcoma cell lines were more resistant to radiotherapy than previously published 2D colony formation assay results, showing SF2 values (surviving fraction of cells after 2 Gy radiation) of SF2= 0.95 in 3D compared to SF2= 0.88 for SW1353 and SF2= 0.83 in 3D compared to SF2= 0.55 for the JJ012 cell line (Figure1b).

Conclusion: We successfully characterised a 3D cell culture alginate model for the production of chondrosarcoma spheroids by assessing matrix production capabilities and resistance to culture-induced changes in IGF1R expression. Chemotherapeutic response comparison of 2D and 3D cell cultures showed both cases of higher resistance within the 3D model, as well as cases of higher sensitivity, indicating more complex differences between the *in vitro* approaches. Ability to assess radiotherapy response was also demonstrated by colony formation in 3D, and this method will be used in future to assess chemo- and radio-therapeutic combination treatment. Further comparisons with *in vivo* data are required in order to fully evaluate the level of representability of the model, however it is a promising step towards a more efficient therapeutic discovery pipeline for chondrosarcoma.



Poster #084 3252983

A RARE CASE OF MALIGNANT PERIVASCULAR EPITHELIOID TUMOR (PECOMA) IN THE LUMBAR SPINE

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Objective: Perivascular epithelioid cell tumor (PEComa) is a rare mesenchymal tumor of varying malignant potential. It has been described to arise from the lung and visceral organs, but PEComas of the bone are exceedingly rare. We herein report a case of malignant PEComa in the lumbar spine and subsequent detection of multiple lung metastases.

Methods: A 45-year-old woman presented with 3 years history of progressive low back pain. Plain radiographs revealed an increasing radiolucency in the L5 vertebral body. An MRI demonstrated destruction of the L5 vertebra with irregular signal changes. With a tentative diagnosis of spinal tumor, a thorough workup was performed to find a possible primary tumor that could result in metastasis, but none was found. A transpedicular biopsy was performed, which yielded a diagnosis of malignant mesenchymal tumor. Total en bloc spondylectomy was performed after preoperative transcatheter arterial embolization. A final diagnosis was malignant PEComa. Two months after the surgery, we confirmed a recurring mass on the right side of the L5 vertebral area on MRI. Because further surgery would not be able to totally resect the tumor, we selected carbon-ion radiotherapy (70.4 GyE / 16 sessions) for the recurrent lesion. One year later, CT scan demonstrated multiple lung lesions, so we performed excision of lung metastases. The patient has no local recurrence and distant metastasis now.

Results: PEComas are mesenchymal tumors composed of distinctive, so-called perivascular epitheloid cells, which were first described by Bonetti in 1992. Clear criteria for malignancy have not been elaborated in this very rare tumor entity until now. Confirmation of the diagnosis includes immunohistochemical studies that should show dual melanomyocytic differentiation. Surgery seems to be the only approach for aggressive cases. Therefore, we performed a wide excision of primary lesion and pulmonary metastasectomy.

Conclusion: We herein report a rare case of malignant PEComa involving the lumbar spine. It is therefore important to be aware of the pathologic features of this rare tumor entity.

Poster #085 3253046

NEUROTOXICITY IN OSTEOSARCOMA PATIENTS FOLLOWING TREATMENT WITH HIGH DOSE METHOTREXATE

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Objective: Osteosarcoma is the most common primary bone tumor in children [i]. Treatment is based on combination of tumor resection as local control, and the use of neoadjuvant and adjuvant chemotherapy as systemic therapy. The most active chemotherapeutic agents for localized osteosarcoma are methotrexate (MTX), Doxorubicin , and Cisplatin. MTX is a structural analog of folic acid, a required cofactor for the synthesis of purines and thymidine, as a result there is a depletion of purines and thymidylate and inhibiton of DNA synthesis[ii]. The occurrence of acute neurotoxicity is described both under parenteral and oral therapy with MTX in various different dosages and can manifest clinically through a series of symptoms such as headaches, loss of appetite, nausea, vomiting, arterial hypertension, confusion, agitation, lethargy, aphasia, pareses and convulsions[iii]

[i] Mirabello L, Troisi RJ, Savage SA. Osteosarcoma incidence and survival rates from 1973 to 2004: data from the Surveillance, Epidemiology, and End Results Program. Cancer 2009;115(7):1531–1543.

[ii] Allegra CJ, Fine RL, Drake JC, et al. Effect of methotrexate on intracellular folate pools in human MCF breast cancer cells. J Biol Chem 1986;261:6478–6485

[iii] ALL INS-2010 AIEOP-BFM ALL 2009 Toxicity (123-127)
23.3.7.2.2 Acute Neurotoxicity/MTX-Encephalopathy

Methods: In order to evaluate the incidence and characteristic of this phenomenon we reviewd all 55 cases of osteosarcoma that were treated in our department between 01.2011 – 12.2018, the management and outcomes were described.

Results: 5 of 55 patients (9%) with osteosarcoma were defined as cases of neurotoxicity following treatment with high dose MTX.

Conclusion: Neurotoxicity due to High dose methotrexate may be a more prevalent phenomenon than considered. The Treatment options of this adverse effect should be available and detailed in the chemotherapy protocol.

Poster #086 3255697

APPROACHES IN IMMUNOTHERAPY CHECKPOINT INHIBITORS FOR CHILDREN WITH REFRACTORY BONE SARCOMAS

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Objective: We aim to describe our experience of using FDA approved anti-PD-1agents (nivolumab and pembrolizumab) for treatment of refractory bone sarcomas. According to the data from Surveillance, Epidemiology, and End Results (SEER), in the year 2019 within the United States, estimated 3500 new cases diagnosed with bone sarcoma, representing less than 0.3%of all new cancers. The death rate is estimated to be 1660 cases per year at a rate of 0.4 deaths per 100,000 patients. SEER has reported a decrease in the five-year overall survival rate for patients with bone sarcomas from 66.9% in 2014 to 66.2% in 2015. There is a new need for therapies. Immunotherapy seeks to harness the class I specificity of the T-cell response and expand a T-cell population that will recognize a particular antigen. Programmed Cell Death Receptor (PD-1) delivers inhibitory signals that limits the initiation and duration of immune response on T and B lymphocytes and natural killers (NK) cells. PD-1 inhibitors, or 'checkpoint inhibitors' block this inhibition allowing full and stimulated immune expression. We provide an overview of patients with this new therapy.

Methods: We conducted a retrospective case review of Rush University Medical Center pediatric bone sarcoma patients who were treated with immune checkpoint inhibitors for immunotherapy approach. We also conducted a literature review of PubMed and Google Scholar using the keywords: "Immunotherapy in bone sarcoma", "PD-1 checkpoint inhibitors", "PD-1 anti-tumor immune response in sarcoma" and "Survival of immune checkpoint inhibitors in sarcoma." The search was limited to the English language.

Results: Case Reports: Patient 1, age 12, had recurrent refractory with metastatic osteosarcoma to the lungs. Patient was given 7 doses every 2 weeks of nivolumab at 3mg/kg. The treatment was well tolerated, and the patient presented no serious immune response adverse events (irEAs), other than fatigue and maintained an ECOG score of one. Patient one, after completing nivolumab immunotherapy, there was an interval decrease in the size of one of the right lower lobe calcified nodules from 2.1 x 1.4 cm to 0.6 x 0.6 cm, and an absence of previous PET uptake *(Fig. 1 and 2).* Patient 2, age 16, with metastatic refractory Ewings sarcoma was given 8 doses of nivolumab which was well tolerated with an ECOG score of one an no serious irAEs except fatigue. The calcified mass also decreased in size. According to our literature review, an ongoing studies are being reported providing positive outcomes of immune checkpoint inhibitors for bone sarcomas.

Conclusion: In both cases, nivolumab was well tolerated and exhibited antitumor activity in the patients with metatstatic refractory osteosarcoma or Ewings sarcoma. There are additional studies of immune checkpoint inhibitors in these diseases that are ongoing. Although multimodal therapies including surgical resection, chemotherapy, and radiation therapy have proven to give clinical outcomes of patients with bone sarcomas, the prognosis of patients has plateau over the years. Immunotherapies using immune checkpoint inhibitors have shown to be safe and effective for several types of refractory cancers with an emerging study for bone sarcoma therapies, although very little for children. We hope these studies and future combination trials will help to define the role of PD-1 blockade in children with bone sarcomas and other cancers. The next step is to continue clinical trials to determine which immune checkpoint inhibitors will benefit patients with refractory bone sarcomas.

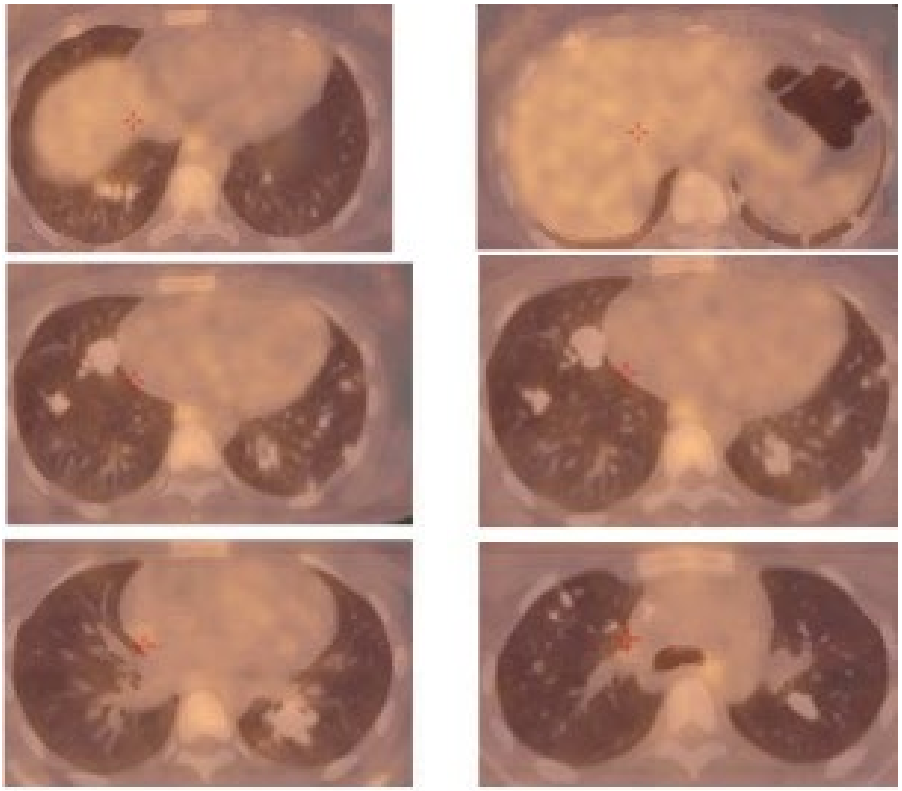

Figure 1. Metastatic Refractory Osteosarcoma to the right lower lobe calcified nodules (3/102) measuring 2.1 x 1.4 cm prior to the nivolumab immunotherpy.

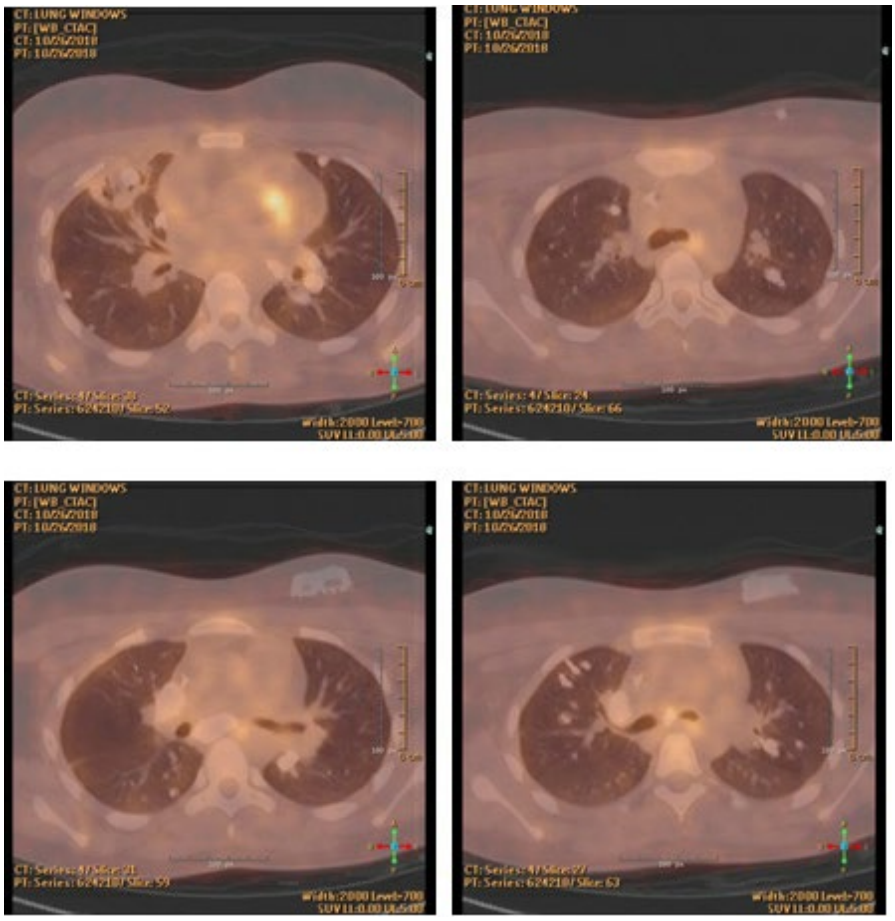

Figure 2. Metastatic Refractory Osteosarcoma to the right lower lobe calcified nodules (3/102) now measuring 0.6 x 0.6 cm during the nivolumab immunotherpy.

Poster #087 3256406

PROLONGED SURVIVAL AFTER SECOND RELAPSE OF OSTEOSARCOMA FOLLOWING REPEATED DOSES OF IMMUNOTHERAPY AND SAMARIUM

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Objective: The survival rate of patients after a relapse of Osteosarcoma (OST) is low. After a second relapse, the survival rate remains dismal. We wish to report a case of prolonged survival after a third disseminated relapse of OST associated with 2 cycles of immunotherapy and samarium.

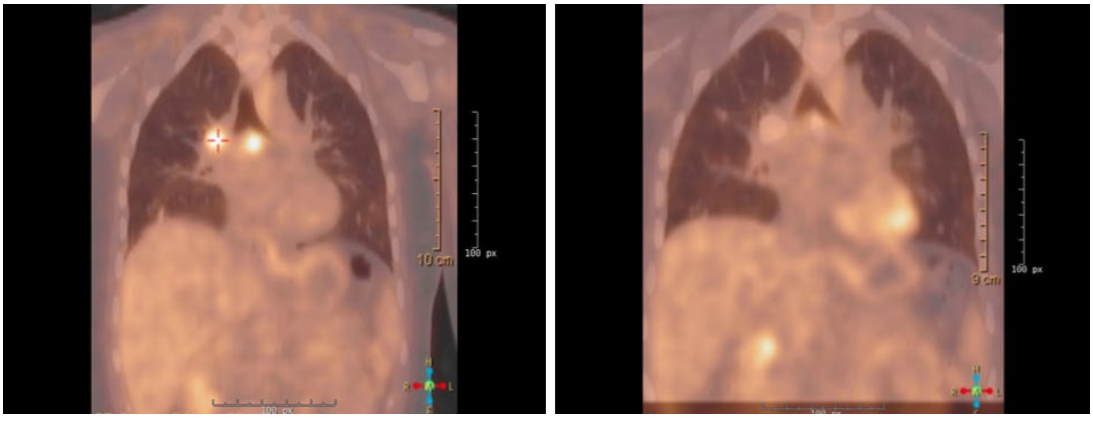
Background: OST is a disease in which malignant tumors form in the long bones of the arms or legs, OST is commonly diagnosed in children and adolescents. The long-term survival rate with localized OST is 70 to 75%. However, after a first-time relapse, the long-term survival rate drops to 20%. The prognosis following a second occurrence of OST is <5%. There are no standard therapies for multiply relapsed patients. The immune system plays an important role in OST as first described with "Cooley's Toxin" more than 100 years ago and more recently with survival advantage for select patients getting interferon therapy. The newest immunotherapies, checkpoint inhibitors, allow CD8 T-cells to overcome tumor-induced T-cell quiescence and recognize tumor antigens. These drugs are often used in combination the hopes that tumor cell injury from radiation or chemotherapy will produce immunoreactive neo-antigens and thus promote a robust T-cell response, similar to the abscopal principle.

Methods: We conducted a literature search on PubMed and Google Scholar with the keywords and phrases: "Osteosarcoma", "Pediatric", "Relapse", "Survival", "Immunotherapy", "Samarium".

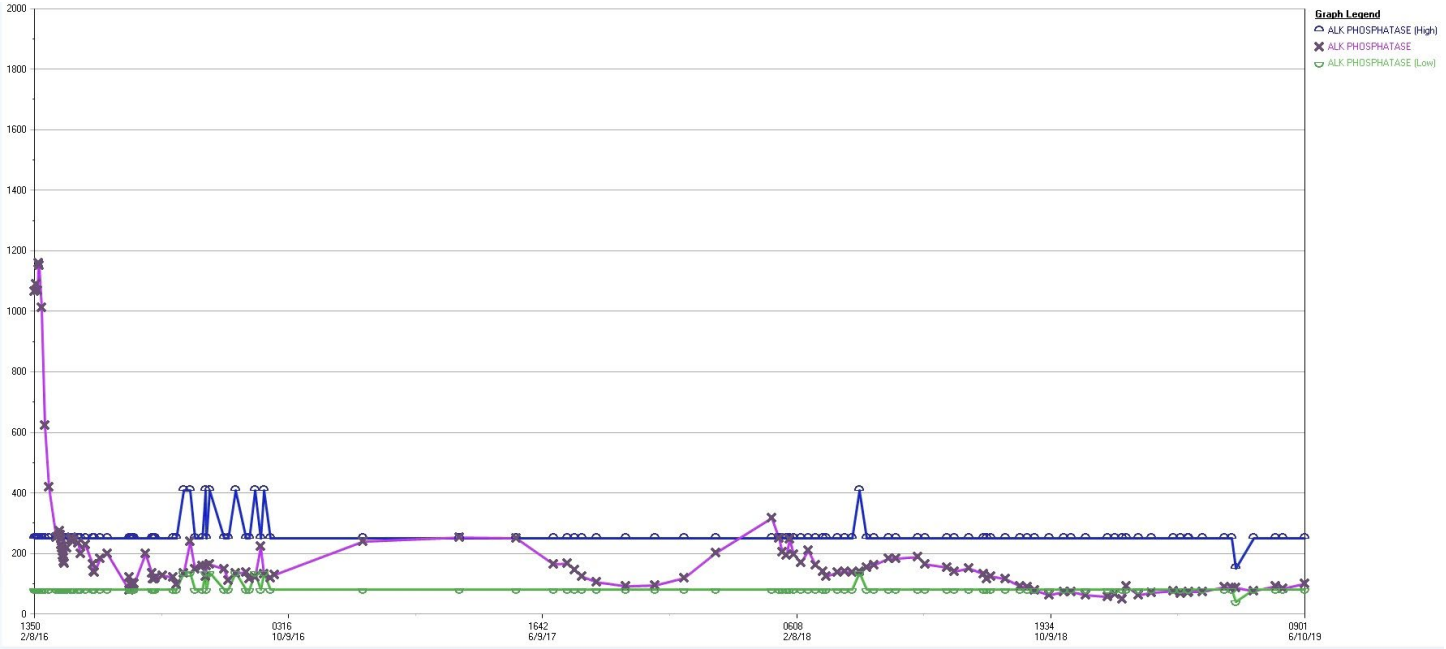
Results: This case seems to be the only reported instance of prolonged survival in a third relapse of OST as a result of immunotherapy and samarium.

Case Report: A 13-year-old female with previous loclaized (tibia) OST with 100% necrosis after initial surgery while on standard intensive chemotherapy (methotrexate, doxorubicin, and cisplatinuum) experienced a first relapse at 9 months after chemotherapy (bone), and then 5 months after that in her bilateral lungs (relapse #2), followed by massive dissemination 4 months later (multiple bones,medistinum) - relapse # 3, despite many agents thought to have activity against OST (gemcitabine, ifosfamide, taxotere, zoledronic acid, denosumab, bevicizumab). The disease was postive on tTc-99m MDP bone scan in bone and soft tissue.
The family and patient were offered, and consented to, concurrent samarium-153-EDTMP with checkpoint inhibitor therapy (Nivolumab). The goal was to augment the radiation tumor damaging effect with concurrent immunostimulation. At the time of writing the patient has had steady clinical and radiologic imrprovement now 12 months from the last relapse with dramatic decrease in tumor marker - alkaline phsophatase [include figure of decreasing tumor marker alkaline phsophates -- included below]

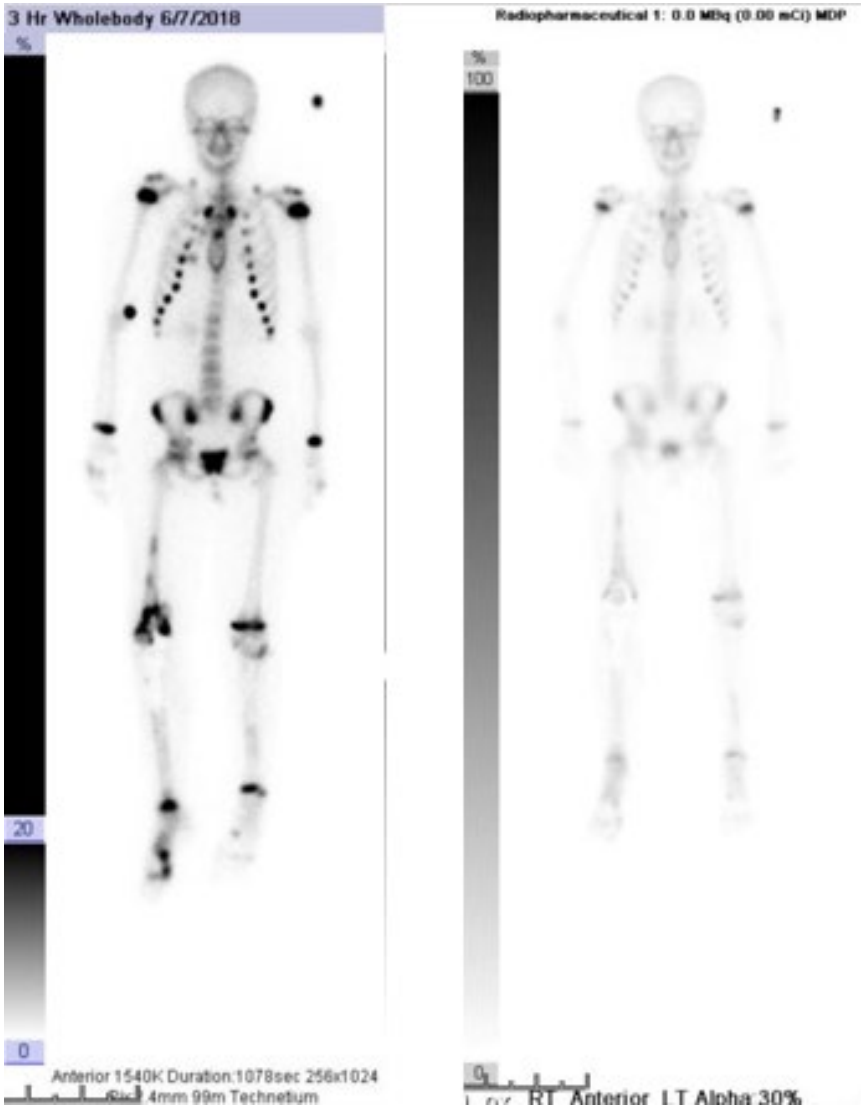
Conclusion: Our patient has had no serious side effects from the nivolumab-samarium combination other then fatigue and mild hypothyroidism corrected by thyroxine. Bone marrow function has remained normal. Her quality of life is very much improved, she has returned to school and is planning summer vacations. We are currently discussing a third samarium-nivolumab course. We believe the combination of check point inhibitors and samarium is worthy of further investigation in select patients with OST relapse and few other options.



PET showing uptake of mediastinal metastasis prior to samarium compared to
PET scans showing resolution of mediastinal disease after 2 cycles of samarium and nivolumab 14 months later.



Tumor marker response (alkaline phosphatase) to immuno-samarium therapy.



Bone scan prior to samarium showing multiple bony lesions compared to bone scan showing resolution of most bony lesions.

Poster #088 3239467

COMPREHENSIVE GENOMIC PROFILING (CGP) OF DESMOPLASTIC SMALL ROUND CELL TUMORS (DSRCT) IDENTIFIES PREDICTED NEOANTIGENIC GENE FUSIONS

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Objective: DSRCT are a rare and aggressive class of sarcomas that are characterized by an *EWSR1-WT1* gene fusion. Treatment of patients (pts) with DSRCT is limited to chemo-radiotherapy and surgical resection, due, in part, to a paucity of actionable genomic alterations (GAs). Despite this aggressive therapy, these pts have a 5-year survival rate of 15-25%. Yang et al. have recently highlighted that gene fusions can be a source of immunogenic neoantigens and identified an exceptional responder to immune checkpoint inhibition (ICI), despite having a low tumor mutational burden (TMB) (PMID: 31011208). We utilized CGP to analyze the predicted neoantigenicity of the *EWSR1-WT1* fusion in DSRCT and to ultimately more fully elucidate the potential of ICI as a therapeutic option for pts with this disease.

Methods: DSRCT were defined by central path review and the presence of the pathognomonic *EWSR1-WT1* fusion. 109 DSRCT were evaluated by hybrid capture-based CGP of 465 genes on DNA with additional fusion detection by RNA-seq of 265 genes. 5 samples did not have definitive *EWSR1-WT1* breakpoints and were filtered out, leaving a total of 104 *EWSR1-WT1* positive DSRCT for subsequent analyses. TMB was calculated on 1.2 Mb of sequenced DNA and microsatellite instability (MSI) was measured from 114 loci. Ancestry was inferred from over 50,000 SNPs that were previously characterized in the 1000 Genomes Project. HLA typing (Optitype) and neoantigen prediction (NetMHCpan) were performed as previously described (PMID: 28231819). Each HLA-A, -B, and -C allele was assessed for loss-of-heterozygosity (LOH) using the framework described in Sun et al. (PMID: 29415044).

Results: In this cohort, DSRCT pts are young (median age 25; range 6-55) and primarily male (79.8% of DSRCT pts v. 46% of other sarcoma pts; OR:4.6, p<3e-12). Using a SNP-based ancestry calling algorithm, pts of African (AFR) ancestry are overrepresented in DSCRT (24% of DSRCT pts v. 9.7% of other sarcoma pts; OR:3.0, p<2e-5). Outside of the *EWSR1-WT1* fusion, molecular characterization of DSRCT identified an average of 1.21 pathogenic GAs. DSRCT never harbored a high TMB (median 1.61 mut/Mb; range 0-9.7) and were never MSI. 86.5% of *EWSR1-WT1* fusions were formed through breakpoints in intron 7 of *EWSR1* and intron 7 of *WT1*. In the most common fusion product, exons 1-7 of *EWSR1* (5' end) are joined with exons 8-10 of *WT1* (3' end), resulting in a novel peptide sequence at the joining point. This peptide sequence was predicted to generate a neoantigen that bound strongly (<50 nM binding affinity) to two HLA types in 11.5% of all DSRCT pts. Outside of this, recurrent breakpoints were also found in intron 8 (4.8%), intron 9 (2.8%), and exon 7 (3.8%) of *EWSR1*. DSRCT never presented with pathogenic alterations in assessable genes that are critical for MHC class I presentation (*CIITA*, *B2M*). Only 1 of the 9 assessable DSRCT had LOH in a strongly bound HLA type.

Conclusion: These data recapitulate previous reports that pts with DSRCT tend to be young (median age 25) and predominantly male (79.8%). Ancestry calling from CGP corroborate previous reports of a high (>20%) AFR-descendant population among DSRCT pts. Examination of the DSRCT driver gene fusions unveiled 11.5% of pts with a strong predicted fusion associated neoantigen (11.5%) that may benefit from ICI. Given the highly recurrent breakpoint (86.5%), which results in a consistent and novel fusion peptide sequence, these data suggest that CGP may identify pts with high peptide-MHC affinity which may benefit from the rational use of immune checkpoint inhibitors, or even possibly potential personalized cancer vaccine options.

Poster #089 3245715

OUTCOME OF PALLIATIVE CHEMOTHERAPY IN ADULT DESMOPLASTIC SMALL ROUND CELL TUMOR PATIENTS: A SINGLE CENTER EXPERIENCE

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Objective: Desmoplastic small round cell tumor (DSRCT) is a rare subset of sarcoma, predominantly occurring in young males. Because of its rarity, little is known about its clinical course or appropriate treatment strategies. Current chemotherapeutic regimens used in this disease are largely based on small-sized studies, and when it comes to the role of second-line-and-above chemotherapy clinical evidence is even scarcer. We analyzed survival outcomes and treatments given in those patients.

Methods: We retrospectively reviewed 14 patients who were treated for DSRCT in Asan Medical Center between 2004 and 2018, using a clinical database system (Asan BiomedicaL research Environment, ABLE).

Results: Median follow-up was 17.2 months (range: 7.5-49.0). The median age at diagnosis was 25 years old (range: 20-40) and 13 out of 14 patients (92.9%) were male. At the time of diagnosis, all 14 patients had intra-abdominal tumor and 10 (71.4%) of them also presented with extra-abdominal metastasis. All but one were diagnosed with core needle biopsy. Median maximal diameter of tumor in the axial CT plane was 12.5 cm (range: 4.5-18.5). Most patients had peritoneal involvement (12 patients, 85.7%) and lymph node involvement (13 patients, 92.9%) at diagnosis, followed by liver (8 patients, 57.1%) and lung (3 patients, 21.4%). Three patients (21.4%) underwent surgery including two R2 resections and one R1 resection.

First-line chemotherapy regimen was either CVD/IE (cyclophosphamide, vincristine, doxorubicin as P6 protocol) (9 patients, 64.3%) or VAC/IE (vincristine, doxorubicin, cyclophosphamide) (5 patients, 35.7%). Best overall response (BOR) to first-line chemotherapy was partial response (PR) in 8 patients (57.1%) and stable disease (SD) in 6 patients (42.9%). Second-line chemotherapy was given to 10 patients. Most commonly used second-line regimens were IE/ICE (ifosfamide, carboplatin, etoposide) for 3 patients and VIP/IP (etoposide, ifosfamide, cisplatin) for 3 patients. BOR to second-line chemotherapy was SD in 5 patients and progressive disease (PD) in one patient.

Radiotherapy was given to 2 patients (14.3%) to abdominopelvic mass for palliation.

Median overall survival (OS) from the initiation of any therapy was 23.7 months (95% CI: 17.6-29.7). Survival rate was 82.5% at 1 year, 36.7% at 2 year, and 18.3% at 3 year, respectively.

Progression-free survival (PFS) for first-line chemotherapy was 9.9 months (95% CI: 6.9-12.8 months). No significant differences in PFS or OS were found between VAC/IE or CVD/IE regimen. PFS for second-line chemotherapy was 4.9 months (95% CI: 0.7-9.1). On univariate analysis for OS, ≤ 2 metastatic sites at presentation (24.5 months vs. 13.7 months, p=0.041) and ≥ 2 surgeries (37.9 months vs. 19.9 months, p=0.024) showed association with longer survival.

Conclusion: DSRCT is rare and chemotherapy-responsive in many cases, yet fatal. Multimodality treatment involving surgery and multiple lines of chemotherapy should be considered if feasible.

Sex	Age at Dx	Extra-abdominal lesion	OS (mo)	1st line CTx	PFS (mo)	BOR	2nd line CTx	PFS (mo)	BOR	3rd line CTx	PFS (mo)	BOR	No. of surgery	Status
M	31	No	49	VAC / IE	23	SD	VIP	12.4	SD	VIP (redo)	3.6	SD	2	Dead
M	20	No	38.1	P6 protocol	20.5	PR	VDC	1.7	NE	GD	2.5	PR	3	Dead
M	40	Yes	26.9	VAC / IE	12.7	SD	VIP	6.2	SD	TP	6.3	SD	0	Dead
M	22	No	24.7	VAC / IE	11.7	PR	Dacarbazine /cisplatin	4.9	SD	VIP	7.3	SD	0	Dead
M	21	Yes	24.1	P6 protocol	10.7	PR	IE	1.4	SD				0	Dead
M	21	Yes	23.9	P6 protocol	7.1	PR	IE (redo)	8.6	SD	GD	2.2	SD	0	Dead
M	26	Yes	20.1	P6 protocol	8	PR	GD	2.1	PD	CYVADIC	4.8	NE	1	Dead
F	32	Yes	14.3	VAC / IE	10.5	SD							0	Dead
M	22	Yes	13.5	P6 protocol	9.7	SD							0	Dead
M	23	No	12	P6 protocol	6.6	SD							0	Dead
M	30	Yes	8.9	VAC / IE	7.9	SD	Trabectedine	0.9	NE				0	Dead
M	23	Yes	Alive	P6 protocol	9.9	PR	IP		Ongoing				0	Alive w/ disease
M	27	Yes	Alive	P6 protocol	7.2	PR	ICE		Ongoing				0	Alive w/ disease
M	36	Yes	Alive	P6 protocol	C	PR							0	Alive w/ disease

Dx=diagnosis; OS=overall survival; mo=months; CTx=chemotherapy; PFS=progression-free survival; BOR=best overall response; VAC/IE=vincristine 2 mg on D1, doxorubicin 75 mg/m2 on D1, cyclophosphamide 1,200 mg/m2 on D1, etoposide 100 mg/m2 on D1-5, ifosfamide 1,800 mg/m2 on D1-5 for every 3 weeks; P6 protocol=cyclophosphamide 2,100 mg/m2/day on D1-2, vincristine 0.67 mg/m2/day continuous infusion on D1-3, doxorubicin 25 mg/m2/day continuous infusion on D1-3 for cycles 1, 2, 3, and 6, ifosfamide 1,800 mg/m2 on D1-5, etoposide 100 mg/m2 on D1-5 for cycles 4, 5, and 7; VIP=etoposide, ifosfamide, cisplatin; VDC=vincristine, dactinomycin, cyclophosphamide; IE=ifosfamide, etoposide; GD=gemcitabine, docetaxel; TP=paclitaxel, cisplatin; CYVADIC=cyclophosphamide, vincristine, doxorubicin, dacarbazine; PR=partial response; SD=stable disease; PD=progressive disease; NE=not evaluable; C=censored

Poster #090 3249075

COMPREHENSIVE GENOMIC AND IMMUNE-PROFILING OF HYPERPROGRESSIVE DESMOPLASTIC SMALL ROUND CELL TUMORS TREATED WITH IMMUNE CHECKPOINT INHIBITORS

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[2]*University of Texas MD Anderson, Houston, TX, USA*

Objective: Desmoplastic small round cell tumors (DSRCT) are highly aggressive sarcomas characterized by the pathognomonic EWSR1-WT1 fusion. Since the long-term survival is poor despite optimal management, patients with advanced DSRCT are often referred to investigational immunotherapy or off-label immunotherapy with checkpoint inhibitors.
Hyper-progression, defined as a >2-fold increase in tumor growth rate (TGR), is observed in multiple tumor types including GIST and has been associated with immunotherapy treatment. Herein, we report this phenomenon in DSRCT and performed comprehensive profiling.

Methods: This pilot study assessed three patients with DSRCT treated with immune checkpoint therapy with anti-PD-1/PD-L1 and/or CTLA-4 blockade. Prior TGR and anti-PD-1/PD-L1 on-treatment TGR were compared. Associations between TGR and clinicopathologic characteristics were computed. Histopathology and immunohistochemistry were reviewed and patients underwent comprehensive clinical next generation sequencing (FoundationOne®) and comprehensive immuno-profiling (NANT GPS). We reviewed AACR GENIE database for TMB and microsatellite stability data.

Results: Three patients with DSRCT had hyperprogression. Two pts received anti-PD-1 antibody (N=2) and 1 patient received combined anti-PD-1 and anti-CTLA-4 antibody. Patients were all re-staged to confirm progression vs pseudo-progression vs hyper-progression. All 3 were males (age 37, 25 and 46 yrs). All tumors harbored EWSR1-WT1 translocation. 2 pts with NGS showed low TMB (2 muts/mb), microsatellite stable disease. Comprehensive immune-profiling in one patient revealed high expression of IDO1 (TPM= 146.65, med=109.56), PDCD1 (TPM=110.09, Median 2.98) and Lag3 (TPM=14.9, Med=4.68) with low CD274/PDL1 (TPM=0.42, Med3.88) and CTLA-4 expression (TPM=0.38, Med 2.94). Comprehensive RNA-seq in one patient showed KDR, ERBB2, NTRK3 and IGF2 overexpression. All patients clinically deteriorated post immunotherapy. AACR GENIE contained 3 DSRCT patients with aberrations in KDR, NTRK1/3 (non-fusion), and PTEN loss.

Conclusion: These hyper-progression cases of DSRCT are intriguing. Lower TMB, MSS and IDO1 pathway activation may explain the immunoresisistance but not hyper-progression. Mechanisms and causality of hyper-progression should further be assessed in DSRCT and other sarcomas. Further investigation is urgently needed.

Poster #091 3253564

LANDSCAPE OF GENOMIC ABERRATIONS IN DESMOPLASTIC SMALL ROUND CELL TUMORS AND EWING'S SARCOMAS REVEALS DIVERSE BIOLOGY: CLINICAL IMPLICATIONS

Jason Roszik[1]*; Joseph A. Ludwig*[1]*; Anthony Conley*[1]*; J. Andrew Livingston*[1]*; Aung Naing*[1]*;*
Roman Groisberg[2]*; Alexander Y. Andreev-Drakhlin*[1]*; Roberto Carmagnani Pestana*[1]*; Vivek Subbiah*[1]
[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Rutgers Cancer institute of New Jersey, New Brunswick, NJ, USA

Objective: Desmoplastic Small Round Cell Tumors (DSRCT) are rare aggressive peritoneal sarcomas characterized by EWSR1-WT1 fusion. Complete cytoreductive surgery and chemotherapy similar to Ewing's sarcoma remain the cornerstone of therapy. Identifying potentially targetable genomic alterations and divergence in biology with Ewing's sarcoma is important to identify treatments and improve patient outcome.

Methods: CLIA-/ISO-certified genomic data from the AACR project Genomics Evidence Neoplasia Information Exchange (GENIE) database was queried for DSRCT and Ewing's sarcoma. Pubmed/Medline was searched for genomic sequencing data including mutations and copy number alterations. We also reviewed the response of pazopanib- and IGF1R/mTOR-based therapies to DSRCT and Ewing's sarcoma from literature and from a large Phase 1 unit.

Results: We found 48 samples from 43 DSRCT patients (pts) and 143 samples of 142 Ewing's sarcoma pts in AACR GENIE. Among these DSRCT pts 13 (30%) were under age 18, and median age was 27 (range 18-47) for the rest of the pts, and 37 were males (86%). 19 pts had primary tumor samples, 20 pts had genomics from a metastatic site, and 3 had both primary and metastatic sample data. Mutations included 6 in PI3K/mTOR pathway (*PTEN, IRS2, TSC1/2, MTOR*), 4 in MAPK pathway (*BRAF, MAP3K, RAF1, HRAS*), 1 DNA damage (ATM), 1 SWI/SNF (SMARCA4), and other tyrosine kinase pathways (EGFR, ERBB3). Copy number alterations available for 40 patients included amplifications in SOX2 (n=2, 5%), FH (n=2, 5%), and CRLF2 copy number loss in three pts (7.5%). 27 pts (67.5%) had no copy number alterations in GENIE. Fusion events included pathognomonic EWSR1-WT1 fusions (n=32, 74%), SLC25A37-EWSR1 (n=1) and RIC3-EWSR1 (n=1).

Median age of Ewing's sarcoma pts was 29 years (range 18-77) not including 47 pts (33%) under 18. 77 (54%) of these Ewing's pts were males. Mutations included TP53 (n=20), DDR pathway (n=14), SWI/SNF (n=11), cell cycle (n=5), PI3K/mTOR (n=8), and MAPK (n=4). Recurrent copy number gains included *CCND1, MYC, NBN, RAD21, CDK4, EXT1, FGFR1, GLI1, MYBL1, PRKDC, ERBB3, KMT2D, MDM2,* and *KRAS*. Gene fusion events included FLI1-EWSR1 (n=50/59 pts with fusion data, 85%), ERG-EWSR1 (n=5, 8%), and one each of ETV4-EWSR1, FEV-EWSR1, and NFATC2-EWSR1. One patient had a DNAJC16-MTOR together with an FLI1-EWSR1 fusion.

Clinically, patients with DSRCT responded better to pazopanib than Ewing's. Among 29 pts with DSRCT 1 patient each had CR and PR as best response and 16 pts had SD, with median PFS=5.63 months and median OS=15.7 months (Oncologist 2018). Another study reported 2/9 (22%) pts with PR and 5/9 (56%) SD with median PFS=9.2 months and median OS=15.4 months. Among Ewing's sarcoma pts who received pazopanib-based therapy 3/11 (27%) pts had stable disease (SD), with PFS=1.9 months and OS=9.2 months. No DSRCT (0/3) patient responded to IGF1R+mTOR therapy when compared to Ewing's sarcoma with 1 CR and 1 PR (2/17) (Naing et al, Clin Cancer Res 2012).

Conclusion: Genomic profiling of DSRCT identifies alterations that are distinctive from Ewing's sarcoma. DSRCT and Ewing's sarcoma show divergent responses to targeted therapies. Higher number of *TP53* alterations in Ewing's sarcoma should be investigated further. Future large-scale, comprehensive transcriptomic and immuno-profiling of DSRCT and Ewing's sarcoma is warranted.

Poster #092 3255247

EWS-WT1 FUSION TRANSCRIPT STRUCTURE IS NOT PREDICTIVE OF PROGNOSIS IN DESMOPLASTIC SMALL ROUND CELL TUMOR

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Objective: Desmoplastic small round cell tumor (DSRCT) is a rare sarcoma arising from serosal surfaces and is associated with a poor prognosis. DSRCT most commonly presents with widespread abdominopelvic serosal involvement in adolescent and young adult males, and is molecularly characterized by a pathognomonic fusion between the *EWS* and *WT1* genes which was initially described in 1991. Since that time there has been only limited literature regarding the *EWS-WT1* transcript structures observed and their potential prognostic significance. We evaluated the *EWS-WT1* fusion breakpoint in a clinically annotated cohort of 57 patients.

Methods: In patients seen at Memorial Sloan Kettering Cancer Center (MSKCC) since January, 2013, 57 patients had *EWS-WT1* fusion transcript structure data available as determined by hybrid capture-based sequencing. In 12 of these patients anchored multiplex PCR had also been performed. Progression-free (PFS) and overall survival (OS) data were available for 53 of these patients. Progression-free and overall survival were evaluated using Kaplan Maier analysis.

Results: Six fusion breakpoints were identified, with the most common being *EWS* exon 7-*WT1* exon 8 (n=33, 62%). Five additional breakpoints were identified. In 16 patients molecular profiling was completed at diagnosis, in 25 while on treatment and prior to relapse, and in 14 following relapse. 10 patients had molecular profiling at more than 1 timepoint, and there were no discrepancies noted between specimens.

Fusion transcripts were categorized into 1) *EWS* exon 7-*WT1* exon 8 and 2) other. The median progression free survival for patients with a *EWS* exon 7-*WT1* exon 8 transcript was 21 months (95% CI, 13.7-28.2) and 19 months (95% CI, 15.4-22.5) for all others. The medial overall survival for patients with a *EWS* exon 7-*WT1* exon 8 transcript was 4.1 years (95% CI 3.2-5.0) and 2.7 years (95% CI 1.2-4.1). These results were not statistically significant with $p>0.1$.

Conclusion: The largest available series, to our knowledge, of clinically annotated *EWS-WT1* fusion transcripts in DSRCT patients is presented here. Six breakpoints between *EWS-WT1* were observed, and did not correlate with PFS or OS.

Poster #093 3255470

UPDATED RESULTS OF A PILOT TRIAL OF IRINOTECAN, TEMOZOLOMIDE AND BEVACIZUMAB FOR TREATMENT OF NEWLY DIAGNOSED DESMOPLASTIC SMALL ROUND CELL TUMOR

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Objective: DSRCT is a rare tumor with a dismal prognosis in the setting of current treatment options. Previously presented preclinical data suggested that VEGF-dependent angiogenesis is important for DSRCT biology and that targeting angiogenesis with bevacizumab in combination with irinotecan was more effective than treatment with irinotecan alone. This pilot study explores the safety, feasibility, and outcome of adding irinotecan, temozolomide, and bevacizumab (ITB) to the existing alkylator-based chemotherapy regimen used to treat newly diagnosed DSRCT.

Methods: Fifteen patients with newly diagnosed DSRCT were enrolled onto this single-institution pilot study. Patients began treatment with two cycles of irinotecan (20 mg/m2/dose x 10 days) and temozolomide (100 mg/m2/dose x 5 days), and bevacizumab 10 mg/kg q2 weeks was added after sufficient time had passed from initial biopsy or surgery. Patients were then treated with cycles of alkylator-based chemotherapy (3 cycles of cyclophosphamide, doxorubicin, vincristine followed by 3 cycles of ifosfamide, etoposide). An initial surgical resection was performed after cycle 5 and a second resection or second look surgery after cycle 8. Toxicity was graded according to CTCAE v.4.0. Secondary efficacy objectives were assessed using RECIST 1.1 criteria and the Kaplan Meier method.

Results: 14 of 15 patients completed planned protocol therapy. One patient was taken off study due to complications associated with surgery after cycle 5 of chemotherapy. Stopping rules for unacceptable toxicity were not met. No patients experienced toxicity attributed to bevacizumab and surgical morbidity was no greater than expected. Grade 3 diarrhea associated with irinotecan was experienced by 2 patients. Both patients required a one-week delay of chemotherapy and 1 patient necessitated a 25% dose reduction of irinotecan with the second cycle. This second cycle was truncated after 4 days due to grade 4 ALT increase which improved to grade 2 within 2 weeks. Expected toxicities with the standard chemotherapy cycles included grade 3/4 hematologic toxicity and admissions for febrile neutropenia in all patients.

Two patients never experienced progression or relapse and remain free from disease at more than 5 and 7 years after diagnosis, respectively. One patient remains free from disease at more than 5 years after diagnosis despite relapse after the completion of planned upfront therapy 2 years after diagnosis.

Response rate to the two investigational cycles was 27% (95% CI 8-55%) and to the 5 pre-resection cycles was 73% (95% CI 45-92%). No patients experienced progression of disease during the window cycles of irinotecan, temozolomide, and bevacizumab. The median time-to-progression was 1.6 years (95%CI: 1.3-2.3). Overall survival at 1 year was 100% and 3 years 60% (95% CI 35-85%). With a median follow-up of 6.7 years the median overall survival was 4.1 years (95%CI: 2.5-NA).

Conclusion: The combination of irinotecan, temozolomide and bevacizumab is active in patients with DSRCT, and it is feasible to combine these agents with standard chemotherapy without greater than expected toxicity. These data highlight that long-term survival despite widely metastatic disease, and even after relapse, is attainable in DSRCT. Continued analyses are required to better understand these unique responses and capitalize upon them therapeutically.

Poster #094 3255482

IMPROVING THE EFFICACY OF ANDROGEN RECEPTOR-BASED ANTI-SENSE THERAPY BY TARGETING EWSR1 OR TAZ FOR THE TREATMENT OF DESMOPLASTIC SMALL ROUND CELL TUMOR

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Objective: Desmoplasticsmallroundcelltumor(DSRCT) is a rare, usually incurable, highly aggressive soft tissue sarcoma that afflicts 50-70 adolescent and young adults(AYA) characterized by the reciprocal EWSR1-WT1 t(11;22)(p13:q12) chromosomal translocation. Given a lack of prospective clinical trials due to its rarity and the molecular and morphological similarities to Ewing sarcoma (ES), DSRCT is typically-treated with ES-based chemotherapies despite differing both in clinical presentation and prognosis. Only recently have molecular characterization and proteomic profiling identified several aberrations that distinguish DSRCT from ES. Among these, androgen receptor (AR) and transcriptional coactivator with PDZ-binding motif (TAZ) are highly expressed in DSRCT patients and may represent a promising therapeutic target as monotherapy or combination with EWSR1 and AR-anti sense blockade, respectively.

Methods: To assess the expression of AR and TAZ in DSRCT vs. ES patients, protein lysates were measured using a reverse-phase protein array (RPPA). Highly upregulated differentially-expressed proteins were subsequently validated by western blotting and immunofluorescence-based technologies. In vitro cell-based proliferation assays and xenografts/PDX drug-testing were performed to evaluate the preclinical efficacy of AR anti-sense, TAZ and EWSR1 monotherapy versus combination therapy of AR/EWSR1 and AR/TAZ blockades for DSRCT.

Results: DSRCT patient samples and the JN-DSRCT cell line expressed high levels of AR and TAZ protein compared to ES samples (Fig. 1A-E). Stimulation of DSRCT, ES TC-71 and prostate cancer LNCaP cell lines with exogenous 5a-dihydrotestosterone (DHT, an AR native ligand) showed increased proliferation in the DSRCT & LNCaP cell lines at high levels of DHT, but not in the TC71 ES cell line which lacks AR expression (Fig. 1F & I). Additionally, inhibition of AR or EWSR1 in the JN-DSRCT cell line by AR or EWSR1 inhibitor (EWSR1i) suppressed cell proliferation (Fig. 1G-H) and reduced AR/EWSR1 protein expression at 14 days (Fig. 1J-K). Furthermore, inhibition of TAZ in JN-DSRCT cells by TAZ inhibitor (TAZi) reduced the expression of TAZ protein significantly after 72 hours of treatment in vitro cell-based assay proliferation (Figure 1L & M). Finally, DSRCT PDXs and JN-DSRCT tumor-bearing NSG immunocompromised mice treated with anti-AR ASOs showed considerably reduced tumor burden, and improved survival compared to mice in the placebo- and control ASO-treated groups (Figure 1N-O, p=0.0129). Ongoing investigations are showing that AR-ASOs combined with EWSR1 or TAZ targeted therapies might be safe to enhance the antineoplastic effect in JN-DSRCT animal (Figure 1N-O) and PDX models (Data not showed). As AR-targeted ASOs have already entered early-phase clinical trials for prostate cancer, the addition of a DSRCT cohort clinical trial within MD Anderson Cancer Center would allow rapid clinical validation.

Conclusion: Proteomic profiling confirms increased expression of AR in both DSRCT patients and cell line samples as part of a molecular characterization to distinguish DSRCT from ES. AR stimulation enhanced in vitro cell proliferation, an effect that was mitigated using anti-AR targeted ASOs. Combination of EWSR1 or TAZ targeted therapies to AR-ASOs blockade might improve the outcome of DSRCT therapy. As AR-targeted ASOs have already entered early-phase clinical trials as an experimental therapy for prostate cancer, the addition of a DSRCT cohort would allow rapid clinical validation. Future and ongoing investigations defining the epigenetic regulation by AR in DSRCT cells or tumors will help to understand the molecular mechanisms that dictate AR cistrome in DSRCT through androgen, TAZ, and EWSR1-WT1 antagonists.

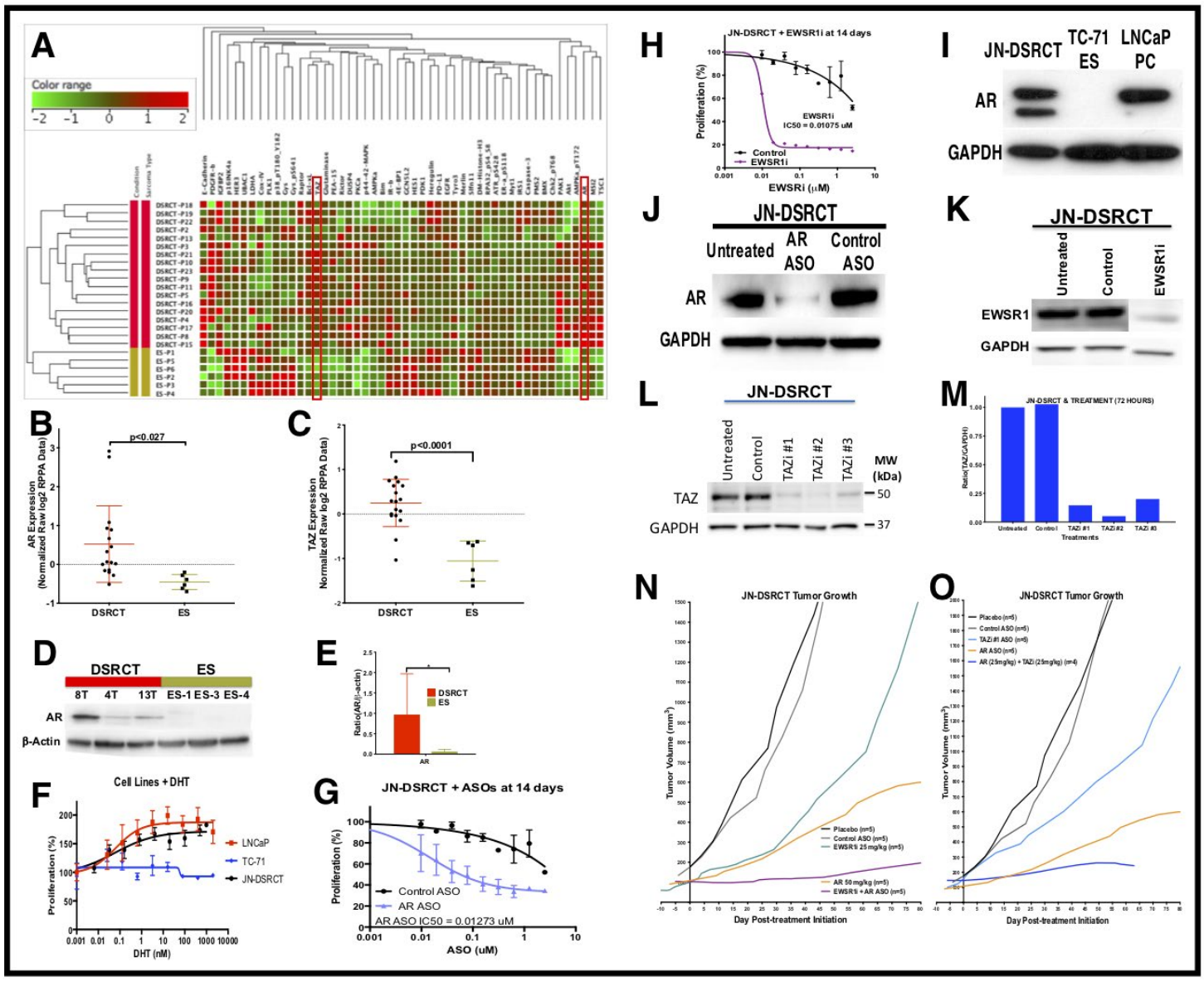

Figure 1: Scientific rationale of targeting AR in DSRCT.

Poster #095 3255856

RESULTS OF DESMOPLASTIC SMALL ROUND CELL TUMOR TREATMENT – SINGLE INSTITUTION EXPERIENCE

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Objective: Desmoplastic small round cell tumor (DSRCT) is a rather chemotherapy- sensitive, but highly lethal, soft tissue sarcoma subtype. It is an uncommon tumor, seen mainly in adolescents and young adults with a strong male predominance. In majority of cases it affects the peritoneum as a multifocal/metastatic disease. The aim of the study was to analyze outcomes of patients with DSRCT treated in a single institution.

Methods: In this retrospective study, we have included 29 consecutive cases of DSRCT treated in our institution between 2000 and 2019, for which clinical data were available. All diagnosis after 2008 were confirmed by assessment of *EWS/WT1* translocation. The count data were summarized by number and percentage and the continuous variables by the median and interquartile range (IQR). Kaplan-Meier estimator was used for survival analysis. Overall survival (OS) was calculated from the time of diagnosis to the date of death and progression-free survival (PFS) - from the start of the treatment to radiological or clinical progression.

Results: There were 23 men and 6 female included in this dataset (M:F ratio = 3.8). The median age was 26 (IQR: 23-36). The most predominant localization of the primary tumor was intraperitoneal space (17 cases, 59%). 22 (76%) patients presented with metastatic disease, with intraperitoneal space (20, 91%) and liver (7, 32%) being the most predominant sites of dissemination. In 15 cases surgical resection has been attempted, including 3 cases were hyperthermic intraperitoneal chemotherapy was also used in the adjuvant setting. All patients received doxorubicin-based, multi-drug chemotherapy regiment as first-line treatment. Median OS in the whole group reached 25.7 months (95% CI: 19.5-37.6) with 5-year OS rate of 8.3% (95% CI: 2.2-31.1%). Neither presence of metastases, primary localization of tumor nor surgical treatment did not influence OS in a statistically significant manner. However, patients who were qualified for surgery with adjuvant chemotherapy and HIPEC fared numerically best with median OS of 52.6 months as opposed to median OS of 33.3 months for surgery+chemotherapy and 21.2 months for chemotherapy alone treatment. Median PFS for 1st line treatment was 12.2 months (95%CI: 9.2-16.3) and 5 months (95%CI: 3.8-11.4) for 2nd line. Incorporation of HIPEC and surgery in the 1st line treatment resulted in statistically significant PFS improvement despite small sample size (27.0 vs. 10.7 for other methods, p = 0.008 by log-rank test).

Conclusion: DSRCT remains a soft tissue sarcoma subtype with very poor prognosis. It seems that a positive effect on the results of the treatment has intensive therapy using multi-drug chemotherapy and modern methods of surgery.

Poster #096 3255901

ADVANCED DESMOPLASTIC SMALL ROUND CELL TUMOR SUCCESSFULLY TREATED IN A 21 YEAR OLD WOMAN, A CASE REPORT

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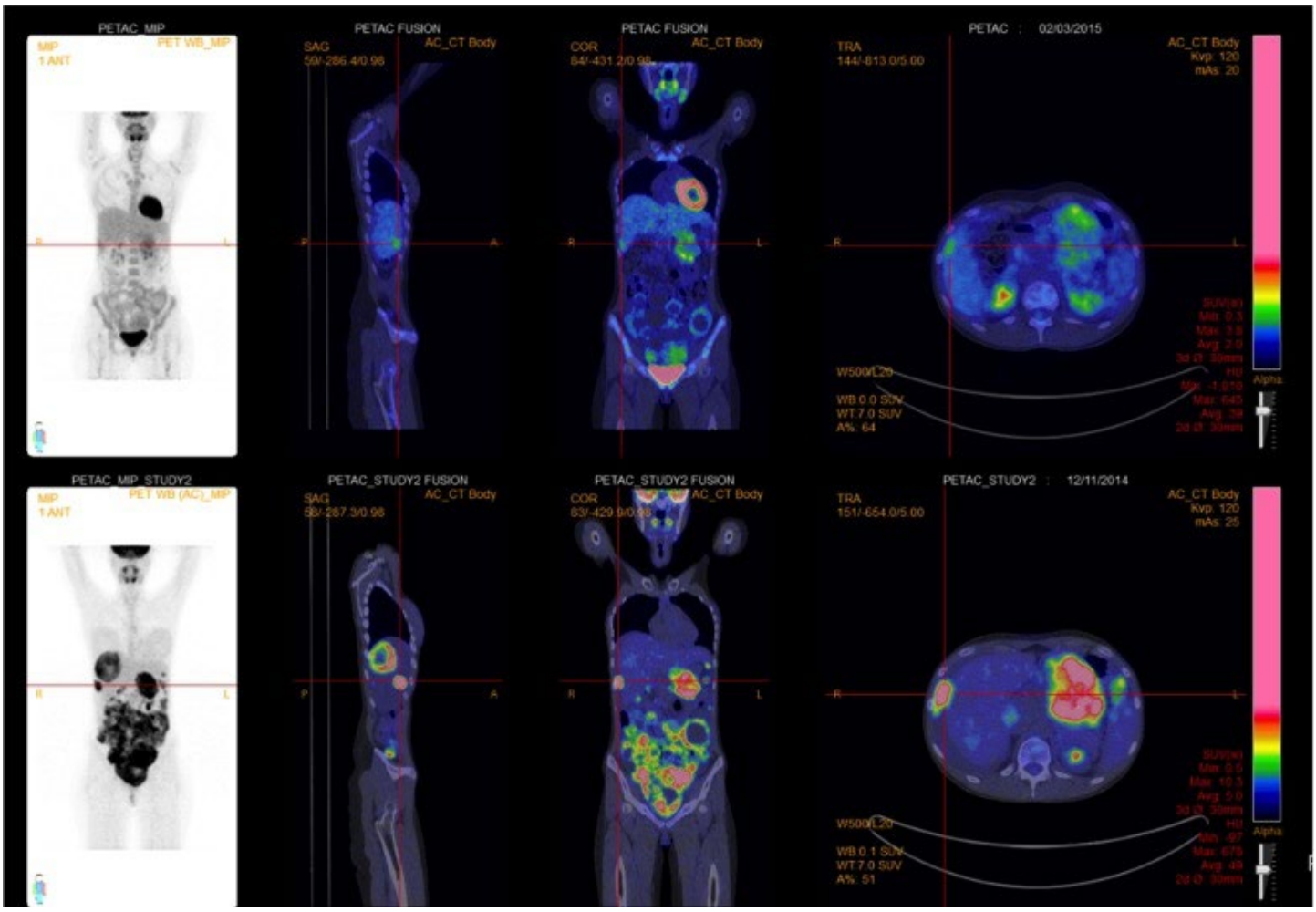
Objective: Desmoplastic small round cell tumor (DSCRT) was described in 1989 by Gerald and Rosai. DSCRT usually affects young adult males with median age 21 years at diagnosis. We present a case of a stage 3 (Hayes-Jordan) DSRCT in a 21-year-old previously healthy female. She presented with several months of fatigue, increasing abdominal circumference and polyuria. CAT scan revealed multiple tumors with heterogenic contrast enhancement and necrosis in peritoneum, ascites and a metastatic lesion in the right liver lobe. The biopsy showed tumor consisting of small cells with hyperchromatic nuclei within nests demarcated by a desmoplastic stroma. Immunohistochemistry showed positivity for cytokeratin and desmin. The FISH analysis revealed EWSR1 (22q12) translocation. The final diagnosis was DSRCT with possible origin in peritoneum.

Methods: The patient was at performance status ECOG 1. The treatment with VIDE (vincristine, ifosfamide, doxorubicin and etoposide) was initiated with aim to obtain volume response that would render the tumor available for resection. After 2 cycles of therapy CAT scan showed 15 % reduction of sum of the largest diameter of target lesions, no new tumors. Due to grade IV febrile neutropenia the dose of etoposide was reduced.
PET CT after the 5th cycle of chemotherapy showed almost complete metabolic response and a significant volume reduction of target lesions (Fig.1); however the response did not meet RECIST criteria for PR. The patient was not accepted for HIPEC therapy due to residual tumor burden. After a total of 7 VIDE cycles the surgery was performed with aim of maximal cytoreduction.

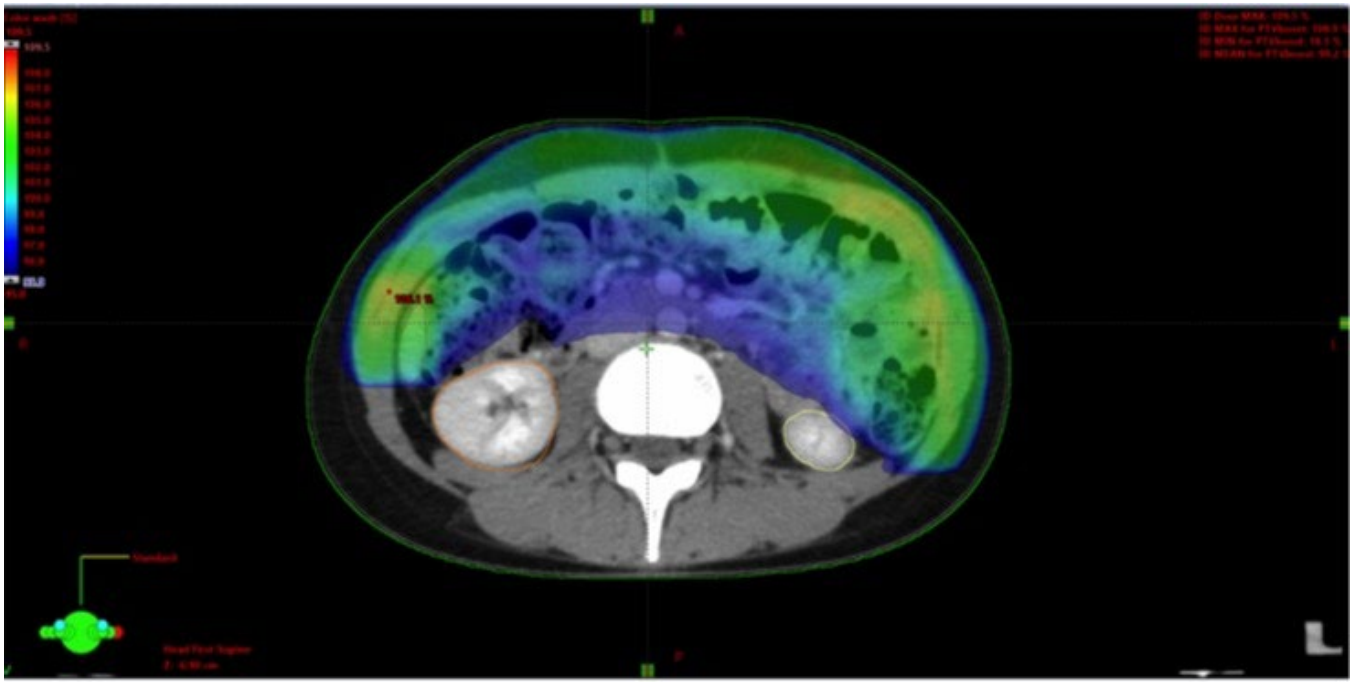
The perioperative findings showed a large tumor adherent pancreas and stomach in the omental bursa, a pelvis filled by tumor masses and a tumor in segment 7 and 6 of the liver. The peritoneum, diaphragm and greater omentum were covered with polypoid cystic tumors. The surgical procedure was as follows: Tumor in omental bursa was skeletonized from the pancreas and stomach. Lesion in the liver was resected by a segment 6 and 7 resection. Peritoneal seeding was debulced by omentectomy and limited peritonectomy in affected areas of the mesentery and the diaphragm. Peritonectomy in the pelvis involved the bladder, uterus, vagina and tubes. A loop sigmoidestomy was fashioned to protect minor muscular damages on the rectum.

Results: There was histologically confirmed viable tumor in the surgical specimen. No tumor rest was seen on postoperative CAT scan. Further therapy contained 2 cycles of vincristine, actinomycinD and cyclophosphamide (VAC) followed by myeloablative chemotherapy therapy with SCT and consolidating 5 cycles of VAC. After completed chemotherapy the abdominal irradiation was performed at the dose 1.5 Gy x 20 (30 Gy) (Fig.2). To avoid nephropathy and liver damage the target volume was modified and the mean kidney dose was kept under 12 Gy and liver dose < 25 Gy.
The patient is without evidence of disease 3.5 years after completed treatment. She receives hormonal substitution due to iatrogenic menopause and has some problems with constipation.

Conclusion: DSCRT is a seldom disease that requires multimodal treatment. Despite aggressive approach the median disease free survival was reported to be 19 months (Hayes-Jordan et al. 2016). DSCRT typically presents as large abdominal mass with peritoneal and visceral metastases. Due to its responsiveness to chemotherapy it is recommended to postpone the surgery until the maximal response to neoadjuvant therapy has been achieved. In the case presented above the patient received 7 cycles with VIDE. The persistent abdominal tumor masses were removed during a R1 resection. The patient was not accepted for HIPEC but she received aggressive pre- and postoperative treatment, including myeloablative chemotherapy with SCT. She is alive without relapse 56 months after diagnosis. We conclude that aggressive treatment with curative intention is justified even when partial response to induction chemotherapy is not achieved.



Baseline PET CT (bottom) and assessment after 5 cycles of VIDE (upper panel)



The radiotherapy dose distribution.

Poster #097 3256316

INTRAPERITONEAL RADIOIMMUNOTHERAPY FOR DESMOPLASTIC SMALL ROUND CELL TUMOR: FINAL RESULTS OF A PHASE I STUDY (CLINICALTRIALS.GOV IDENTIFIER NCT01099644)

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Objective: Desmoplastic small round cell tumor (DSRCT), a rare sarcoma of adolescents and young adults, has a long-term survival of <20% despite aggressive multimodality therapy, warranting a search for novel treatments. The murine monoclonal IgG1 antibody omburtamab (previously termed 8H9) recognizes cell surface antigen B7H3 and binds to 96% of DSRCTs with restricted normal tissue reactivity. DSRCT recurrences often present as multifocal peritoneal implants. We hypothesized that intraperitoneal (IP) radioimmunotherapy (RIT) by virtue of prolonged residence time and slow transfer to the circulation, may selectively target IP DSRCT.

Methods: We conducted a phase I study of IP radioiodinated omburtamab to evaluate toxicity, pharmacokinetics, biodistribution and efficacy. After thyroid blockade with potassium iodide and liothyronine, cohorts of 3-6 patients were treated with escalated doses of IP ^{131}I-omburtamab. After recommended phase II dose was established, an expanded cohort was treated to obtain further data on safety. A prior dose of 2mCi ^{124}I-omburtamab IP was used to acquire serial PET images and biodistribution data. Toxicity was monitored clinically and biochemically. Pharmacokinetics was studied using serial blood draws.

Results: Forty-seven patients with DSRCT were treated at doses of 740-3330 MBq/m^2. Maximum tolerated dose was not reached; there were no dose-limiting toxicities. Major adverse events (n=1 each) were transient: grade 3 transaminitis, neutropenia, and thrombocytopenia. Mean total body and peritoneal residence times were 51.7±8.6 and 22.4±7.9 hours, respectively. Recommended phase II dose was 2960 MBq (80mCi)/m^2: a total of 24 patients received this dose. Mean projected doses for ^{131}I-omburtamab were calculated using ^{124}I-omburtamab dosimetry. Mean projected peritoneal self-dose (maximum) was 4.18±1.56 mGy/MBq. Mean projected absorbed doses to blood, kidney, liver, lung and spleen were well below tolerable levels: 2.0,0.37,0.51, 0.11and 0.35 mGy/MBq ^{131}I-omburtamab, respectively. Dehalogenation was insignificant: >80% blood ^{131}I remained protein-bound 66 h post-RIT. Human antimouse antibody developed in 5% (2/38 patients tested). Hypothyroidism was not encountered. Patients receiving IP-RIT after R1-resection (n= 34) had improved survival compared to those with gross residual disease (n=13): median progression-free survival (PFS) 15±0.6 versus 8.4±4 months; median overall survival (OS) 52.8±5.3 versus 16.9±5.3 months, respectively ($p<0.05$ for both). Patients undergoing R1-resection of abdominal disease received 3000 cGy external beam intensity-modulated whole-abdominopelvic radiotherapy (WAP-IMRT) after completing protocol therapy and observation (n=25). Two-year PFS and OS for this group is 40±11% and 81±8% respectively.

Conclusion: ^{124}I-omburtamab-directed radioimmuno-PET successfully determined biodistribution, whole-body and organ exposure. ^{131}I-8H9 IP RIT had a satisfactory safety profile and appears to have activity against micro-metastatic DSRCT. A phase II trial combining IP RIT and WAP-IMRT is anticipated to start accruing in July 2019.

Poster #098 3256475

MSK-IMPACT GENOMIC PROFILING OF DESMOPLASTIC SMALL ROUND CELL SARCOMA REVEALS RECURRENT COPY NUMBER ALTERATIONS

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Objective: Desmoplastic small round cell tumors (DSCRT) are rare and highly aggressive sarcomas which typically present with widespread abdominopelvic disease. Molecularly, they are characterized by a recurrent t(11;22)(p13;q12) translocation resulting in the pathognomonic *EWSR1-WT1* gene fusion. Aside from the characteristic *EWSR1-WT1* fusion, additional recurrent alterations of associated oncogenes or genomically defined subsets of DSRCT have not been identified. Herein, we utilized MSK-IMPACT, an FDA-approved next-generation sequencing (NGS) assay to describe the molecular landscape of a large cohort of DSRCTs.

Methods: 56 samples from 49 patients (44 male, 5 female) were included in this study. The average age at diagnosis in this cohort was 23.8 years. All tumors were sequenced on the clinical MSK-IMPACT assay, a hybridization capture-based NGS assay for targeted deep sequencing of all exons and selected introns (including *EWSR1*) of 468 key cancer genes. Tumor samples were analyzed for somatic mutations, copy number alterations, and structural variants. All findings were manually reviewed. Furthermore, allele-specific copy number analysis of the cohort was performed using FACETS (Fraction and Allele-Specific Copy Number Estimates from Tumor Sequencing).

Results: All samples showed presence of the disease defining *EWSR1-WT1* fusion. No other recurrent gene mutations were observed. Average tumor mutation burden (TMB) across the cohort was 1.43 mutation/MB. Median TMB in female patients was 0.33 and in males was 1.44. Allele-specific copy number analysis revealed 41% (n=23) of the samples harbored recurrent loss-of-heterozygosity (LOH) in chromosome 16 and 26% (n=15) had LOH in chromosome 11 with ten samples having LOH in both chromosomes 11 and 16. Chromosome 5 gains were observed in 29% (n=16) samples. Ten samples harbored LOH in either chromosome 11 and/or 16 along with a gain of chromosome 5.

Conclusion: DSRCT is driven by the oncogenic EWSR1-WT1 chimeric protein through aberrant transcriptional activity. The presence and clinical relevance of additional recurrent genomic alterations are unknown. In this study, we performed a comprehensive genomic analysis of a large cohort of DSRCT tumor samples and identified recurrent copy number changes in chromosomes 5, 11, and 16. These novel findings need to be correlated with clinical features to assess for associations with clinical presentation and disease outcomes.

Poster #099 3256523

COMPUTATIONAL SEARCH FOR GENE ABNORMALITIES IN DSRCT AND ASSOCIATED POSSIBLE THERAPEUTIC AGENTS

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Objective: Desmoplastic small round cell tumor(DSRCT) is a highly aggressive, polyphenotypic sarcoma that usually targets young males. The overall disease-specific survival is less than 25% despite does-intense chemotherapy, aggressive surgical debulking, and radiotherapy. Clearly new agents with effectiveness against this tumor are required. The KEGG[1] and NCBI[2] databases contain large amounts of annotated genetic data, including DSRCT. These databases were searched for gene abnormalities associated with DSRCT. Associated therapeutic agents were then identified as possible candidates for inclusion in DSRCT therapy.

Methods: The KEGG and NCBI curated databases were searched for gene abnormalities associated with DSRCT. Keywords used included: desmoplastic small round cell tumor , and DSRCT. Scripting for this project was done in Python 3.6[3]. Genes are identified based on a series of extensive gene networks in the databases. Once the genes were identified a second search of this gene network identified possible therapeutic agents. Only genes with known inhibitory agents are reported.

Results: In KEGG , mutations were identified in WT1, MET, and PIK3CA. In NCBI, mutations in WT1,IGF1, EWSR1, and SLC29A4 were reported. Agents listed in the table are reported as a possible therapeutic agent when these mutations are present. Eight IGF1R inhibitors, 13 Met inhibitors, and 11 P13K inhibitors are included.

Conclusion: In this exploratory study using two large curated genetic databases, we identified a number of genes that are mutated or abnormally expressed in DSRCT. These genes were then used to search for inhibitory agents that might be of use in DSRCT therapy.

Inhibitory Agents

Agents found in NCBI	Agents found in KEGG	
IGF1-R inhibitors	MET inhibitors	P13K inhibition
Cixutumumab Dalotuzumab Figitumumab Ganitumab Istiratumab Robatumumab Teprotumumab Masoprocol	Altiratinib Amuvatinib Cabozantinib Capmatinib Foretinib Glesatinib Golvatinib Onartuzumab Savolitinib Sitravatinib Telisotuzumab vedotin Tepotinib Tivantinib	Alpelisib Apitolisib Bimiralisib Buparlisib Copanlisib Dactolisib Gedatolisib Leniolisib Omipalisib Pictilisib Samotolisib

1. Kyoto Encyclopedia of Genes and Genomes 2. National Center for Biotechnology Information 3. Python Software Foundation. Python Language Reference, version 3.6. Available at http://www.python.org

Poster #100 3256525

GENERATION OF PATIENT DERIVED XENOGRAFT MODELS OF DESMOPLASTIC SMALL ROUND CELL TUMOR

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Objective: Desmoplastic small round cell tumor (DSRCT) is a rare and aggressive small round blue cell malignancy which harbors the pathognomonic *EWSR1-WT1* translocation, originally described in the late 1980s and 1990s by William Gerald, Juan Rosai and Marc Ladanyi. DSRCT arises from serosal surfaces, occurs predominantly in males, and is associated with a poor prognosis. Overall survival ranges from 11 to 28% despite intensive multi-modal therapy, and treatment is toxic. Translational research has been hindered by a lack of model systems in which to examine biology and identify and evaluate novel therapeutic targets. We sought to establish a bank of DSRCT patient derived xenograft (PDX) models to overcome this limitation.

Methods: Beginning in November, 2016 DSRCT surgical specimens were subcutaneously transplanted into the flank of NOD SCID gamma (NSG) mice to generate the passage 0 (P0) generation. If successful engraftment was achieved, and upon reaching a tumor width of ~1 cm, the PDX P0 tumors were collected and expanded into a larger cohort. Hybrid capture-based sequencing evaluating 468 cancer-related genes was performed for each engrafted model and compared with equivalent patient-derived hybrid capture-based sequencing. When multiple specimens from disparate metastatic sites in a single patient were collected for PDX generation, sequencing was performed from patient derived material from each corresponding site as long as material was sufficient. The presence of an *EWSR1-WT1* fusion was used to confirm the validity of each model.

Results: Between November, 2016 and May, 2019, 97 DSRCT PDX models were implanted from 32 unique patients. Thirty-four models engrafted at an average of 5.8 months, and 27 of these models have been molecularly characterized thus far. Detailed clinical annotation including patient tumor derived molecular profiling, treatment course/response, pathologic response, surgical outcomes, imaging results, and progression-free and overall survival are available for all models. All but 3 of these models harbored the expected *EWSR1-WT1* fusion. Thirty-seven models did not engraft, and 26 models are pending engraftment.

Conclusion: This effort has generated the largest, to our knowledge, genomically characterized bank of DSRCT PDX models, and efforts are ongoing. It is feasible to use patient derived material to yield DSRCT PDX models which recapitulate the *EWSR1-WT1* fusion, the primary oncogenic driver in this disease. We hope that these tools will provide a rich resource for ongoing pre-clinical efforts to improve outcomes for this disease.

Poster #101 3256529

COMPASSIONATE USE OF BIVALENT ANTI-GD2/GD3 VACCINE WITH IMMUNOLOGICAL ADJUVANT OPT-821 IN COMBINATION WITH ORAL BETA-GLUCAN FOR THE TREATMENT OF RELAPSED GD2+ DESMOPLASTIC SMALL ROUND CELL TUMOR

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Objective: Desmoplastic small round cell tumor (DSRCT) is a rare and aggressive small round blue cell tumor with a male predominance which occurs in adolescents and young adults. DSRCT is characterized by a pathognomonic oncogenic rearrangement resulting in the *EWSR1-WT1* fusion. For those that do not experience progressive disease on therapy, relapse is common, and overall outcomes remain poor despite multi-modality, high-intensity therapy. GD2 is a known tumor associated glycolipid antigen that is expressed in up to 70% of desmoplastic small round cell tumors, and is rarely expressed in normal tissues except neurons and skin cells. Additionally, GD2 expression is rarely lost, even after relapse in patients previously treated with anti-GD2 therapy, making it an ideal anti-tumor target. We hypothesized that the use of bivalent GD2L-KLH+GD3L-KLH combined with OPT-821 and oral beta-glucan might induce anti-GD2 and anti-GD3 IgG antibody responses in DSRCT patients who had reached a radiographically negative disease status thereby preventing or forestalling relapse.

Methods: Following confirmation of GD2 expression via immunohistochemical analysis, we sought approval for a single patient use protocol utilizing GD2L-KLH+GD3L-KLH (anti-GD2/GD2 bivalent vaccine) with OPT-821 (immune adjuvant) in combination with oral beta glucan for a 15 year-old male with relapsed DSRCT. This patient had experienced localized (stomach wall) relapse of disease approximately 1 year following the completion of planned upfront therapy, after which time he had undergone repeat resection and 12 cycles of irinotecan, temozolomide, and bevacizumab. Imaging at the completion of the 12th cycle did not yield radiographic evidence for disease, and anti-GD2 vaccine therapy as above was thereafter initiated. Injections were given weekly for 3 weeks and at weeks 8 and 20, and are planned for weeks 32 and 52. Oral beta-glucan 40 mg/kg daily has been given on a 14 day-on, followed by 14 day off schedule.

Results: Treatment has thus far been well tolerated. Grade 1 swelling and erythema was noted at the injection site following the initial 3 injections. The patient remains radiographically free from disease 6 months following the initiation of therapy.

Conclusion: The use of bivalent GD2L-KLH+GD3L-KLH combined with OPT-821 and oral beta-glucan in a patient with proven GD2-expressing DSRCT after relapse is feasible and well tolerated. Treatment and monitoring are ongoing and will be reported. We propose a clinical trial effort for the use of this approach in all GD2-expressing DSRCT patients who have reached a state of radiographic remission at the completion of planned upfront therapy.

Poster #102 3256531

CHK1 KINASE INHIBITION IN DESMOPLASTIC SMALL ROUND CELL TUMOR

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Objective: Desmoplastic small round cell tumor (DSRCT) is a rare and aggressive malignancy which harbors the pathognomonic *EWSR1-WT1* t(11;22) (p13:q12) translocation. While there is no consensus standard of care approach, treatment usually consists of high-dose alkylator based therapy, in combination with surgery and often radiation. Overall survival from retrospective series ranges from 11-28% despite this high-intensity, multi-modal approach, and new approaches to treatment are urgently required. Checkpoint kinase 1 (CHK1) regulates the cell cycle, DNA-damage response (DDR), and replication stress through the modulation of cell cycle checkpoints and replication fork licensing. Prexasertib (LY2606368) is an ATP-competitive small molecule inhibitor of CHK1. Prexasertib blocks phosphorylation of CHK proteins disrupting DNA replication, inducing DNA damage, and preventing DNA repair, leading to mitotic catastrophe due to the presence of unresolved DNA breaks. Histologic subtypes with high levels of replication stress and/or defects in DNA damage repair pathways may therefore be susceptible to CHK1 inhibition.

Methods: A large-scale screen of DDR agents in bone and soft tissue sarcoma cell lines was performed. Prexasertib was then evaluated *in vitro* for anti-proliferative effect, cell cycle effects, pharmacodynamic profile, and CHK1 dependence using 4 DSRCT cell lines. One standard xenograft and 3 patient-derived xenograft DSRCT models were used to evaluate efficacy of LY2606368 *in vivo*.

Results: Prexasertib was broadly effective across multiple cell lines representing bone and soft-tissue sarcoma histologies and was chosen for further evaluation in DSRCT. Three out of 4 tested cell lines were exquisitely sensitive to prexasertib *in vitro*, with IC_{50} values of ~10 nM. One cell line demonstrated resistance to prexasertib therapy. Pharmacodynamic analyses revealed expected engagement of phosphorylation targets. Cell cycle analyses by both caspase-glo assay and flow cytometric analyses revealed evidence for both apoptosis as well as cell cycle arrest. Standard xenograft and patient derived models demonstrated universal and exquisite sensitivity to prexasertib treatment, including rapid regression. Response was durable in 3 models following removal of prexasertib therapy, and was responsive to re-exposure in a 4^{th} model which demonstrated slow regrowth of tumor approximately 2 months off of treatment.

Conclusion: With the exception of one cell line, DSRCT *in vitro* and *in vivo* models are exquisitely sensitive to CHK1 kinase inhibition with prexasertib, suggesting that CHK1 kinase is a therapeutic vulnerability in DSRCT. Further investigation is required to determine the potential mechanisms of resistance observed in one *in vitro* model, as well the biologic basis for therapeutic vulnerability in this histology. Based on these results, a single-institution phase I/II dose escalation/dose expansion investigator initiated study of prexasertib in combination with irinotecan and temozolomide in relapsed or refractory DSRCT patients has been planned and is impending opening.

Poster #103 3256819

THERAPEUTIC POTENTIAL OF NTRK3 IN DESMOPLASTIC SMALL ROUND CELL TUMOR

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Objective: Desmoplastic small round cell tumor (DSRCT) is a soft-tissue sarcoma that predominantly affects adolescent and young adult males and has a dismal prognosis, despite aggressive treatment. It is characterized by the t(11;22)(p13:q12) translocation that generates the EWSR1-WT1 chimeric transcription factor, a powerful oncogene and the main molecular driver of DSRCT. EWSR1-WT1 rewires global gene expression networks and activates aberrant expression of targets that contribute to an oncogenic expression program. It has been previously described that EWSR1-WT1 can activate neural gene expression.

Methods: Among those markers, we demonstrated prominent expression of neurotrophic tyrosine kinase receptor 3 (NTRK3; TrkC), a druggable receptor tyrosine kinase, specifically highly expressed in DSRCT compared to other translocation-driven sarcomas. We investigated the therapeutic potential of NTRK3 both in *in vitro* and *in vivo* models of DSRCT.

Results: We find that EWSR1-WT1 directly activates *NTRK3* mRNA expression. Indeed, mRNA expression of the NTRK3 kinase domain is higher in DSRCT than in other sarcomas or than in cancers with *NTRK3* fusions and that most DSRCT tumors are strongly immunoreactive for NTRK3 protein. Abrogation of NTRK3 by silencing reduces growth of DSRCT cells and pharmacologic targeting of NTRK3 using entrectinib is effective both in *in vitro* and *in vivo* models of DSRCT.

Conclusion: Our results indicate that EWSR1-WT1 directly activates NTRK3 expression in DSRCT cells, which are dependent on its expression and activity for growth. Pharmacologic inhibition of NTRK3 by entrectinib significantly reduces growth of DSRCT cells both in vitro and in vivo , providing a rationale for clinical evaluation of NTRK3 as a therapeutic target in DSRCT.

Poster #104 3256561

ULTRA-HIGH FIELD MRI (7 TESLA): ARE WE HEADING TO THE FUTURE OF TUMOURS MUSCULOSKELETAL IMAGING?

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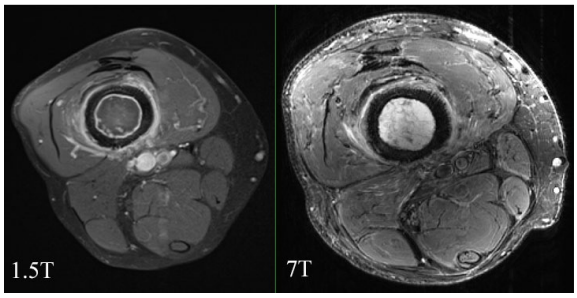
Objective: Planning sarcoma resection on the basis of a preoperative MRI with expert radiologists optimizes the opportunities to spare noble structures. However, per operative conditions may vary from MR observations, resulting in compromising safe removal or creating unscheduled technical difficulties. With classical MRI resolution and routinely performed sequences, uncertainties remain regarding tumoral surrounding (inflammatory reaction or tumor?) thereby resulting in frequent unnecessary sacrifice of healthy tissue.

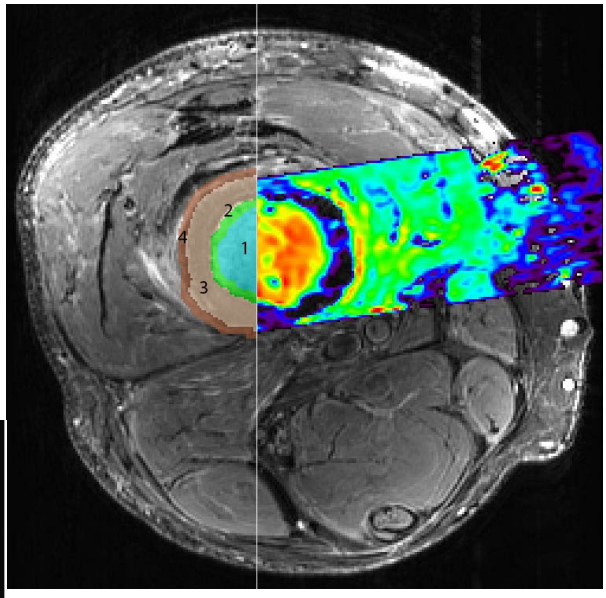
Purpose: evaluate in a preliminary study the feasibility and the new potential offered by ultra-high field MRI (7T) in the pre-operative assessment of malignant bone tumor.

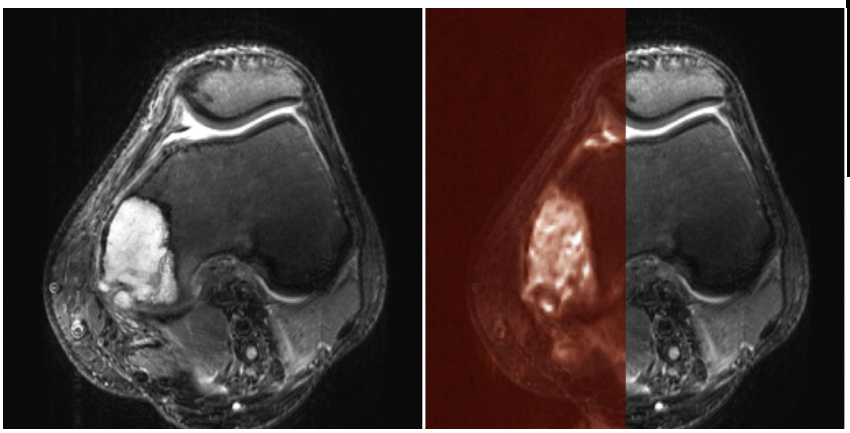
Methods: Two patients suffering from distal femur chondrosarcoma were imaged using CT, conventional 1.5 T MRI and 7-T MRI in our research facility. Conventional T1, T2W and diffusion-tensor imaging were performed. As a preliminary approach, tumor expert radiologists compared image quality, diffusion coefficients and zones of interest (soft tissue involvement, edema analysis, tumor limits) between both MRI and CT-scan.

Results: Cortical layers and bone marrow spatial resolution was largely superior to conventional MRI and was equivalent to what can be observed on a CT-scan. Distal limits of the tumor were clearly visible at 7T compared to blurry signal at 1.5 T. Tumor and edema could be clearly distinguished at 7T but not at 1.5 T (Figure 1). Interestingly, 7T diffusion coefficient was significantly superior in the tumor compared to the surrounding edema, thereby allowing a clear distinction between tumoral tissue and inflammatory reaction (Figure 2). Using ADC map also helped us assessing the involvment of collateral ligament and cortical disruption, which guided us for the surgery and which were not visible at 1.5 tesla (Figures 3).

Conclusion: Considering the spatial resolution of MR images obtained at 7T, ultra-high field MRI of musculo-skeletal tumors seems very promising. Thanks to the enhanced signal to noise ratio, tumor can be more accurately delimited and distinguished from edema. One can reasonably expect an important impact of ultra-high field MRI on the planning of sarcoma resection and sparing of healthy tissue.







Poster #105 3257777

COMPUTED-TOMOGRAPHY (CT) SCAN IN RETROPERITONEAL SARCOMAS (RPS): A RADIOMIC ANALYSIS OF THE SARCOMICS STUDY

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Objective: Survival of patients with RPS ranges widely and is determined by clinical and pathological features including patient age, tumour size, malignancy grade and histological sub-type. Radiomic features have improved prognostic risk stratification in other solid tumours. As a part of the SARCOMICS project, the present study was aimed at investigating the association of CT scan radiomic features and patient prognosis in terms of disease-free survival (DFS).

Methods: Clinical data from patients who had contrast-enhanced (CE) CT scan stored at Fondazione IRCCS Istituto Nazionale dei Tumori (INT) and underwent surgery at INT between Jan 2011 and Dec 2015 were extracted from a prospectively maintained database. Radiomic features were extracted from Digital Imaging and Communications in Medicine (DICOM) of pre-contrast and contrasted CT scan. DFS was the outcome variable. Firstly, an unsupervised features selection was performed assessing stability of the features to image acquisition parameters. The best radiomic features for outcome prediction were selected based on the minimum redundancy maximum relevance (mrMR) method which resulted in a radiomic signature representing a linear combination of the selected features with DFS. The coefficients of the features were obtained by fitting a Cox Proportional Hazard Regression model to the data in order to maximize concordance between radiomic features and DFS. Bootstraping was used to cross-validate the final model and assess the model performance on unseen data and the C-index was used as a metric of performance.

Results: One-hundred ninety-five patients were selected. Sarcoma histology was well differentiated liposarcomca, dedifferentiated liposarcoma, leiomyosarcoma, solitary fibrous tumour and other in 51 (26%), 91 (47%), 33 (17%), 10 (5%), and 10 (5%) patients, respectively. Tumour malignancy grade was G1, G2, and G3 and in 59 (%), 80 (%), and 56 (%) patients, respectively. Median tumour size was 21 cm (interquartile range, IQR 14-28). Median follow-up was 50 months (IQR, 34-61 months). Among the total, 85 patients experienced either death or recurrence (36 patients had local recurrence 31 patients had metastasis, 10 experienced both, 8 had death without event). 3-yr and 5-yr DFS were 65% and 51%, respectively.

A Preliminary analysis was conducted on a sample of 87 patients. We analysed 536 features in pre- and contrasted CT (N = 1,072). Among the analyzed features, 820 were stable to image acquisition parameters. The selection of the best radiomic features resulted in the identification of a four-feature prognostic signature for DFS (HR=2.29, 95%CI 1.24-4.22, p<0.001). These features were obtained from non-contrasted CT images and provided information on the intensity of the grey levels (waveletLLL_firstorder_90Percentile, waveletLLL_firstorder_Median, original_firstorder_90Percentile, and original_firstorder_Median). Multiple bootstrap iterations led to a mean C-index of 0.59 (95%CI 0.41-0.77). We also investigated correlation between the radiomic signature and the clinical-pathological characteristics and identified differences between histologies (p<0.001 in a Kruskall-Wallis test), with well differentiated liposarcoma having the lowest signature values, and a positive correlation between the signature and tumour malignancy grade (Spearman ρ=0.37, p<0.001).

Conclusion: We identified a radiomic signature based on CT scan to predict risk of developing recurrences in patients with RPS, which will be analysed in a larger series and validated in an independent sample that is currently being collected within the SARCOMICS project. The project results are expected to allow improvement of the prognostic nomogram Sarculator, which is currently based on clinical and pathological features, to refine patient risk stratification for existing and innovative treatment strategies.

Poster #106 3257781

MAGNETIC RESONANCE IMAGING (MRI) SCAN IN EXTREMITY SOFT TISSUE SARCOMAS (ESTS): A RADIOMIC ANALYSIS OF THE SARCOMICS STUDY

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Objective: Survival of patients with ESTS ranges widely and is determined by clinical and pathological features including patient age, tumour size, malignancy grade and histology. Radiomic features have improved prognostic risk stratification in other solid tumours. This study was aimed at investigating the association of MRI radiomic features and patient prognosis in ESTS.

Methods: Data from patients who had contrast-enhanced (CE) MRI images stored at Fondazione IRCCS Istituto Nazionale dei Tumori (INT) and underwent surgery at INT between Jan 2011 and Dec 2015 were extracted from a prospectively maintained database. Study outcome was disease-free survival (DFS). Radiomic features were extracted from Digital Imaging and Communications in Medicine (DICOM) of four MRI modalities: T1-weighted with and without CE, T2-weighted, and diffusion-weighted MRI images. Firstly, an unsupervised features selection was performed assessing stability of the features to image acquisition parameters. The best radiomic features for outcome prediction were selected based on the minimum redundancy maximum relevance (mrMR) method which resulted in a radiomic signature representing a linear combination of the selected features with DFS. The coefficients of the features were obtained by fitting a Cox Proportional Hazard Regression model to the data in order to maximize concordance between radiomic features and DFS. A hundred bootstrap iterations were used to cross-validate the final model and assess the model performance on unseen data and the C-index was used as a metric of performance.

Results: One-hundred patients were selected. Sarcoma histology was undifferentiated pleomorphic sarcoma (UPS), myxofibrosarcoma, myxoid liposarcoma, dedifferentiated/pleomorphic liposarcoma, and other in 28, 21, 18, 9, and 24 patients, respectively. Tumour malignancy grade was G1, G2, and G3 and in 24, 21, and 55 patients, respectively. Median tumour size was 8 cm (interquartile range, IQR 5-10). At the median follow-of 61 months (IQR 48–77 months), 30 patients developed an event (local or distant recurrence). 3-yr and 5-yr DFS were 71% and 67%, respectively, while 3-yr and 5-yr overall survival were 84% and 78%, respectively.

A preliminary analysis was conducted on data from 93 patients. We analysed 536 features in four MRI modalities (N = 2,144). Among the analyzed features, 1207 were stable to image acquisition parameters. The selection of the best radiomic features resulted in the identification of a two-features prognostic signature for DFS (HR=2.72, 95%CI 1.89-3.09, $p<0.001$). Both features were obtained from diffusion-weighted images and both account for spatial distribution of the gray levels (ADC_waveletLHL_glrlm_RunLengthNonUniformity and ADC_waveletHLH_glrlm_RunLengthNonUniformity). Multiple bootstrap iterations led to a mean C-index of 0.71 (95%CI 0.54-0.86). Larger tumours were characterised by higher signature values (Spearman $\rho=0.83$, $p<0.001$) and there were significant differences between histologies ($p=0.03$ in a Kruskall-Wallis test) having UPS the highest signature values. A correlation with grade was also present, though with a borderline statistical significance (Spearman $\rho=0.20$, $p=0.06$).

Conclusion: We identified a radiomic signature based on MRI to predict risk of developing a tumour recurrence in patients with ESTS to be validated in an independent sample, which is currently being collected within the prospective SARCOMICS study. These data are expected to improve the prognostic model Sarculator, which is currently based on clinical and pathological features, to refine patient risk stratification for existing and innovative treatment strategies.

Poster #107 3232369

APPLYING RADIOMICS IN PREDICTING OUTCOMES IN PATIENTS WITH RETROPERITONEAL SARCOMA TREATED WITH PREOPERATIVE RADIOTHERAPY

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Objective: Retroperitoneal sarcomas (RPS) are a rare group of malignancies with worse overall outcomes compared with matched histologies of the extremity. Preoperative radiotherapy (RT) is increasingly used in RPS as it may be associated with increased local control rates with acceptable toxicity although confirmatory data is pending. We assessed whether quantitative imaging features ('radiomics') on radiotherapy simulation CTs provide additional prognostic information to clinical features.

Methods: This single-institution retrospective study included scan and clinical data of patients with RPS who were treated with preoperative RT from 2008. A standard radiotherapy dose of 50.4Gy in 28 fractions was delivered. Radiomics features were extracted from the tumour as manually contoured on non-contrast radiotherapy simulation CTs. Radiomic features and clinical variables were used to develop random forests to predict progression free survival (PFS), overall survival (OS), time to local recurrence (TLR) and time to distant metastasis (TDM). Radiomic feature reduction was performed by excluding one of each pair of correlated features with absolute spearman's rank of >0.8, reducing the number of features from 105 to 27.

Results: A total of 73 patients were identified with 63 patients having scans that allowed radiomic analysis. Baseline demographics were as follows: Mean age = 56 years (IQR 47-65); 24% Grade 3; Histological median max dimension (cm) = 16 (4.2-37.5). Predominant sarcoma subtype was: well-diff/ de-diff liposarcoma (40%), well-diff liposarcoma (22%) and leiomyosarcoma (16%). The median PFS was not reached and the median OS was 7.4 years (5.9, NA). Univariate analysis identified age, ECOG, grade and organ invasion as predictors of PFS and ECOG and Grade as predictors of OS. A total of 2, 3, 5 and 3 of the 27 radiomic features were statistically significant ($P<0.05$, no adjustment for multiplicity) in predicting PFS, OS, TLR and TDM respectively. The c-index for the clinical, radiomics and clinical/radiomics model is shown in Table 1. Most important feature by variable importance (>1%) in predicting outcomes in the combined clinical/radiomics model were: Grade and first-order 90th Percentile (PFS); Grade, ECOG, histological max dimension and GLSZM Gray Level Non Uniformity (OS); histological max dimension, GLDM Gray Level Variance and GLSZM Gray Level Non Uniformity (TLR); Grade, first-order 90th Percentile, first-order 10th Percentile (TDM).

Conclusion: An algorithm using the combination of clinical and radiomics features did not improve the predictive capacity compared to clinical features alone.

Table 1

	C-index (mean (Standard error))			
Event	Clinical	Radiomics	Clinical + Radiomics	# Events
Progression Free Survival	0.61 (0.003)	0.50 (0.004)	0.57 (0.004)	23
Overall Survival	0.74 (0.003)	0.51 (0.006)	0.60 (0.005)	16
Time Until Local Recurrence	0.55 (0.003)	0.59 (0.006)	0.62 (0.006)	13
Time Until Distant Metastasis	0.72 (0.004)	0.57 (0.006)	0.60 (0.007)	14

Poster #108 3241854

DIMENSIONAL AND NON-DIMENSIONAL CHANGES WITH LOW-DOSE CHEMOTHERAPY IN SPORADIC DESMOID TUMORS (DT)

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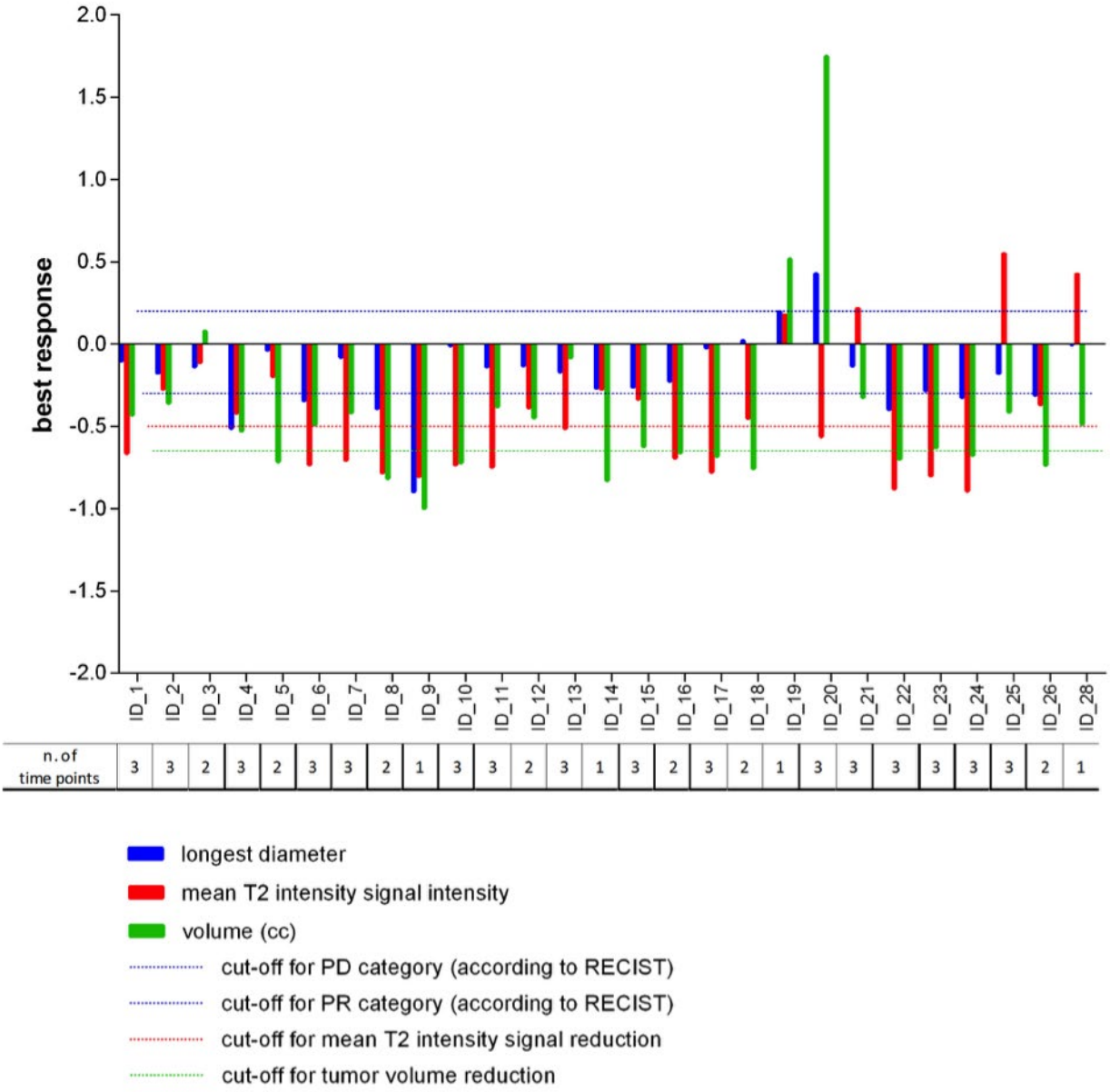
Objective: A number of medical therapies were shown to be active in DT, including low-dose methotrexate (MTX) plus vinca alkaloids. Considering that RECIST criteria may underestimate chemotherapy activity, we herein report on the results of a retrospective study investigating changes in volume and MRI T2-weighted signal intensity in sporadic DT treated with low-dose MTX plus vinca alkaloids.

Methods: We retrospectively reviewed all cases of sporadic DT treated with low-dose weekly MTX plus vinca alkaloids at our institution over the last 20 years, evaluated by Magnetic Resonance Imaging (MRI). Chemotherapy was administered weekly until reaching a number of cycles between 40 and 50 or until reaching one year of treatment. MRI at baseline, at 6 and 12 months from start of chemotherapy, at the end of treatment and during follow-up were analyzed. A manual segmentation of the lesions in a slice-by-slice fashion was performed using IntelliSpace Portal Tumor Tracking software (Philips); diameters, volume and mean T2 signal intensity of the lesions (which was then normalized to the intensity of the muscle) were obtained. Descriptive statistics and graphical representation were implemented.

Results: We identified 27 sporadic DT patients eligible for the study. There were 23 females (85%) and 4 males (15%). The median age was 39,8 years (range 18,1-68,4 years). Tumor site was: extremities/girdles, abdominal wall, thoracic wall, neck and intra-abdominal in 11 (41%), 7 (26%), 4 (15%), 3 (11%) and 2 (7%) patients, respectively. All patients were progressing before starting chemotherapy. The median duration of chemotherapy was 13,9 months (range 3,5-18,5 months) for a median number of cycles of 40 (range 12-63). Reasons for chemotherapy discontinuation were treatment completion in 26 patients (96%) and progressive disease according to RECIST in 1 case (4%). According to RECIST criteria, best response was: partial response (PR) in 7 patients (26%), stable disease (SD) in 18 (67%; with a minor dimensional reduction in 17 and a minor increase in 1) and progressive disease (PD) in 2 (7%). When considering tumor volume, a reduction of at least 65% (roughly equivalent to 30% decrease in one diameter as per RECIST) was achieved in 11 subjects (41%), a smaller volume decrease in 13 (48%) and a tumor volume increase in 3 (11%). Six patients (22%) had a minor decrease or even a slight increase in longest diameter while showing a tumor volume reduction greater than 65% (apparently, lesions shrank without diminishing in the main diameter). When considering normalized T2 signal intensity, a decrease of at least 50%, as best response, was observed in 14 patients (52%), a minor reduction in 9 patients (33%) and an increase in 4 patients (15%). By looking at the three parameters altogether, Figure 1 reports best responses achieved with chemotherapy for each patient. In 3 cases an important discrepancy between dimensional (mono-dimensional and volumetric) changes and T2 signal intensity changes was observed. In particular, in 2 patients T2 signal intensity increased despite a decrease in volume: in one case, clinical worsening was observed during treatment and several further treatments were administered after chemotherapy interruption; the other patient was asymptomatic and stopped treatment just one year ago. In one additional case, volume increased significantly during the first months of treatment, than a reduction was observed, while T2 signal intensity decreased; the patient stopped treatment 3 years ago and is asymptomatic.

Conclusion: In this series of DT treated with low-dose chemotherapy, dimensional reductions were observed in the vast majority of patients, even if RECIST partial responses were achieved in a relatively small number. Normalized T2 signal intensity changes may be more informative, especially when diverging from dimensional variations. An effort to better understand correlations between dimensional changes, T2 signal intensity changes and clinical outcome is ongoing.



Needle plot with the best response according to the three radiological parameters on the y-axis and the patients ID on the x-axis. The table reports the number of available time-points for each patients. Blue dashed lines indicates the PD and PR cut-offs of RECIST, respectively. The red and green dashed lines indicates the cut-offs for mean T2 intensity and volume reduction, respectively.

Poster #109 3253768

LINEAR MIXED EFFECTS MODELS FOR ESTIMATION OF PULMONARY METASTASIS GROWTH RATE: IMPLICATIONS FOR CHEST CT SCREENING IN PATIENTS WITH SARCOMA

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Objective: Sarcomas are rare tumors of mesenchymal origins, and many have the propensity to metastasize to the lungs. Patients with sarcomas often undergo surveillance chest computed tomography (CT) for detection of pulmonary metastases. No data exist on what the optimal screening interval for chest CT. Too frequent screening results in (1) increased radiation to patient (2) increased anxiety for the patient and (3) increased burden on medical infrastructure/healthcare cost. Too infrequent screening results in potential missed opportunities for treatment (wedge resection, radiation therapy, starting chemotherapy). The aim of this study is (a) to estimate lung metastasis growth rate in (i) untreated and (ii) treated patients with metastatic sarcoma and (b) to assess whether pulmonary metastasis growth rate varies within individual and (c) to evaluate whether the pulmonary metastasis growth rate varies by sarcoma subtype.

Methods: Retrospective review of patients with either biopsy confirmed (n=44) or imaging confirmed (n=52) pulmonary metastasis. Patient age, sex, maximum tumor size, tumor grade, sarcoma subtype and size of the pulmonary metastasis over successive chest CT scans was recorded. Inclusion criteria included a histologic diagnosis of primary bone or soft tissue sarcoma. Pulmonary metastases were excluded after they were radiated or resected. Two nodules per patient were chosen if possible – one biopsy proven; the other randomly chosen. The size of the pulmonary metastasis in maximal dimension on each CT scan and the time between CT scans were recorded. Linear mixed effects models were used to estimate pulmonary metastasis growth rate.

Results: Of 1,000 patients with sarcoma, 96 (9.6%) had pulmonary metastases. The sarcoma subtypes include 4 (4.2%) Ewing, 5 (5.2%) chondrosarcoma, 16 (16.7%) undifferentiated pleomorphic sarcoma, 10 (10.4%) myxofibrosarcoma, 9 (9.4%) synovial sarcoma, 21 (21.9%) non-uterine leiomyosarcoma and 3 (3.1%) non-retroperitoneal liposarcoma. Pulmonary metastasis growth rate was approximately 0.04 mm/day (1.2 mm/month) ($P<0.001$) for untreated pulmonary metastases and unchanged for treated pulmonary metastases. Pulmonary metastasis treatment started on average at a size of 12 mm. There was significant intra-patient variation in pulmonary metastasis growth rate ($P<0.001$). No significant difference existed in the growth rate of pulmonary metastases by sarcoma type ($P>0.05$).

Conclusion: Surveillance chest CTs can be performed every 7 months if the initial staging chest CT is negative, assuming that an intervention can be done when a nodule is at least 8 mm in size. Chemotherapy did not alter pulmonary nodule growth rate. There was significant intra-patient variation in pulmonary metastasis growth rate possibly related to the metastasis microenvironment or related to tumoral heterogeneity within the metastasis. The rate of pulmonary metastasis growth did not vary by sarcoma subtype.

Poster #110 3254463

DISTINCTION BETWEEN BENIGN AND MALIGNANT SOFT TISSUE TUMORS BASED ON AN ULTRASONOGRAPHIC EVALUATION OF VASCULARITY AND ELASTICITY

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Objective: Soft tissue tumors (STTs) can exhibit a variety of tissue morphologies, making them potentially difficult to diagnose. Ultrasonography (US) is a simple imaging diagnostic tool with low invasiveness that has improved through technical advancements and is increasingly being utilized in orthopedic cases. This study aims to determine the diagnostic accuracy of STTs in the extremities and the trunk by establishing a scoring system (SS) based on vascularity and elasticity assessments.

Methods: This retrospective study targeted 167 STTs in 164 cases that were examined by US prior to a biopsy, surgery, and pathological tissue diagnosis at our hospital from April 2016 to September 2018. The pathological tissue diagnosis was based on the World Health Organization classification 2013, and was divided into 3 groups: benign, intermediate, and malignant. The 4 evaluation items used are as follows: vascularity index (VI) for Superb-Microvascular Imaging, maximal shear velocity (MSV) for Shear Wave Elastography, tumor size, and tumor depth. The Aplio 500 (Toshiba Medical Systems Corporation) was used as the US diagnostic device with a linear-type probe PLT-1005BT. VI (Figure 1A) and MSV (Figure 1B) were evaluated by US, and tumor size and depth were evaluated by MRI. An SS was finally established utilizing the cut-off values to calculate the sensitivity and specificity. Distributions and mean values of the total scores were also compared among the respective groups.

Results: VI scores, MSV values, and tumor sizes were significantly higher in the malignant group compared with the benign-intermediate group. Tumor depth was more often superficial in the benign-intermediate group compared with the malignant group while tumors were more often deep in the malignant group. An SS with 7 points as the total score consisting of all 4 items showed 4 points of the cut-off value with an area under the curve value of 0.90, 85% sensitivity, and 83% specificity (Figure 2). In the score distribution for the SS, 7 malignant lesions had scores < 4 points and 40 of the other lesions had scores ≥ 4 points (Figure 3A). The scores for the benign-intermediate group and the malignant group were 2.2 ± 1.7 and 5.3 ± 1.6, respectively, with significantly higher scores for the malignant group compared with the benign-intermediate group (Figure 3B).

Conclusion: Evaluating vascularity and elasticity of STTs by US were useful techniques to distinguish between benign and malignant tumors, even if the evaluations were performed separately. Furthermore, an SS established based on these evaluations improved the diagnostic accuracy for STTs. Hence, an SS based on the vascularity and the elasticity determined by US data is useful for the distinction between benign and malignant STTs.

Figure 1

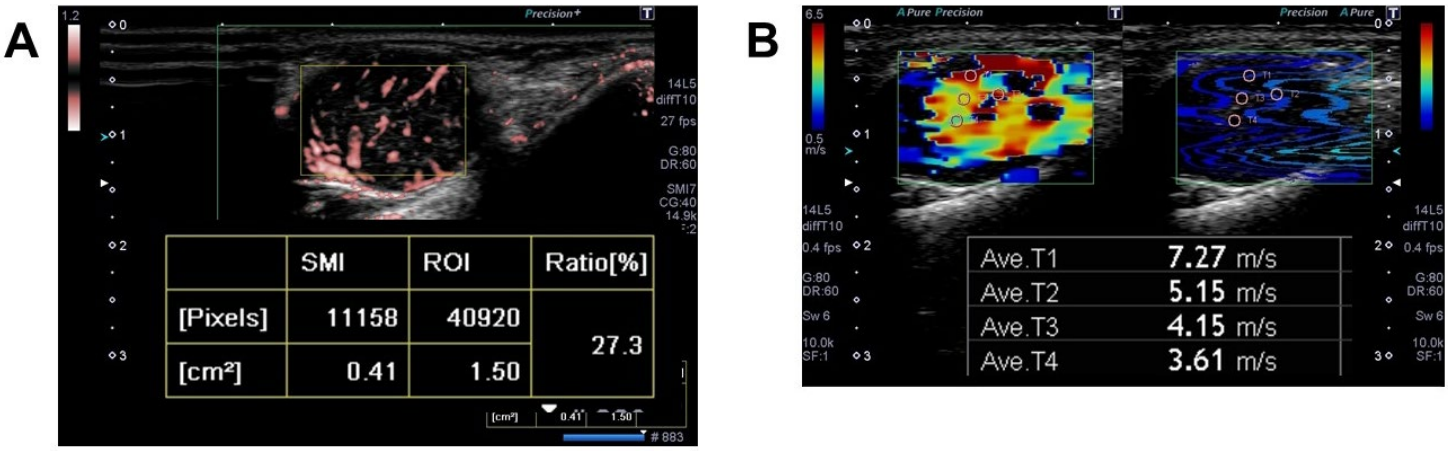


Figure 2

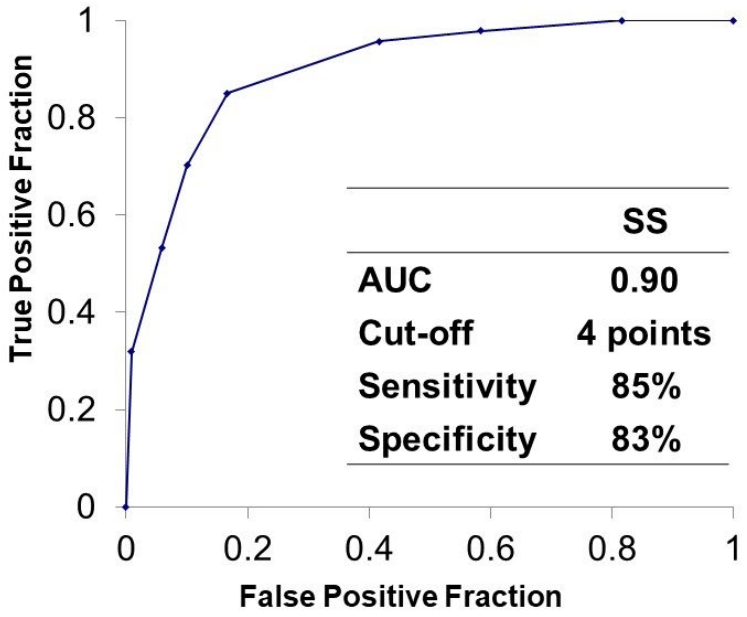
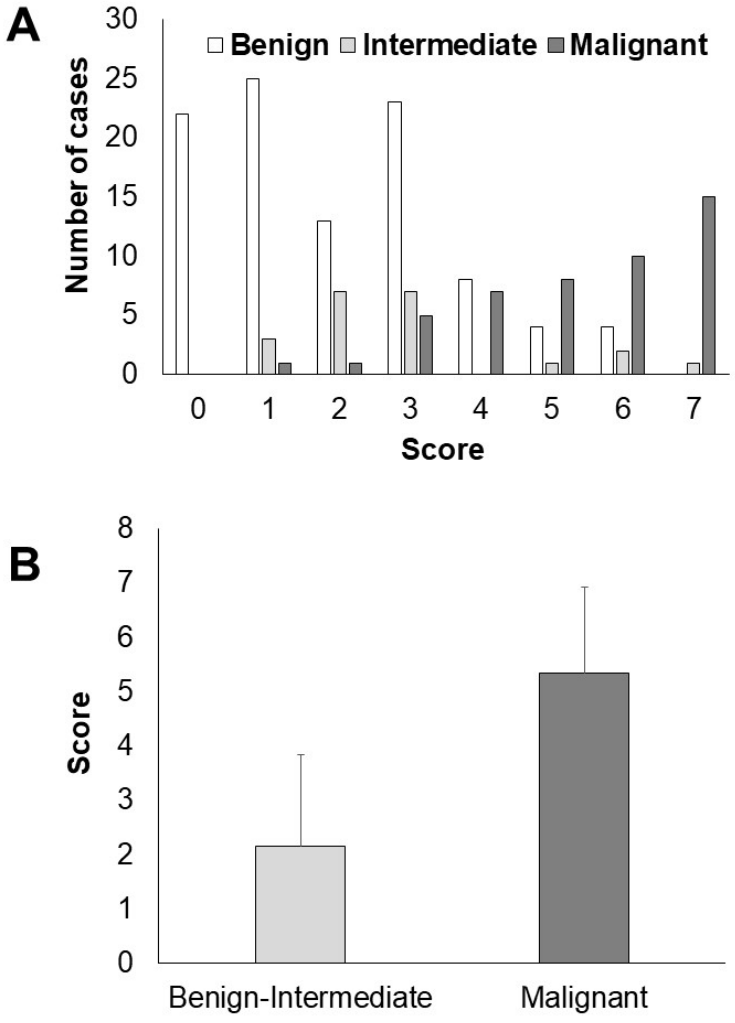


Figure 3



Poster #111 3255153

DIAGNOSTIC EFFICACY OF POSITRON EMISSION TOMOGRAPHY IN ADIPOCYTIC TUMORS

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Objective: Adipocytic tumors are one of the most frequent soft tissue tumors in orthopedic oncological clinics. Preoperative differential diagnosis of MRI between lipoma and atypical lipomatous tumor (ALT) has been well studied and reported since their clinical characteristics and image findings are very similar. Recently, positron emission tomography (PET) has been utilized for cancer diagnosis and staging. However, few reports using PET for differential diagnosis between lipoma and ALT have been reported. In the current study, we evaluated diagnostic efficacy of PET-CT in adipocytic tumors.

Methods: A retrospective review of 15 patients with histopathologically diagnosed as adipocytic tumors was performed. All underwent fluorodeoxyglucose (FDG)-PET CT, evaluating maximum standardized uptake value (SUV max) of FDG.

Results: Patients consisted of 9 men and 6 women with averaged age of 66.7 years old. Of the 15 patients, 3 were diagnosed as lipoma, 9 as ALT, and 3 as dedifferentiated liposarcoma with 17.9 months follow-up. Averaged SUV max are 0.00 in lipoma, 2.37±0.4 in ALT, and 9.79±1.6 in dedifferentiated liposarcoma, respectively. SUV max in dedifferentiated liposarcoma was significantly higher compared to those in lipoma and ALT. Interestingly, no uptake of FDG can be observed in all cases of lipoma although ALT has slight up take of FDG.

Conclusion: Lipoma and ALT sometimes have overlapping MRI characteristics, causing difficulty in differential diagnosis. FDG-PET can be useful for distinguishing between lipoma and ALT.

Poster #112 3253128

GEMCITABINE PLUS PACLITAXEL THERAPY AGAINST ADVANCED BONE AND SOFT TISSUE SARCOMA

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Objective: A randomized prospective phase 2 study analyzing patients with various soft tissue sarcomas revealed that gemcitabine and docetaxel combination exhibited a relatively high response rate of 16% in salvage line therapy. Based on these data, the combination of gemcitabine and docetaxel for soft tissue sarcoma has been widely adopted over the last decade. Paclitaxel showed clinical benefit in a phase 2 trial in patients with angiosarcoma, however the therapeutic efficacy of the combination of gemcitabine and paclitaxel in the other sarcoma subtypes have never been examined. The aim of the present study is to analyze the efficacy and toxicity of gemcitabine with paclitaxel in patients with advanced bone and soft tissue sarcoma.

Methods: A total of 42 patients with advanced bone and soft tissue sarcoma had received this combination therapy with gemcitabine and paclitaxel between January 2009 and May 2019 in our institution. The regimen is composed of 1000 mg/m^2 gemcitabine by intravenous infusion for 30 min on day 1 and 8, and 175 mg/m^2 of paclitaxel by intravenous infusion for 180 min on day 8, every 3 weeks. Prior to paclitaxel administration, all patients had received premedication with dexamethasone (20 mg), diphenhydramine (50 mg), and famotidine (20 mg) IV 30 minutes before chemotherapy. This regimen was approved by the review committee for chemotherapeutic regimen of Niigata University Medical and Dental Hospital. We retrospectively analyzed the effect of gemcitabine and paclitaxel therapy on overall response, progression-free survival, overall survival, and toxicity in each patient using electrical medical record. Statistical analysis was performed with SPSS version 21 software.

Results: Two patients treated with adjuvant setting were excluded and 40 of 42 patients were enrolled in this study. The median age was 48 years (range, 17 to 80 years).The patients included 22 men and 18 women. Ten patients had bone sarcoma and 30 had soft tissue sarcoma. The primary tumor site was the extremities or trunk in 22 patients, retroperitoneal or abdominal in 12 patients, and mediastinum or lung in 6 patients. Thirty-four patients (85%) had previously been treated with one or more chemotherapeutic regimens. Gemcitabine and paclitaxel were administrated at a median dose of 80% and duration of 4.3 months (range, 0.7 to 32.6 months) and 5.5 cycles (range, 1 to 45 cycles). The overall response rate was 17.5% and the disease control rate was 67.5%. The median progression-free survival was 5.6 months (95% CI, 5.0 to 6.3) and the median overall survival was 14.4 months (95% CI, 9.2 to 19.5). Reasons for discontinuing this treatment included progressive disease (n=33), toxicity (n=5), and complication of intestinal obstruction (n=2). There were no grade 4 complications and febrile neutropenia during this treatment. Grade 3 complications included: neutropenia (n=7, 25%), gemcitabine-related pneumonitis (n=2), anaphylaxis to paclitaxel (n=1), rash acneiform (n=1) and peripheral neuropathy (n=1). Pneumonitis was noted at the initial cycle in one patient and after completion of four cycles in another patient.

Conclusion: The response rate was almost equivalent with other previous reports treated with the combination of gemcitabine and docetaxel. Paclitaxel or docetaxel combined with gemcitabine had different toxicity profiles, and neuropathy was observed more frequently compared with the reported case of docetaxel regimen. However, most of toxicities were enough manageable in this study. In addition, some patients had long survival with a good response. Our study supports the notion that gemcitabine and paclitaxel therapy is an appropriate option for salvage-line therapy for patients with advanced bone and soft tissue sarcoma. Future larger and prospective trials are warranted to establish the efficacy and safety of this combination therapy in bone and soft tissue sarcoma.

Poster #113 3225830

THE ANALYSIS OF EPIDEMIOLOGICAL CHARACTERISTICS OF 1624 SOFT TISSUE SARCOMA CASES IN 2006-2016 IN HENAN PROVINCE CANCER HOSPITAL, CHINA

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Objective: To analyze the epidemiological incidence characteristics of 1624 inpatients with soft tissue sarcoma (STS) during 2006 to 2016 in Henan Province Cancer Hospital, China.

Methods: The information of electronic medical record from the first hospitalized patients with STS in Henan Province Cancer Hospital during January 1, 2006 to December 31, 2016 was collected, and descriptive statistics was analyzed on age, gender and pathological type by using SPSS21.0 software.

Results: There were 1624 inpatients with STS in Henan Province Cancer Hospital in 2006~2016. The top nine pathological subtypes of STS with high constituent ratio were undifferentiated pleomorphic sarcoma (UPS, 23.83%), synovial sarcoma (16.69%), liposarcoma (13.67%), fibrosarcoma (10.22%), sarcoma without definite type (8.99%), leiomyosarcoma (7.02%), dermatofibrosarcoma protuberant (5.79%), rhabdomyosarcoma (4.68%) and malignant peripheral nerve sheath tumor (4.25%). The average age of inpatients was 44.71±17.91, and the inpatients aged 35-59 accounted for 47.6%. The number of UPS inpatients reached the peak at the age of 55 to 64; The proportion of rhabdomyosarcoma between 0~4 and 5~9 years old can reach above 46%. In total 1624 inpatients of STS, the number of male and female inpatients were 923 and 701, respectively. The gender ratio was 1.32:1. The proportion of UPS in either male or female inpatients was the highest, accounting for 23.10% and 24.80%, respectively. The number of male inpatients was more than that of female in the top nine pathological subtypes of STS except leiomyosarcoma (the gender ratio was 0.84:1).

Conclusion: The top three pathological subtypes of STS with high constituent ratio were UPS, synovial sarcoma and liposarcoma.UPS should be paid more attention on the prevention, trearment and research in Henan in future for its highest proportion of STS.

Poster #114 3219647

REFERRAL PATTERN OF RETROPERITONEAL SARCOMAS TO A SURGICAL ONCOLOGY SERVICE WITH SARCOMA INTEREST IN A DEVELOPING COUNTRY

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Objective: Management of retroperitoneal sarcomas pose specific challenges due to large size at presentation as well as propensity for local recurrence. Ideally these complex problems should be managed at an expert centre with multidisciplinary care. Pakistan lacks dedicated expert sarcoma centres therefore the retroperitoneal sarcomas are seen and managed mostly by general surgeons with no concentration of volumes or referrals. We describe the referral pattern of retroperitoneal sarcomas to a surgical oncology service in urban Karachi after communicating an interest in the management of retroperitoneal sarcomas.

Methods: The surgical oncology service at Patel Hospital was started in September 2016. An interest in the management of retroperitoneal sarcomas was communicated to the oncology and surgery community of the metropolis with a population of more than 20 million. A sarcoma pathologist with experience and interest in soft tissue sarcomas was identified to review all sarcoma pathologies. Active collaboration with the sarcoma team at Istituto Nazionale dei Tumori, Milan was established in Jan 2018 and since then all cases with RPS are discussed with the sarcoma centre. The lead surgeon of our service has also enrolled in the European School of Soft Tissue Sarcoma Surgery training program to obtain better understanding and structured training in the management of soft tissue sarcomas. Presentations and seminars regarding multidisciplinary evaluation and management of retroperitoneal sarcomas targetting surgeons and oncologists have been organized to generate awareness on the topic.

Results: Between September 2016 and June 2019, a total of 19 referrals for retroperitoneal sarcomas were received by the service. Of these 10 patients had primary while 9 patients had recurrent retroperitoneal sarcomas. The histopathological distribution was: well differentiated liposarcoma 6 patients, dedifferentiated liposarcoma 9 patients (3 had imaging features but no biopsy), Leiomyosarcoma 2 patients, Malignant Peripheral Nerve Sheath Tumor 1 patient, and one patient had inconclusive biopsy. Of these 8 patient were offered resection, 4 patients were advised further work-up but lost to follow-up, 4 were offered neoadjuvant therapy before attempting resection while 3 were not considered resectable. Since January 2018, coordination with an expert sarcoma service was established and all sarcoma cases reviewed by the service have been discussed with the sarcoma team. This has helped not only in the appropriate decision making for the patients but also generated awareness about the interest in the management of sarcoma in the community of surgeons and oncologists in the city. The number of referrals per year was 2016: 1, 2017: 5, 2018:7, 2019 (until June):6.

Conclusion: With a network of communication with the oncologists and surgeons in the city as well as at national fora, we have been able to generate an awareness regarding our service's interest in the management of retroperitoneal sarcomas. This is reflected by an increase in the number of referrals of this rare cancer over the last 3 years. Discussion of all cases with an expert sarcoma centre helps provide specialty multidisciplinary decision making for these patients. This as well as training and collaboration through the European School of Soft Tissue Sarcoma Surgery training program will hopefully enable our service to develop into a referral centre for retroperitoneal sarcomas.

Poster #115 3252957

TUMOUR NECROSIS IS AN INDEPENDENT PROGNOSTIC FACTOR FOR OVERALL SURVIVAL AFTER CURATIVE RESECTION OF GIST

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Objective: Tumour necrosis is associated with poorer outcomes in several malignancies, however in GIST the literature is inconclusive. We aimed to determine whether tumour necrosis was significantly associated with survival in resectable GISTs.

Methods: We retrospectively analysed a database of curative GIST resections performed from 2006-2017 in a specialist sarcoma unit. The database comprised open and laparoscopic resections. Patients who were treated with neo-adjuvant imatinib therapy were excluded on the basis that pathological diagnosis of tumour necrosis would be inaccurate. Tumour necrosis, location, histology (mixed, spindle, epithelioid), genetic mutation, codon, age and Joensuu 2008 risk score were analysed. Overall survival was estimated with the Kaplan-Meier method, and associations with prognosis were assessed using Cox regression models. Multivariable analyses were then performed, to assess whether necrosis was independently associated with patient outcome.

Results: 129 patients (78M: 51F) with a median age of 66 years (IQR: 54-73) were eligible for analysis. 73% (94) of patients had a gastric GIST. 42% (53) patients were classed as high risk, 25% (32) intermediate risk and 33% (43) low risk. 5 year overall survival in those without tumour necrosis was 83.4% compared to 60% in those with tumour necrosis. On multivariable analysis tumour necrosis was a significant independent predictor of shorter recurrence-free survival (HR:9.37, $p<0.001$) and of overall survival (HR:2.57, $p=0.045$). Increasing patient age was also associated with significantly poorer survival outcomes in both models. The Joensuu 2008 Risk Score was then combined with tumour necrosis to assess whether this could result in a risk score with improved prognostic accuracy. Patients without necrosis that were classified as high risk had near identical recurrence-free survival to those with necrosis that were low/intermediate risk, at 69% at five years for both groups.

Conclusion: This work adds to a growing body of evidence that tumour necrosis should be added as a valuable prognostic factor to the current NIH classification. Potential implications are the use of adjuvant imatinib therapy in intermediate risk patients with tumour necrosis to reduce local recurrence rates. Collaboration with the Royal Marsden Hospital is currently underway in combining datasets to validate these findings in a wider context.

Poster #116 3255281

QUANTITATIVE MASS SPECTROMETRY IMAGING IN SECONDARY RESISTANT GIST LIVER METASTASIS DEMONSTRATES LACK OF IMATINIB DISTRIBUTION

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Objective: Mass spectrometry imaging (MSI) is an enabling technology for label-free drug disposition studies at high spatial resolution in life science- and pharmaceutical research. Recent advances in the use of stable isotope-labeled internal standards have suggested that MSI could become a quantitative drug imaging methodology also in clinical settings. We were interested to examine whether MSI would allow to analysze imatinib intratumoral distribution in GIST patients undergoing resection for metastases.

Methods: Patient Tissue Samples

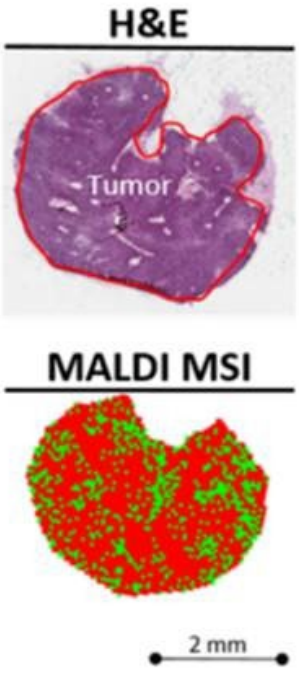
Human GIST and adjacent not-tumor involved tissues had been surgically removed from 28 patients for clinical indications. All pts. had biopsy-proven progressive GIST mets. resistant to imatinib. All patients were still under imatinib treatment at the time of surgery and had taken their respective drug dose according mutational status including the day before surgery. The major part of the resection specimen went to pathology for characterisation and analysis for 2ndary mutations. Representative tumor tissue parts were snap-frozen as were uninvolved tissue samples. Probes were stored at -80 °C in the biobank.The Medical Ethics Committee II of the Medical Faculty Mannheim of Heidelberg University approved the study.

Experimental Setup

Each sample was sectioned in six steps at –20 °C in a CM 1950 cryostat (Leica, Germany) in triplicate. After trimming, the first 8-µm tissue section of each sample was thaw-mounted onto a gold target for MALDI-TOF qMSI. Two consecutive slices were then put onto Starfrost adhesive microscope slides for H&E and scanned in an Aperio CS2 (Leica Biosystems). Afterwards, four consecutive sections were collected for quantitative drug determination by HPLC-ESI-QToF-MS. Finally, some exemplary sections were mounted on conductive ITO-slides for additional qMSI with a high resolving FTICR-MS with n = 3. For MALDI MSI, each ITO slide featured duplicate spots of an imatinib dilution series (25, 12.5, 6.25, 3.125, 1.56, 0.78 pmol and a blank control) spotted onto a porcine liver section.

For normalization, nine layers of imatinib-D8 were deposited on the slides using a SunCollect sprayer. For positive-ion mode measurements, five layers (flow rates of 10, 15, 3 × 20 µL/min) of DHB matrix (60 mg/mL in 50% acetonitrile, 0.5% TFA) were subsequently sprayed onto the tissue at 300 mm/min as described previously . qMSI data acquisition was performed on an ultrafleXtreme MS using flexControl 3.4 (Bruker Daltonics) The raster width was 200 µm for calibration curves and 50 µm for all human samples. Geometric information was generated using external quadratic mass calibration with peptide calibration standard II including dasatinib were done in flexImaging 4.1

Results: In comparison with linear calibration, a nonlinear calibration model enabled better fitting of the data and reduced slide-to-slide variability as well as nonlinearities arising from the multiparametric stochastic chemical MALDI processes. Direct on-tissue quantification by qMSI compared well with conventional HPLC-MS-based imatinib quantification from tissue extracts, as limits of quantification were 1.8 and 1.0 , respectively. Imatinib was heterogeneously distributed in most tissues tested. In a subset of samples corresponding to liver tissue from metastatic patients contained imatinib above the level of quantitation (LOQ). Interestingly, in these cases tumor tissue in contrast to normal control tissue was virtually devoid of imatinib depending on the mutation status particularly when previously unknown secondary mutations could be detected.



Conclusion: Imatinib tissue spatial maps revealed strikingdifferences in drug penetration into liver metastases in patients with secondry mutations. This provides evidence for secondary drug resistance. Our results suggest that qMSI may have utility also in the human setting of clinical pharmacology in solid tumors.

Poster #117 3256201

EXON 9 MUTATED GIST AND ADJUVANT IMATINIB: A MULTICENTRIC RETROSPECTIVE STUDY

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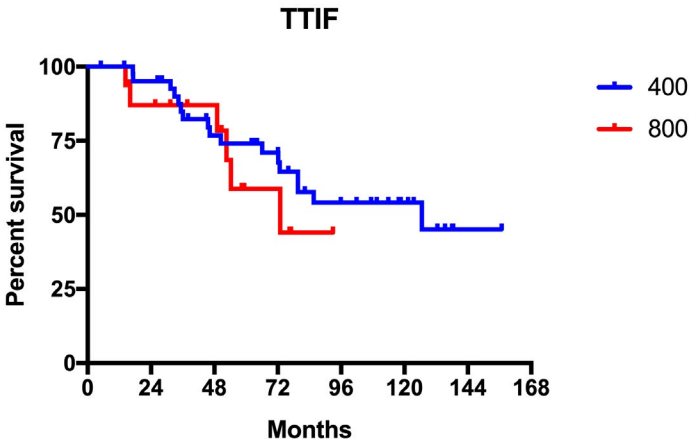
Objective: Exon 9 mutated GISTs represent the 10–15% of newly diagnosed cases. There is no concordance in term of Ex9 mutation prognostic impact. In literature, both a better relapse free survival after curative resection and a greater malignant potential have been reported. It is well established that Ex9 Gists benefit less from Imatinib than other mutated Gists in both the adjuvant and metastatic setting. However significantly higher response rates and longer progression-free survival are observed at doses of Imatinib higher than 400 mg per day in exon 9 mutated metastatic GIST. At the moment no data about higher doses of Imatinib in the adjuvant setting have been reported.

Methods: Eighty-eight patients affected by Exon 9 mutated Gist who received adjuvant Imatinib were retrospectively collected from 12 different center between January 2005 and December 2018. Sixty-six pts (31 males and 35 females) out of 88 met all the inclusion criteria and were considered eligible for safety and survival analysis. All pts underwent radical resection of the primary tumor. As adjuvant treatment, 19 pts received Imatinib 800 mg/d and 47 pts received Imatinib 400 mg/d. There were 30 recurrences, 11 of which occurred during adjuvant treatment. The aim of this retrospective study was to investigate the effect of the two different doses of Imatinib in terms of Time To Imatinib Failure (TTIF) in patients with exon 9 mutated Gist.

Results: Nineteen pts were treated with Imatinib 800 mg/d while 47 pts were treated with Imatinib 400 mg/d. Median age at diagnosis was 54 years (range 27 y – 80 y). The primary site of disease was the small bowel (Jejunum/ileum) in 50 pts, duodenum in 7 pts, stomach in 7 pts and other sites in 2 pts. Median tumor size was 100 mm and the risk of recurrence (Miettinen classification) was high in the majority of pts. Median treatment duration was 30.5 mos (range 7 mos – 132 mos). Tumor rupture occurred in 7 pts. Fifteen pts had peritoneal relapse, 12 pts liver relapse and 3 pts recurred in both sites. After recurrence, 25 pts were treated with Imatinib, 4 pts with Sunitinib and one pts underwent surgical resection of isolated liver metastases. Median TTIF was 126.6 mo in the 400 mg group and 72.9 mo in the 800 mg group, with an HR of 0.68 (95% CI: 0.24-1.91; p: 0.40). Thirty-seven (56%) pts developed at least one adverse event with only 3 pts experiencing a grade G3-G4 toxicity.

Conclusion: This retrospective analysis showed no difference in TTIF between the two groups of adjuvant treatment, with a not statistically significant trend for the 400 mg group. Although the retrospective nature and the small number of pts, we could assume that Imatinib 400 mg is a reasonable choice. Otherwise in pts starting with Imatinib 800 mg, a reduction of the dose due to intolerance or other reasons, could not affect the efficacy of the adjuvant treatment.



Poster #118 3253758

MUTATIONAL PROFILING IS COST-EFFECTIVE FOR TAILORING FIRST-LINE TREATMENT IN PATIENTS WITH METASTATIC GASTROINTESTINAL STROMAL TUMOR: RESULTS OF A MARKOV MODEL ANALYSIS

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Objective: Gastrointestinal stromal tumor (GIST) is the most common sarcoma and these are frequently driven by oncogenic *KIT* mutations. In the late 1990s, imatinib targeting of KIT marked a new era in GIST treatment and ushered in precision oncology for all solid malignancies. However, studies on the molecular epidemiology of GIST have shown that tumors respond differentially to imatinib treatment. Approximately 67% of GISTs harbor *KIT* exon 11 mutations that respond to 400 mg imatinib dosing. Another 12% of GISTs harbor *KIT* exon 9 mutations that require 800 mg imatinib dosing for clinical benefit. Finally, the majority of remaining tumors have mutations that are generally imatinib-resistant. Despite this knowledge, only ~15% of patients currently undergo genetic testing at diagnosis and 400 mg imatinib is mainstay of first-line therapy for all GIST. Barriers to genetic profiling include concerns about the cost and the utility of testing. To investigate this, we evaluated the cost-effectiveness of mutational profiling for patients with metastatic GIST.

Methods: We developed a Markov model to compare the cost and effectiveness of next generation sequencing (NGS) for patients with metastatic GIST from the US payer perspective. Health outcome was quality-adjusted life years (QALYs). Cost of NGS testing ($2,919 [USD]) was obtained from Medicare claims data. Annual costs of imatinib (IM) and sunitinib (SUT) therapy were obtained for pharmaceutical and literature values [IM 400 mg: $57,863; SUT: $43,051]. Cost and frequency of adverse events were extracted from clinical trials (Jabbour *et al. Blood* 2009 and Motzer *et al. NEJM* 2007). Progression-free survival (PFS) and overall survival (OS) were modeled based on prospective, randomized clinical trial data for treatment with imatinib or sunitinib in patients with Stage IV disease (Debiec-Rychter *et al. EJC,* 2006, MetaGIST Group, *JCO*, 2010, and Heinrich *et al. JCO*, 2007). Long-term OS for patients with metastatic GIST was extracted from the SEER database (Ma *et al. Cancer Epidemiol. Biomark. Prev.*, 2015). Individual Markov groups were constructed for three mutational profiles based on stratification in the original clinical trials (*KIT* exon 11, *KIT* exon 9 and other mutations). The molecularly matched approach involved first-line 800 mg dose imatinib for patients with *KIT* exon 9 mutations and 400 mg dose imatinib for patients with *KIT* exon 11 or "other" mutation status (such as *PDGFRA*, *SDHx*, *BRAF*, and *NF1*). This was compared to the traditional empiric imatinib approach, which entailed first-line treatment with standard dose imatinib for all patients *(Figure A)*. Willingness-to-pay (WTP) threshold (acceptable cost of mutational matched therapy per increase in one QALY) was set at $100,000. The model was run for a 10-year time horizon and a discounting rate of 3% was applied.

Results: NGS and molecularly matched therapy was associated with an increase in QALYs of 0.10 and a cost increase of $7,577 compared to the empiric imatinib approach. The incremental cost-effectiveness ratio (ICER) was $73,390, which is less than the WTP threshold suggesting that the matched approach is cost-effective *(Figure B)*. These findings were robust to sensitivity analyses for the costs of NGS, drugs, and health utility model inputs. Sensitivity analysis indicated that the matched approach remained cost-effective at an NGS cost up to $5,345.

Conclusion: For the first time, we report a Markov model assessing the cost-effectiveness of using NGS to tailor imatinib therapy in patients with metastatic GIST. Matched treatment of *KIT* mutations to imatinib dosing, based on NGS panels costing less than $5,345, was a cost-effective approach for personalized and precise imatinib treatment compared to empiric imatinib. These findings suggest that NGS profiling and personalized imatinib dosing should be considered standard-of-care for the first-line treatment of patients with metastatic GIST.

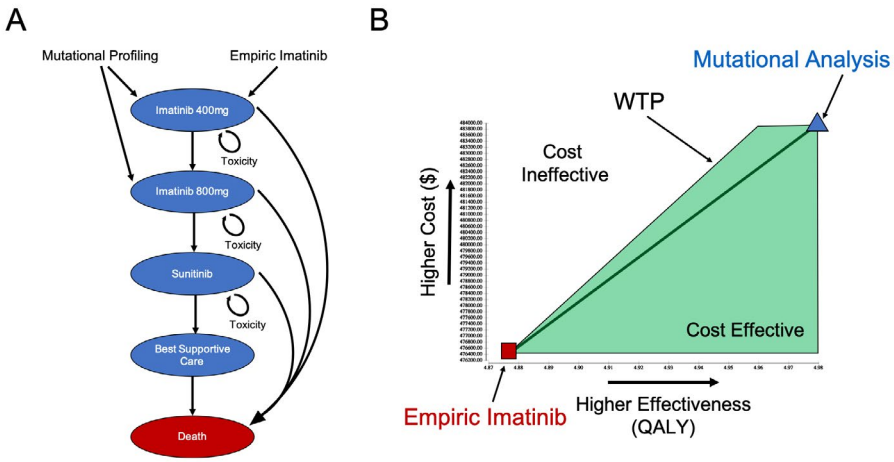

Figure: (A) State transition diagram for the Markov model comparing molecularly matched therapy to the empiric imatinib approach, (B) Cost-effectiveness results.

Poster #119 3254407

PATTERNS OF MULTIDISCIPLINARY CARE AND OUTCOMES OF PATIENTS WITH METASTATIC GIST IN A REAL-LIFE SETTING: THE METAGIST OBSERVATIONAL STUDY FROM 3 COORDINATING CENTERS OF THE GSF-GETO

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Objective: Gastro intestinal stromal tumors (GIST) are rare mesenchymal tumors characterized by *KIT* or *PDGFRalpha* mutations. Metastatic patients are currently treated with oral KIT and PDGFR tyrosine-kinase inhibitors (TKI) such as imatinib, sunitinib and regorafenib. Over two decades, significant changes in drug discovery have impacted treatment strategies and outcomes. Our objective was to detail patterns of sequential treatments used in real life setting, especially the proportions of patients with metastatic GIST eventually benefiting from access to locoregional (LR) procedures and clinical trials and their results on survival.

Methods: The patterns of care, outcomes, and prognostic factors of a cohort of patients with a metastatic GIST treated in one of the three French national reference network centers from 1990 to 2018 were analyzed. The primary objective was to describe clinico-biological profiles and treatment modalities of patients with metastatic GIST in a real-life setting, including access to LR procedures such as surgery (SUR), radiofrequency (RF), radiotherapy (RT) and cryotherapy (CRYO), and inclusion in clinical trials. Secondary objectives were to evaluate 1/ patients outcome for each line of palliative systemic treatment in terms of time to next treatment (TNT), and survival, 2/ the impact of access to LR procedures and clinical trials on TNT and survival, 3/ evolution of patients survival from metastasis diagnostic among 4 periods of time with different access to TKI: < 2002 (pre-imatinib era), 2002-2007 (pre-sunitinib era), 2006-2014 (pre-regorafenib era), post 2014, 4/ clinical and molecular factors associated with prolonged/short TNT and overall survival (OS) in univariate and multivariate analysis.

Results: 1038 patients were included in the database. Of them, 492 met inclusion criteria: 259 had metastatic disease at diagnosis and 233 a metachrone metastatic relapse. Patients characteristics at baseline are given in table 1. Location of first metastasis was the liver in 36.8%, the peritoneum 35.8%, and multisite in 22.4% of cases. Overall, 461 patients (93.7%) received systemic treatment for palliative indication**,** with a median of 3 lines (range 1-15). Imatinib was the main TKI used in 1^{rst} line, for 384 (83.3%) patients, and in 2nd line, for 136 (44.7%) patients, followed by sunitinib for 104 (34.2%) patients. In 3nd line the main TKI used were sunitinib (39.6%), imatinib (23.7%), regorafenib (7.8%) sorafenib (5.3%) and pazopanib (4.9%). Overall, 171 (34.8%) patients received four or more lines of treatment, mainly imatinib and sunitinib.

Among metastatic patients at diagnosis, 193 (74.5%) had surgery of their primary tumor, and 139 (53.7%) underwent additional LR procedures to metastasis, including SUR in 89.9%, RF in 10.8%, RT in 7.2% and CRYO in 1.4% of cases. Among patients with metastatic relapse, 110 (47.2%) underwent LR procedures in this setting, including surgery in 85.5%, RF in 18.2%, RT in 10.9% and CRYO in 2.7% of cases. Overall, 15.7% of patients had multiple LR procedures. 269 patients (54.7%) eventually participated in a clinical trial during the course of their metastatic disease. The proportion of patients included in a clinical trial among subsequent lines was sustained: 177 patients (38.4%) in 1^{rst} line, 92 (30.3%) in 2nd line, 62 (25.3%) in 3rd line, 54 (31.6%) in 4^{rth} line and 39 (30.5%) in 5th line.

Conclusion: Patients with metastatic GIST should be treated in multidisciplinary expert centers with early access to clinical trials. Complete results on TNT and survival data among predefined periods, as well as univariate and multivariate analysis for TNT and survival including mutational status, LR procedures and clinical trial inclusion will be presented at the meeting.

Patients characteristics at baseline primary presentation

	All patients (n=1038)		Study population (n=492)	
	n	%	n	%
Centre				
Institut Bergonié, Bordeaux	255	24.6	131	26.6
Centre Léon Bérard, Lyon	550	53	220	44.7
Gustave Roussy, Villejuif	233	22.4	141	28.7
Status at referral to expert center				
First event	871	83.9	349	70.9
Relapse	155	14.9	143	29.1
NA	12	1.2	.	.
Sex				
Male	547	53	292	59
Female	491	47	200	41
Median age (years)	61 (19-93)		59 (19-93)	
Significant previous history				
No	850	82	424	86
Previous cancer	107	10	36	7
NF1	26	2.5	8	1.6
Other	15	1.4	6	1.2
Other malignancy in family	15	1.4	11	2
Carney Triad, Carney Stratakis Dyad	3	0.3	1	0.2
Familial GISTs	1	0.1	.	.
Li Fraumeni syndrome	1	0.1	.	.
Other genetic disease	1	0.1	.	.
NA	19	2	6	1
Tumour site				
Stomach	527	50.8	204	41.5
Small intestine	327	31.5	192	39
Duodenum	60	5.8	26	5.3
Rectum	55	5.3	24	4.9
Peritoneum	30	2.9	19	3.9
Colon	24	2.3	17	3.5
Oesophagus	15	1.4	10	2
Median tumour size (mm)	80 (3 - 450)		100 (18 - 400)	
Metastatic at diagnostic				
No	774	74.6	233	47.4
Yes*	260	25	259	52.6
NA	4	0.4	.	.
Miettinen AFIP group				
High risk	501	48.3	340	69.1
Intermediate risk	186	17.9	69	14
Low risk	137	13.2	18	3.7
Very low risk	124	11.9	5	1
NA	90	8.7	60	12.2
KIT and PDGFRa mutational status				
KIT Exon 11	543	52.3	302	61.4
KIT Exon 9	75	7.2	43	8.7
PDGFRa Exon 18	96	9.2	31	6.3
KIT Exon 13	20	1.9	12	2.4
KIT Exon 17	12	1.2	11	2.2
PDGFRa Exon 12	12	1.2	5	1
PDGFRa Exon 14	3	0.3	1	0.2
Wild type	226	21.8	61	12.4
Non Amplifiable DNA	53	5.1	18	3.7
NA	121	11.6	51	10.4
Surgery				
Yes	937	90.3	421	86.6
No	98	9.4	66	13.4
NA	3	0.3	.	.
Type of surgery				
Wide resection	729	77.8	351	82.4
Excision	99	10.6	31	7.3
Compartimentectomy	79	8.4	31	7.3
NA	30	3.2	13	3.1
Tumour spillage				
No	774	82.6	313	73.5
Yes	90	9.6	61	14.3
NA	73	7.8	52	12.2
Surgical margins				
R0	653	69.7	244	56.2
R1	120	12.8	66	15.5
R2	30	3.2	22	5.2
Not evaluable	58	6.2	41	9.6
NA	76	8.1	53	12.4
Systemic treatment				
No	528	50.9	176	35.8
Yes	509	49	316	64.2
NA	1	0.1	.	.
Indication of systemic treatment				
Palliative**	275	54	244	77.2
Adjuvant	175	34.4	54	17.1
Neo-adjuvant	31	6.1	5	1.6
Neo-adjuvant and adjuvant	17	3.3	9	2.8
NA	11	2.2	4	1.3
Clinical trial inclusion				
No	848	81.7	425	86.4
Yes	198	18.2	67	13.6
NA	1	0.1	.	.

*Non-informative patient was not included in the study population; **31 patients had advanced locoregional disease and received palliative systemic treatment for primary tumour but they were not included in the study population.

Poster #120 3255128

PRECLINICAL ACTIVITY OF AXITINIB IN GIST CELL MODELS WITH CLINICALLY REPRESENTATIVE KIT PRIMARY AND SECONDARY MUTATIONS

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Objective: Gastrointestinal stromal tumor (GIST) initiation and evolution is usually framed by KIT/PDGFRA oncogenic activation, and in later stages by the polyclonal expansion of resistant subpopulations harboring KIT secondary mutations (muts) after the onset of imatinib (IM) resistance. KIT resistance mut cluster in the ATP binding pocket (exons 13 and 14) and the activation loop (exons 17 and 18). Tyrosine kinase inhibitors (TKIs) sunitinib (SU) and regorafenib (RE) are approved in IM-resistant disease, but only target a subset of resistance mut, thereby leading to a modest clinical benefit. Axitinib (AXI) is a TKI that inhibits potently VEGFR and KIT. We evaluated the *in vitro* activity of AXI compared with IM, SU and RE.

Methods: AXI, IM, SU and RE inhibition of viability (CellTiter-Glo) and KIT and KIT-downstream pathways phosphorylation (ERK1/2, AKT-S473) by immunoblotting were assessed in human GIST cell lines with clinical representative KIT primary and secondary mut (Table 1).

Results: All four TKIs showed inhibition of KIT and KIT-downstream effectors phosphorylation in IM-sensitive GIST models. AXI inhibited more potently KIT exon 11 than exon 13 primary mutation. Likewise, KIT secondary mut V654A (exon 13) was barely inhibited by AXI and RE, whereas SU was more active, confirming known evidence. By contrast, KIT secondary mut T670I (exon 14) was similarly inhibited by AXI and TKIs approved in IM-resistance. AXI showed suppression of KIT signaling and cell viability impairment at intermediate doses in activation-loop mutants. KIT-independent cell line GIST48B confirmed that AXI doses <1000nM are on-target, KIT-mediated effects.

Conclusion: *In vitro* studies confirm that AXI is a potent inhibitor of *KIT* exon 11 mut in GIST. Regarding resistant disease, AXI follows the typical TKI pattern of activity against a subset of KIT secondary mutations. AXI shows activity against the KIT exon 14 T670I secondary mut (gatekeeper), and against mutations in the activation loop (KIT exon 17), thereby showing a comparable activity profile to RE. By contrast, AXI appears to be less effective against mutations in the ATP binding pocket (exon13). The study of AXI in GIST merits further preclinical work.

IC50 values for AXI and approved TKIs in GIST

CELL LINE	IMATINIB	KIT GENOTYPE	AXI (nM)	IM (nM)	SU (nM)	RE (nM)
GIST-T1	Sensitive	Ex 11	5.6	10.6	5.9	28.8
GIST882	Sensitive	Ex 13	881.4	119.9	48.5	556.9
GIST430/654	Resistant	Ex 11 + 13	3729.5	>5000	515.6	1921.0
GIST-T1/670	Resistant	Ex 11 + 14	660.4	>5000	120.0	529.4
GIST-T1/816	Resistant	Ex 11 + 17	371.5	911.6	3571.7	369.2
GIST-T1/820	Resistant	Ex 11 + 17	616.7	>5000	2089.9	807.8
GIST48B	Resistant	KIT-indep	940.9	>5000	>5000	>5000

Poster #121 3255526

ROLE OF PAZOPANIB IN METASTATIC GASTROINTESTINAL STROMAL TUMOR (GIST), PROGRESSING AFTER STANDARD OF CARE THERAPY

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Objective: Gastrointestinal stromal tumors (GIST) are the most common mesenchymal neoplasms of the gastrointestinal tract, and patients who present with metastases or have a recurrence, in general, need life-long tyrosine kinase inhibition. The standard of care therapeutic options for metastatic GIST in the United States are imatinib (first-line), sunitinib (second-line), and regorafenib (third-line). Several other tyrosine kinase inhibitors (TKI) have been investigated with limited activity, and are often utilized after exhausting approved therapies. Pazopanib is one of these broad-spectrum TKI targeting KIT, PDGFR and VEGFR receptors. In a phase 2 randomized trial (pazopanib plus best supportive care vs best supportive care alone) in the 3rd line setting after imatinib and sunitinib failure, the median progression free-survival (PFS) for pazopanib was 3.4 months, median duration of exposure was 3.8 months and best response was SD in 84% patients (Mir et al, PazoGIST, Lancet 2016). Recent availability of more specific KIT/PDGFR inhibitors (avapritinib and ripretinib) in clinical trials have increased the number of effective lines of therapy available, but with eventual progression. Herein, we report a case series of our experience with pazopanib, describing efficacy in metastatic GIST after progression on multiple lines of therapy.

Methods: We conducted a retrospective chart review of patients with metastatic GIST who were treated with pazopanib at the University of Texas MD Anderson Cancer Center between 2015 and 2018. Patients were identified using the pharmacy database and the date for data cut-off was 6/18/2019. Clinical characteristics of these patients and their GIST, number of regimens used, and duration of therapy with each of the regimens were retrieved from medical records. Imaging studies were reviewed by the study team to determine best tumor response by RECIST 1.1 on pazopanib and other lines of therapy prior to pazopanib.

Results: Fourteen patients were identified, out of which 11 patients were evaluable and included in our study (Table 1). Median follow-up duration was 47 months (Range 14 to 231 months). There were seven males and four females with a median age of 58 years (Range 35 to 69 years). One patient was Asian while others were Caucasian. Primary site of the tumor was gastric in seven of the patients, followed by small intestine in four patients. All patients were treated for metastatic disease, but seven patients had localized disease at the time of diagnosis. KIT exon 11 mutation was the most common mutation seen in seven patients, while one patient had an exon 17 primary mutation and three patients had no mutations identified on targeted sequencing of KIT/PDGFR. Median lines of therapy prior to pazopanib was 5 (Range 3 to 7). Median duration of response of the patients who are off pazopanib (N=4) was 4 months (Range 0.36 to 15) and the median duration of response for those who remain on pazopanib at their last follow up was 5+ (Range 2+ to 9+). Four out of the eleven patients had a partial response (36%), three had stable disease (27%) and four had progressive disease (36%). Interestingly, two out of four patients who received Ripretinib and progressed at two and four months respectively, remain on pazopanib beyond 4 months at the time of data cut-off and one of them had partial response. Median starting dose of pazopanib was 400 mg (Range 200mg to 800mg) and while majority of the patients (75%) received the full-dose of 800 mg at some point during the therapy. Dose reduction was required in four patients (36%). Only one patient had to stop pazopanib due to toxicity (severe diarrhea).

Conclusion: Pazopanib still appears to be a reasonable option for metastatic GIST patients who have exhausted currently available treatments for GIST with a relatively good safety profile. Data from a larger cohort of patients would be important to determine the role of pazopanib in the changing GIST treatment landscape.

Table 1: Characteristics of 11 patients on pazopanib (P):

patients #	Age	Regimen before P #	Median duration on P (months)	Reasons for stopping P	OS* (months)	Primary mutation	Secondary mutation	Starting dose of P (mg)	Maximum dose on P (mg)	Best response
1	47	4	1	PD	42	KIT exon 11	KIT exon 13	400	800	PD
2	51	4	2+	NA†	612+	KIT exon 11	None	200	800	SD
3	69	2	1	PD	31+	None	None	400	400	PD
4	66	3	5+	NA	101+	KIT exon 11	KIT exon 17	400	400	PR
5	60	4	4	Toxicity (GI)	24	KIT exon 11	TSC1	400	800	PD
6	58	2	10+	NA	16+	KIT exon 17	None	400	400	SD
7	44	4	20	PD	64+	KIT exon 11	None	800	800	SD
8	66	4	4+	NA	48+	None	None	200	800	PR
9	51	6	4	PD	51	KIT exon 11	None	800	800	PD
10	59	4	4+	NA	65+	KIT exon 11	None	400	800	PR
11	35	3	15	PD	49+	None	None	400	800	PR

*Overall survival calculated from time of metastatic disease diagnosis until death or for those who are alive at the time of the study it was calculated till 6/19/2019 (data cut-off point). + Beside the number indicates that the patient is still alive at the time of data cut-off point. †not applicable as the patient is still on pazopanib at the time of data cut-off point. PR, partial response; SD, stable disease; PD, progressive disease; OS, overall survival.

Table 2: Duration and responses to lines of therapy prior to pazopanib:

Patients#	1st line/ DOR/ Best response	2nd line/ DOR/ Best response	3rd line/ DOR/ Best response	4th line/ DOR/ Best response	5th line/ DOR/ Best response	6th line/ DOR/ Best response
1	IM/ 14/ PR	S/ 9/ SD	R/ 8/ PD	So/ 1/ PD	N/ 1/ PD	-
2	IM/ 73/ PR	So/ 9/ SD	D/ 8/ SD	N/ 1/ PD	S/ 2/ PD	-
3	IM/ 2/ PD	R/ 1/ PD	-	-	-	-
4	IM/ 14/ PD	S/ 63/ SD	R/ 32/ SD	-	-	-
5	IM/ 51/ PD	S/ 1/ PD	Ri/ 2/ PD	R/ 3/ PD	-	-
6	IM/ 44/ SD	S/ 2/ PD	-	-	-	-
7	IM/ 20/ PD	S/ 2/ PD	R/ 17/ PD	N/ 5/ PD	-	-
8	IM/ 23/ PR	S/ 10/ CR	Ri/ 4/ SD	R/ 6/ PR	N/ 4/ SD	-
9	IM/ 4/ SD	S/ 6/ PR	R/ 4/ PD	So/ 2/ PD	Ri/ 2/ PD	N/ 4/ PD
10	IM/ 4/ SD	S/ 11/ PR	R/ 3/ PD	Ri/ 6/ SD	-	-
11	IM/ 7/ PD	S/ 3/ PD	R/ 2/ PD	-	-	-

*Sequence of the patient is similar to the previous table. DOR, Duration of Response; PR, partial response; SD, stable disease; PD, progressive disease. IM, imatinib; S, sunitinib; So, sorafenib; N, nilotinib; D, Dasatinib; R, regorafenib; DCC-2618, Ripretinib. Ri, Ripretinib

Poster #122 3255898

PRESERVATION OF ORGAN FUNCTION BY MINIMIZING SURGICAL RESECTION BY NEOADJUVANT IMATINIB THERAPY IN GASTROINTESTINAL STROMAL TUMORS (GIST)

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Objective: GISTs are often only noticed late and are treated by multivisceral resection due to a lack of preoperative histological diagnosis and high vascularization. This leads to morbidity in the patient (loss of rectum, E-C fundus resection with reflux, totalgastrecomy). Gastrectomy affects adjuvant drug therapy, as imatinib is absorbed to a inferior extent and therapeutic blood levels might not be reached later.

We analyzed the functional outcome of patients with a histologically confirmed, locally advanced GIST without evidence of distant metastases (M0) in whom a multivisceral resection or complete removal of an organ (complete rectal excision, Whipple, total gastrectomy) would have been necessary for an R0 resection.

Methods: From 2004-18, 96 patients with the problem described were scheduled for neoadjuvant therapy. Of these, 16 patients had already undergone an exploratory laparotomy in another hospital, which documented in inoperability. Primary tumor locations are shown in table1 (46% stomach, 20% rectum). Primary tumor size at start of therapy was significantly different for the locations: rectum 6.4cm vs. stomach 11.5 cm ($p<0.01$, see table 1). Median follow-up is 60.2 months (range, 2-176 mos.)

Results: Feasibility: In 6 pts it turned out that there was not an imatinib-sensitive mutation after start of therapy, another 7 pts. with exon 9 mutations were treated with imatinib 800 mg/d, in three responding patients no mutation analysis could b performed even not from the resection specimen. All other patients had exon 11 mutations, except of one patient with an exon 13 mutation (K642E). In 28 patients, we used 18F-FDG-PET imaging for response control.

Drug compliance: 4 patients had to discontinue therapy earlier due to drug toxicity.

Median duration: Neoadjuvant drug therapy was intended to treat until no further reduction in tumor size could be documented. In median, surgery was performed 8.3 months after start.

Complications: In two patients significant complications developed. One patient had a perforation of a stomach GIST due to regression while another patient d to undergo emergency surgery for bleeding of a GIST of the small bowel.

Surgical results: 89/96 (92.7%) of patients underwent elective surgery. The R0 resection rate was 91% (81/89), the surgical and 30-day mortality was 0%. Median disease-free survival postop was 76 months, disease-specific survival after 7 years was 80%. According to the extent of surgery classification of EORTC-STBSG (multivisceral, complete organ resection, partial organ resection, wedge resection), 73/89 patients (84%) could be operated on with a less extensive procedure than before . There was no need for a total gastrectomy, none of the patients with a rectal GIST resulted in a permanent colostomy. There was one patient who still had an inoperable situs, owever only one fourth of the patients initially scheduled for multivisceral resection had to undergo this after neoadjuvant therapy. In the long-term follow-up, six patients developed a locoregional recurrence: 1/3 pts with rectal GIST recurrence ended up with permant colostomy and 1/3 pts with recurrence at the cardia/esophagus level required extensive resection and reconstruction.

Location of GIST primary tumors	Number (n=96)	Proportion	Average tumor size
Esophagus	5	5.2%	6.4 cm (2.2.-11 cm)
Cardia	7	7.3%	6.6 cm (4.6-10 cm)
Stomach	46	48%	**11.5 cm** (4.5- 30 cm)
Duodenum	10	10.5%	10 cm (58-20 cm)
Small bowel	5	5.2%	17.6 cm (6-25 cm)
Rectum/rectovaginal space	20	21%	**6.4 cm** (5-8.5 cm)
Unclear (at start of therapy)	3	2.8%	
			p<0.01

Conclusion: The neoadjuvant treatment of GIST with imatinib is safe, the indication should be for critical tumor localizations (E-C transition, duodenum, rectum). Almost always a smaller extent of surgery extent results preserving organ function. The prerequisite for the strategy is the mutation analysis of the KIT receptor.

Poster #123 3256451

CIRCULATING MIRNAS AS BIOMARKERS OF IMATINIB RESISTANCE IN GIST- LIQUID BIOPSIES AND FUNCTIONAL VALIDATION

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Objective: Liquid biopsy is a promising approach to monitor tumor evolution during drug treatment. Nonetheless, as of today disease progression after imatinib (and subsequent therapies) administration in GIST is heavily demanded to clinical evaluation and imaging. Circulating nucleic acids such as cell-free DNA (cfDNA) and miRNAs might predict the emergence of resistant tumor clones. Escaping mechanisms are sustained by cellular components of both local tumor microenvironment and distant metastasis niches by the active release of molecular effectors shuttled by extracellular vesicles (EVs). We hypothesize that blood-borne miRNAs might be predictive biomarkers of imatinib-resistance in GIST and play functional roles in crosstalk between tumor and its microenvironment.

Methods: Starting from 2014, within the prospective observational trial NCT02443948, plasma samples were collected from GIST patients before the beginning of imatinib administration, during response, and at disease progression as defined by RECIST 1.1 criteria. Circulating miRNAs and cfDNA were isolated by Maxwell RSC technology. NGS targeted panel screened the mutational status of c-KIT and PDGFRα. Comprehensive miRNA expression profile was performed using microfluidic cards and differential expressed miRNAs was confirmed by RT-qPCR. Target gene prediction was done by DIANA miRPath and miRDB bioinformatics tools. Imatinib-resistant (IM-R) GIST models was generated *i) in vitro* by stepwise exposing imatinib- sensitive (IM-S) GIST cells to increasing imatinib concentrations and *ii) in vivo* by subcutaneous implant of one imatinib- resistant GIST (PDGFRαV842D) in NSG mice (PDX). EVs were precipitated from cell culture medium and plasma and characterized by Nanoparticle Tracking Analysis (NTA) and western blot. Finally, miRNA mimics, antagomirs, and EVs were used for functional assays in vitro.

Results: The emergence of c-kit and PDGFRα mutations was detectable in plasma samples from imatinib-resistant patients and PDX. A panel of 14 circulating miRNAs was enriched both in plasma from imatinib-resistant GIST patients and cell line-derived EVs. Interestingly, we found a recurrent miRNA subset in plasma from imatinib- resistant GIST patients and PDX that was not present in EV produced by pure tumor cell cultures in vitro, speculating its implication in tumor- microenvironment crosstalk. In vitro assays showed that after 2 months of imatinib treatment of IM-S cells (c-KIT exon 11 V570-Y578del8), the IC50 was 29.3 fold higher and c-KIT exon 17 D820Y mutation emerged. EVs isolated from IM-R and their parental counterpart showed an average size of 200 nm by NTA and displayed exosomic protein markers. EV-derived miRNA profiles was obtained from both IM-S and IM-R cells and compared with those generated from plasma samples from GIST patients (c-KIT exon 11 mutations) before and after the occurrence of IM-resistance (PD and confirmed emergence of c-KIT exon 17 mutations, exon 9 and 13 mutations). Thirteen miRNA subsets were upregulated and one downregulated (log fold change>l2l) both in plasma and EVs if compared with IM-S counterparts. Computational target prediction revealed that identified miRNAs were involved in TGFβ and Ras-MAPK and PI3K pathways ($p<0.01$). The functional validation by mimics and antagomirs of selected miRNAs in both IM-S and IM-R cells are ongoing.

Conclusion: The emergence of imatinib resistance in GIST is traceable by liquid biopsies. Circulating miRNAs are promising biomarkers with an active role in tumor- microenvironment crosstalk of GIST and deserve further clinical investigation.

Poster #124 3258000

AVAPRITINIB FOR THE TREATMENT OF GIST: ANALYSIS OF EFFICACY, SAFETY, AND PATIENT MANAGEMENT STRATEGIES AT THE RECOMMENDED PHASE 2 DOSE

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Objective: Avapritinib is an investigational, potent, and selective kinase inhibitor that is active against oncogenic PDGFRA and KIT mutations. It is currently in development for the treatment of unresectable or metastatic GIST. In the NAVIGATOR study (NCT02508532), 300 mg daily was determined to be the recommended phase 2 dose. To date, presented clinical data have pooled the 300/400 mg treatment experiences. The objective of this analysis was to review the clinical profile of the recommended 300 mg dose, including strategies for managing adverse events (AEs).

Methods: Patients with unresectable or metastatic PDGFRA mutant GIST (any line of therapy), or other mutant GIST (KIT or PDGFRA) who progressed on imatinib and ≥ 1 other tyrosine kinase inhibitor, were treated with avapritinib at doses ranging from 30 mg to 600 mg once daily. This is a pooled analysis of 154 patients from NAVIGATOR and 30 patients from the ongoing VOYAGER clinical trial evaluating avapritinib vs regorafenib in unresectable or metastatic GIST (NCT03465722). Efficacy analyses in patients with tumors harboring PDGFRA exon 18 mutations, 4L+ patients, and safety analyses at the 300 mg dose level are presented.

Results: 184 patients were treated at the 300 mg dose. Dose interruptions (63%) and reductions (42%) were utilized to establish the individual optimal dose for trial patients. Only 16 patients (9%) had a treatment-related AE that led to treatment discontinuation. The most common AEs were (any grade, regardless of causality): nausea (58%), fatigue (49%), anemia (46%), decreased appetite (34%), periorbital edema (34%), diarrhea (32%) and vomiting (30%). The most common AEs ≥ Grade 3 (regardless of causality) were anemia (23%), abdominal pain (7%) and blood bilirubin increase (5%). Cognitive effects and intracranial bleeding were reported in 35% and 1% of patients, respectively. The median time to improvement for cognitive effects was 8.3 weeks. In the NAVIGATOR study, for patients treated at the 300 mg dose, the overall response rates were 91% (one pending) for patients with a PDGFRA exon 18 mutation (duration of response (DOR) = not reached) and 24% (one pending) for patients (regardless of the type of PDGFRA or KIT mutation) who progressed after 3 prior lines of therapy (DOR = not reached). Patients who required dose modification (including interruption, reduction, or both) on the NAVIGATOR trial had comparable PFS to those who did not dose modify.

Conclusion: Avapritinib was efficacious and generally well tolerated at the recommended 300 mg dose. Most adverse events were consistent with on target inhibition of KIT and PDGFRA, oral kinase inhibitors in general, and the underlying malignancy. Patients with cognitive effects should be carefully monitored and timely dose modifications (interruption or reduction) should be implemented for optimal treatment outcome. This analysis supports tolerability guided dose adjustment as an effective way to manage treatment related AEs without compromising efficacy.

Poster #125 3231084

A DANISH PROSPECTIVE STUDY INCLUDING LIQUID BIOPSIES, PLASMA CONCENTRATION OF TYROSINE KINASE INHIBITORS (TKIS) AND QUALITY OF LIFE IN PATIENTS WITH GASTROINTESTINAL STROMAL TUMOR (GIST)

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Objective: Background

A retrospective study of > 400 patients with GIST in Eastern Denmark where > 80% have available mutation status.

Plasma concentration of TKIs

Studies confirm that the plasma concentration of imatinib (c_{im}) have a high inter-patient variability and correlation between c_{im} and treatment response. A lower limit of c_{im} has not yet been defined. Whether toxicity and quality of life (QoL) vary with c_{im} and other TKI's (c_{TKI}) is unknown.

The objectives are to investigate if c_{TKI}:
- decrease over time
- influence treatment response
- influence the grade of toxicity and QoL.

DNA mutations (liquid biopsy and tissue) and exosomes

Primary mutations found in circulating tumor DNA (ctDNA) and tissue correlate as well as mutated free circulating DNA and clinical response correlate in patients with GIST. GIST has been proved releasing extracellular vesicles, exosomes, containing c-KIT. Mutations (liquid biopsy and correlating tissue) and exosomes should be examined.

The objectives are to investigate if:
- mutation analysis from liquid biopsy (ctDNA) and solid tumor correlate
- the amount of ctDNA assist in the evaluation of treatment response
- secondary mutation can be detected at tumor progression
- the amount of ctDNA and exosomes increase perioperatively

Methods: Study 1 include patients with GIST treated with a TKI and study 2 include all patients with GIST at our institution from 2019-2021, respectively.

Study 1: plasma concentration of TKIs

Blood samples will be collected at day 29 after treatment start and every third month. Synchronized with blood samples an EORTC QLQ-C30 questionnaire will be filled in and toxicity will be graded according to CTCAE 4.0. Blood samples will be collected at Herlev and analyzed at the Department of Medical Pharmacology, CHU, University of Bordeaux, France through liquid chromatography mass spectrometry.

End points:
Primary end points: Time to progression and change in c_{TKI} over time.
Secondary endpoints: grade of toxicity and the QoL.

Study 2: liquid biopsy and exosomes

Blood samples will be collected at inclusion and every third month. Patients with GIST, planned for surgery at Rigshospitalet will be included in a sub study with collection of blood samples perioperative. Chromosomal DNA from pathology selected tissue will be macrodissected, extracted and the concentration determined. Sequencing will be performed through Next Generation Sequencing. C-KIT and PDGFR mutated sequences of ctDNA will be determined with realtime PCR. At tumor progression an extended mutation analysis will be performed to analyze for secondary mutations. Analysis for exosomes will be performed at the Department of Clinical Immunology at Ålborg University Hospital. The Extracellular Vesicle (EV) Array is based on protein microarray technology.

End points:
Primary end point: Relationship between image verified progression/regression and the amount of ctDNA and exosomes. Sub study primary end point: change in the amount of ctDNA and exosomes perioperative. Secondary end points: Secondary mutations and grade of correlation between tissue material and ctDNA mutation status.

Results: Currently, 64 patients are included in study 1 and 69 in study 2. This exceeds the minimum inclusion of 50 patients. Soon, Aarhus University Hospital will start inclusion of patients into the study regarding liquid biopsy and exosomes, making this part of the study nationwide. One patient is included in the sub study with perioperative blood samples. We aim to present preliminary data at CTOS, Tokyo.

Conclusion: The analysis of plasma concentration of TKIs may lead to improved personalized treatment through determination of an individual dose of TKIs. This can benefit future patients with GIST through optimized treatment effect, QoL and minimized toxicity. The study can also make it possible to monitor the development of GIST through blood samples (ctDNA and exosomes) and thereby enable earlier detection of progressive disease leading to change of treatment with better treatment effect.

Poster #126 3253856

PROTEIN EXPRESSION ANALYSIS BY REGULATING C-KIT AND KCTD12 EXPRESSION IN GASTROINTESTINAL STROMAL TUMOR

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Objective: Gastrointestinal stromal tumor (GIST) is a mesenchymal tumor and is classified as a soft tissue tumor in the WHO classification. GIST has *KIT* mutations in 80-90% of cases, and as a result of development of tyrosine kinase inhibitor (TKI), good patients' outcomes are obtained. We have shown a correlation between pfetin (encoded by *KCTD12*) expression and patients' prognosis (Suehara et al. 2008). However, acquisition of secondary TKI resistance and treatment-resistance in GISTs still associate with poor prognosis. *KIT* mutations are involved in the development of GIST, mechanisms involved in the progression or metastasis are unclear, although we have recently shown a possible interaction between pfetin expression and c-kit expression (Suehara et al. 2018). In this study, we performed comprehensive protein expression analysis using tumor cell lines and surgical specimens in GIST.

Methods: We performed RNAi for GIST T1 cell lines and generated protein expression profiling data by using i-TRAQ (isobaric tags for relative and absolute quantification) for the following samples: T1 (control: knocked down by scramble siRNAs), *KIT* knocked-down T1 and *KCTD12* knocked-down T1. Based on these profiling data, we referenced our previously published protein expression analysis databases related to GIST patients' prognosis (Suehara et al. 2008) and tried to elucidate the clinical and biological impacts of these protein expressions.

Results: Approximately 1500-2000 protein expression dynamics were observed by i-TRAQ method. By *KIT* knockdown, 125 proteins were identified as differentially expressed ($p < 0.05$). In contrast, by *KCTD12* knockdown, only 16 proteins were identified as differentially expression ($p < 0.05$). Four overlapping proteins were identified between *KIT* and *KCTD12* knockdown lists. Among them, translocation protein SEC62 shown to contribute to aggressive behavior in malignant tumors, was revealed as only one commonly regulated protein. Between the patients' prognosis database and *KIT* knockdown database, 6 proteins were considered as common proteins associated with biological behavior. Between the patients' prognosis database and *KCTD12* knockdown database, only 1 protein was considered as a common protein associated with biological behavior. In particular, heat shock protein (HSP) 90-beta, contributing to the growth of cancer cells, was considered as an important protein in the biological behavior of GIST.

Conclusion: The *SEC62* resides on chromosome 3q, and amplification of 3q has been suggested to be a prognostic factor in some cancers. HSP 90-beta is currently suggested to be a therapeutic target for HSP 90 inhibitors against imatinib-resistant GIST. The duplicate protein list includes prognostic factors and proteins for which drug could be developed as a therapeutic targets in the previous research, and thus could be considered as a reliable protein list.

Poster #127 3246597

TYK2 PROMOTES MALIGNANT PERIPHERAL NERVE SHEATH TUMOR PROGRESSION THROUGH INHIBITION OF CELL DEATH

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Objective: Malignant peripheral nerve sheath tumors (MPNSTs) are aggressive sarcomas that arise most commonly in the setting of the Neurofibromatosis Type 1 (NF1) cancer predisposition syndrome. Despite aggressive multimodality therapy, outcomes are dismal and most patients die within 5 years of diagnosis. Prior genomic studies in our lab identified *tyrosine kinase 2* (*TYK2*) as a frequently mutated gene in MPNST. Herein, we explored the function of TYK2 in MPNST pathogenesis.

Methods: Immunohistochemistry was utilized to examine expression of TYK2 in MPNSTs and other sarcomas. To establish a role for TYK2 in MPNST pathogenesis, murine and human TYK2 knockdown and knockout cells were established using shRNA and Crispr/Cas 9 systems respectively.

Results: We have demonstrated that TYK2 was highly expressed in the majority of human MPNSTs examined. Additionally, we demonstrated that knockdown of *Tyk2/TYK2* in murine and human MPNST cells significantly increased cell death *in vitro*. These effects were accompanied by a decrease in levels of activated Stats and Bcl-2 as well as an increase in levels of cleaved caspase-3. In addition, *Tyk2*-KD cells demonstrated impaired growth in subcutaneous and metastasis models *in vivo*.

Conclusion: These data illustrate the importance of TYK2 in MPNST pathogenesis and suggest that the TYK2 pathway may be a potential therapeutic target for these deadly cancers.

Poster #128 3253528

GENOME ENGINEERING OF DISEASE SPECIFIC CELL TYPES REVEALS HIDDEN VULNERABILITIES AND NEW THERAPEUTIC APPROACHES FOR TREATMENT OF NEUROFIBROMATOSIS TYPE-1 RELATED CANCER

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Objective: NF1 is a common genetic disorder caused by mutations in the tumor suppressor gene *NF1*. Among other manifestations, NF1 results in formation of benign Schwann cell tumors (neurofibromas) of the peripheral nervous system. These can progress to malignant peripheral nerve sheath tumors (MPNSTs), the deadliest soft tissue sarcoma and a leading cause of mortality among NF1 patients. The majority of NF1-associated MPNSTs develop within preexisting plexiform neurofibromas.

Genome engineering technologies, such as CRISPR/Cas9, offer exciting opportunities to build more relevant cell line based models to advance cancer research. These techniques allow introduction of clinically relevant mutations into cells of the correct tissue type for the disease being studied. Using these principles we built models of tumors that arise in a prevalent cancer predisposition syndrome known as Neurofibromatosis Type 1 (NF1) and used these models for therapeutics discovery with synthetic lethal pharmacogenomic screens.

Methods: Given plexiform neurofibromas and MPNSTs arise within the Schwann cell linage, we developed a drug discovery pipeline to identify targeted therapeutics for treating NF1-related neoplasia. Using CRISPR/Cas9, we created immortalized human Schwann cell lines that are deficient for the *NF1* gene or *NF1* and *SUZ12*. ~80% of all MPNST harbor loss of function mutations in Polycomb Repressive Complex 2 (PRC2) genes, such as *SUZ12*, which is highly suggestive that perturbation of epigenetic homeostasis plays a role in malignant transformation of neurofibromas. These cell line based models were used to perform synthetic lethality based high-and medium-throughput drug screening to identify compounds capable of selectivly killing either the *NF1* or *NF1/SUZ12* deficient human Schwann cells compared to isogenic matched parental controls.

Results: Our small molecule screening efforts identified compounds showing selective lethality towards either *NF1* deficient cells or *NF1/SUZ12* double mutants. Clinically interesting drug candidates were advanced and tested in *in vivo* models of neurofibroma and MPNST, where some have shown dramatic efficacy. Moreover, many of these drugs showed strong synergy *in vitro* when tested in combination against *NF1/SUZ12* deficient human Schwann and MPNST cell lines. Informed by these studies we tested the most promising drug combinations using *in vivo* models of MPNST. To date, we have been able to attain long term durable responses in animal models of MPNST.

Conclusion: These pharmacogenomic screens leveraged synthetic lethal interactions with *NF1* and *SUZ12* to identify therapeutics for the treatment of NF1-related neoplasia. The discovery of agents effective against models of MPNST is exciting, as to date there are no approved targeted therapies for MPNST. Results from our studies are forming the basis for clinical trials we hope to propose for the treatment of MPNSTs and aggressive plexiform neurofibromas.

Poster #129 3256376

ROLE OF FDG PET-CT IN MALIGNANT PERIPHERAL NERVE SHEET TUMOR (MPNST)

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Objective: Malignant peripheral nerve sheet tumors, are malignant tumors arising from a peripheral nerve or in extraneural soft tissue and having nerve sheath differentiation. They are rare tumor, comprises about 5% of all soft tissue sarcomas. They are aggressive tumor associated with poor prognosis. FDG PET/CT has been used to differentiate between benign and malignant lesion in Neurofibromatosis (NF-1). The purpose of this study is to evaluate further role of FDG PET/CT in management of MPNST.

Methods: Retrospective evaluation of consecutive MPNST patients, those were referred to our department for FDG PET-CT. FDG PET done to differentiate between benign and malignant lesions, baseline evaluation, response to therapy, recurrent disease or metastatic workup was included in study. Details from conventional imaging done were collected along with the reports of histopathology post biopsy or post-surgery specimens. Ability of FDG-PET to differentiate between benign and malignant lesion, for detection of primary and metastatic lesions was assessed. Maximum standardized uptake values (SUVmax) were measured for each primary/recurrent and metastatic lesion. Univariate analysis was performed using the SPSS software package (version 23.0; IBM).

Results: Thirty patients (17 males, 13 females) were enrolled in the study, out of which 12 patients (40%) of NF-1 underwent FDG PET/CT to differentiate between benign and malignant lesions. FDG PET/CT was done for staging in 10 patients, and it identified metastasis in 6 patients at baseline. Twenty patients had recurrence post-surgical excision which was identified by FDG PET/CT imaging. In follow-up imaging done in 4 patients for response assessment, they had progressive disease which prompted treatment intensification. SUVmax of primary lesion showed correlation with histopathological grade ($r=0.712$, $p=0.034$). Metabolic Tumor Volume (MTV), Total lesion glycolysis (TLG) and SUVmax showed correlation with event free survival.

Conclusion: In MPNST, FDG PET/CT can be used for staging, prognostication, restaging for recurrence and therapy response assessment, other than its already proven role in differentiating benign and malignant lesions in NF-1, predicting transformation of plexiform neurofibroma into MPNST in NF-1.

Poster #130 3257924

ACTIVITY OF NEO-ADJUVANT CHEMOTHERAPY ALONE OR COMBINED WITH RADIATION-THERAPY IN SPORADIC VERSUS NF1-RELATED MPNST IN THE CONTEXT OF TWO INTERNATIONAL, PHASE III, RANDOMIZED CLINICAL TRIALS IN LOCALIZED HIGH-RISK SOFT TISSUE SARCOMA

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Objective: A poor activity of chemotherapy has been reported in NF1-related MPNST. Herein, we report on the activity of chemotherapy alone or combined with radiation-therapy in sporadic MPNST versus NF1-related MPNST in the context of two multicentre, international, phase III, randomized clinical trials on neoadjuvant chemotherapy in localized high-risk soft tissue sarcoma. In the first trial, conducted by the Italian Sarcoma Group (ISG) in collaboration with the Spanish Sarcoma Group (GEIS), from 2002 to 2007, 3 neo-adjuvant cycles of epirubicin plus ifosfamide were compared to 3 neo-adjuvant plus 2 adjuvant cycles of the same regimen. In the second trial, conducted by the ISG in collaboration with the GEIS, the French Sarcoma Group (FSG) and the Polish Sarcoma Group (PSG), from 2011 to 2016, 3 neo-adjuvant cycles of epirubicine plus ifosfamide were compared to an histology driven chemotherapy, being 3 cycles of etoposide plus ifosfamide in MPNST. In both studies, in MPNST, radiation-therapy could be either delivered in the pre-operative or post-operative setting.

Methods: All patients (pts) with MPNST enrolled in the two clinical trials were reviewed. Responses were assessed according to RECIST criteria as complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). The association of NF1 status with RECIST responses was investigated by means of the Pearson chi-square statistic or Fisher's exact test whenever appropriate. The strength of association with NF1 status was assessed by resorting to univariate logistic regression model by considering RECIST variable as SD/PD versus PR. The 95% confidence Interval (CI) of the proportion of PR patients within NF1 status was computed by the exact binomial method.

Results: Forty-nine pts with MPNST were enrolled in the two clinical trials and 27 pts were included in this analysis. Nineteen pts were excluded because not evaluable for response, being enrolled after inadequate surgery in the absence of measurable disease. Five additional pts were excluded because data on NF1 status and/or response assessment was missing. Out of 27 pts, sporadic MPNST were 19, NF1-related MPNST were 8. Male were 19 and female 8. Median age was 47 years (range: 20-71 years). Fifteen pts received neo-adjuvant chemotherapy alone (epirubicin+ifosfamide in 12 pts, etoposide+ifosfamide in 3 pts). Twelve patients received concomitant chemotherapy and radiation-therapy (epirubicin+ifosfamide in 10 pts, etoposide+ifosfamide in 2 pts). With chemotherapy alone, best responses according to RECIST were: 3/9 PR and 6/9 SD in sporadic MPNST; 3/6 PR, 2/6 SD, 1/6 PD in NF1-related MPNST. With concomitant chemo- and radiation-therapy responses were: 2/10 PR, 6/10 SD and 2/10 PD in sporadic MPNST; 1/2 SD and 1/2 PD in NF1-related MPNST. By considering all 27 MPNST pts, we found no statistically significant association between NF1 status and RECIST response according to the Fisher exact test (p.value = 0.46) and logistic regression analysis modeling the probability of PR (Odds ratio sporadic vs NF1-related MPNST: 0.60; 95% CI: 0.10-3.45, p.value 0.56). Moreover, in the 15 MPNST pts that received neo-adjuvant chemotherapy alone, we found no statistically significant association between NF1 status and RECIST response according to the Fisher exact test (p.value = 0.39); the proportion of PR in NF1-related and sporadic MPNST was 0.5 (3/6, 95% exact CI 0.12-0.88) and 0.33 (3/9; 95% exact CI 0.07-0.70), respectively.

Conclusion: In this series, with the limitations of the very small number of patients, chemotherapy with epirubicin+ifosfamide or etoposide+ifosfamide does not seem to be less active in NF1-related MPNST than in sporadic MPNST.

Poster #131 3253329

EVALUATION OF CANCER-TESTIS ANTIGENS IN OSTEOSARCOMA AND DEDIFFERENTIATED LIPOSARCOMA AS TARGETS FOR IMMUNOTHERAPY

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Objective: T-cell based immunotherapies are a promising alternative to traditional cancer treatments due to their ability to target only malignant cells, leaving benign cells unharmed. The development of successful immunotherapy requires the identification and characterization of targetable immunogenic tumor antigens. Cancer testis antigens (CTA) are a group of highly immunogenic tumor-associated proteins that have emerged as potential targets for CD8+ T-cell recognition. Unlike other auto-antigens, CTAs exhibit restricted expression in normal tissue, limiting potential therapeutic side effects. Other parameters that are crucial for CD8+ T-cell recognition of tumor cells, such as their ability to infiltrate the tumor and the expression of HLA-peptide complexes on the surface of cancer cells, also play important roles in the outcome of immunotherapy.

NanoString nCounter technology generates sensitive gene expression profiles for hundreds of genes from RNA obtained from formalin-fixed, paraffin-embedded samples. The PanCancer Immune-profiling panel contains multiple genes related to antigen processing and presentation (e.g. HLA, natural killer function, T- and B-cell receptor signalling), as well as 30 genes for commonly tested CTAs (including MAGE-A3, SSX2 and NY-ESO-1). By correlating expression of multiple markers associated to specific immune cell populations, this technology characterizes the tumor immune profile in a way that cannot be easily achieved using immunohistochemistry (IHC). However, IHC enables the visualization of heterogeneity in antigen expression as well as the spatial relationship of tumor and immune cells. Therefore, the goal of this study is to screen for CTA expression, HLA expression, and tumor T-cell infiltration in human dedifferentiated liposarcoma (DDLPS) and osteosarcoma (OS) by both IHC and NanoString, in order to identify targetable immunogenic antigens for T-cell based immunotherapy.

Methods: Human tissue micro-arrays composed of 50 cores of OS and 18 cores of DDLPS were obtained, along with matched control tissues from the same patients. IHC for the cancer testis antigens NY-ESO-1, MAGE-A3, and SSX/SSX2 was performed, and the staining results were scored by two authors based on maximal staining intensity on a scale of 0 to 3 (absent=0, weak=1, moderate=2, or strong=3) and the percentage of tumor cells that stained. IHC for CD8 and CD3 was also performed, and T-cell tumor infiltration was defined as either brisk, nonbrisk, or absent, as described in melanoma literature. Concurrently, evaluation of 38 human DDLPS specimens and 10 healthy human fat specimens by the Nanostring nCounter platform is underway for identification of novel antigen targets and to establish the immune profile of DDLPS.

Results: Immunohistochemical analysis of CTA expression showed considerable inter- and intra-tumoral heterogeneity. DDLPS showed relatively low expression of all CTAs tested, with only 11% of samples exhibiting MAGE-A3 and 1 sample each (5.5%) showing expression of SSX2 and NY-ESO-1 in low percentages of tumor cells. By contrast, in osteosarcoma, 100% of samples expressed MAGE-A3 and 89% expressed SSX, both with >80% of positive cases showing moderate to high expression. NY-ESO-1 was expressed in 78% of OS samples, predominantly at low levels. Brisk infiltration of CD8+ T cells was observed in over 70% of both sarcoma types tested. Furthermore, all sarcoma samples tested were positive for HLA expression.

Conclusion: To date, these results show promising expression of CTAs MAGE-A3 and SSX in human OS, which may be used as targets in the future development of an immunotherapy for sarcoma. DDLPS shows relatively low expression, highlighting the need for more exploratory study with NanoString, the results of which are expected in early fall 2019. The data generated throughout this project will provide insight into the immune profile of DDLPS – information that is critical for immunotherapy design.

Poster #132 3223596

PROGNOSTIC SIGNIFICANCE OF PD-L1 EXPRESSION AND MICROSATELLITE INSTABILITY IN PATIENTS WITH RETROPERITONEAL LEIOMYOSARCOMAS

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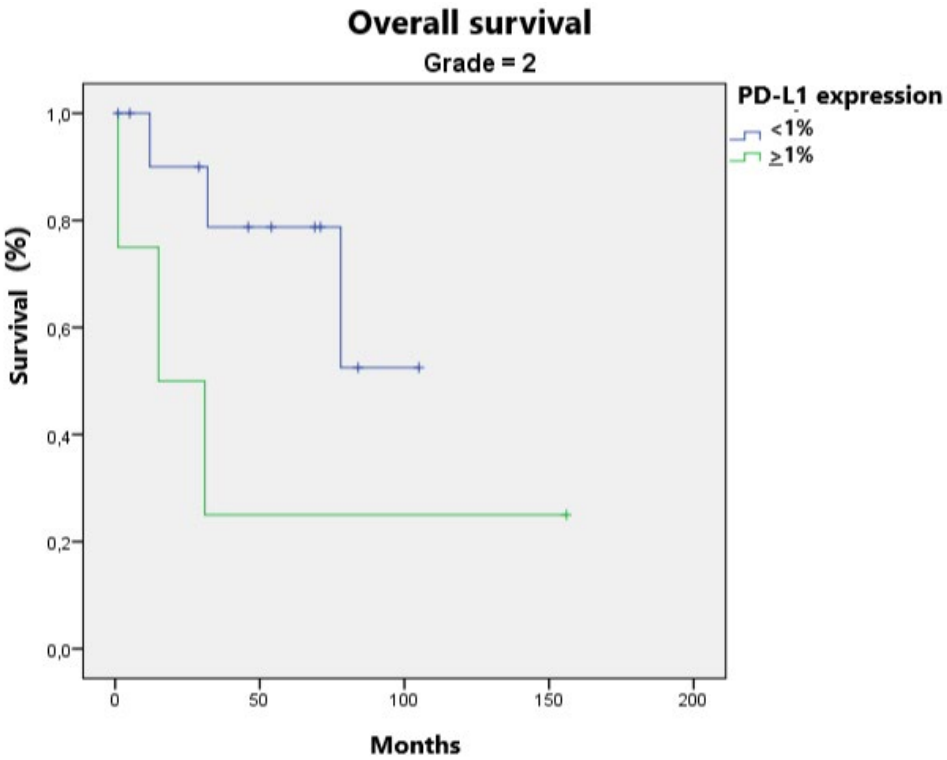
Objective: to define rate of positive PD-L1 expression and microsatellite instability in patients with retroperitoneal leiomyosarcomas and its prognostic significance and correlation with clinico-morphological features.

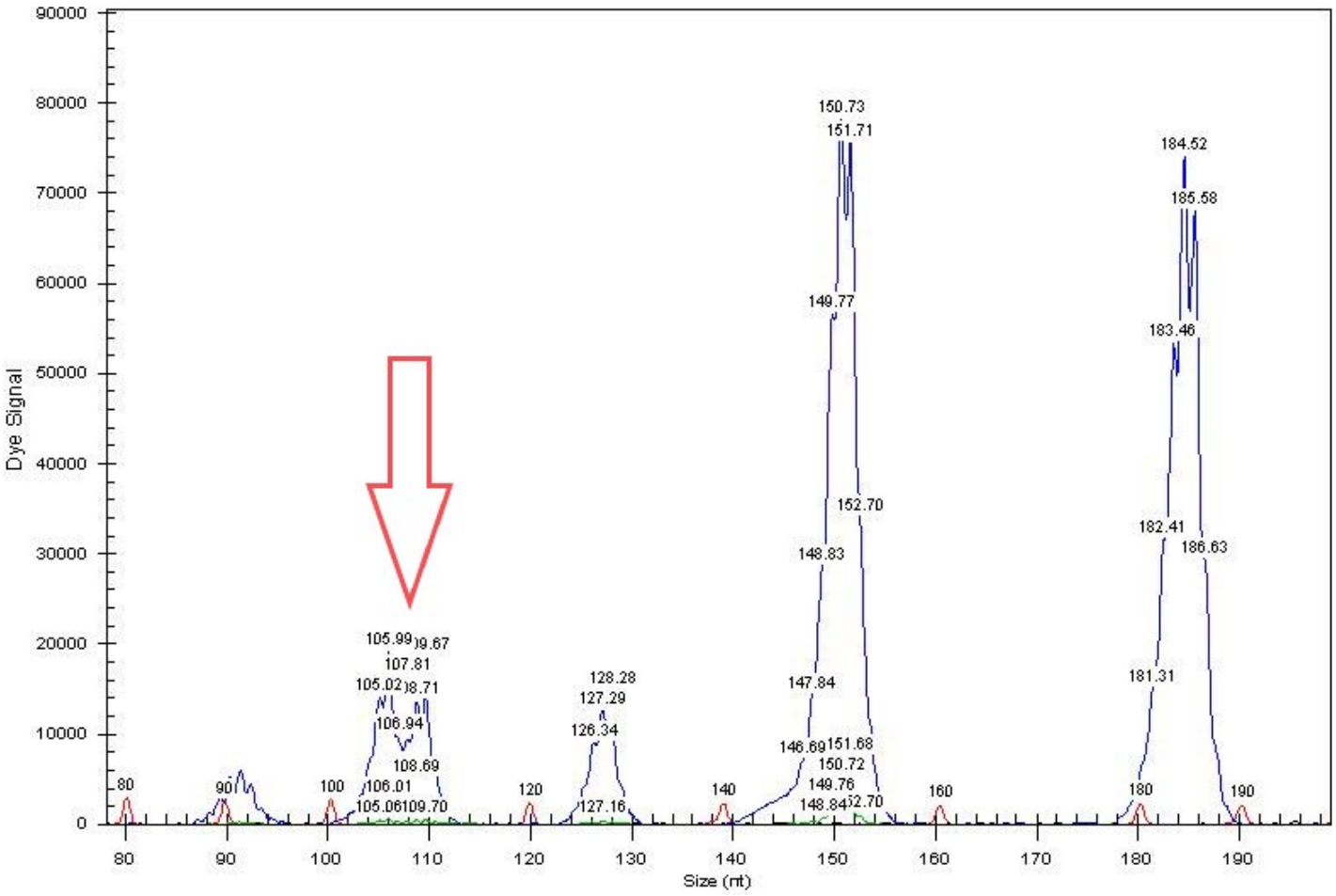
Methods: 57 patients with retroperitoneal leiomyosarcomas which have underwent surgical or combined treatment at N.N. Blokhin National Medical Research Center of Cancer since 2003 to 2018 were retrospectively reviewed. Data included clinico-demographic characteristics, morphological features of tumors and long-term results of surgical resection. Degree of PD-L1 expression were assessed by immunohistochemical analysis, while evaluation of MSI status was performed by PCR using panel with five MSI markers.

Results: 57 patients were included in the study, and PD-L1 expression and MSI status were evaluated in 41 patients. Positive PD-L1 expression was identified in 24% of patients (10 out of 41) with the level of expression in the range of 3-50%. The MSI analysis showed MSI-low tumor in 1 patient (2.4%). The disease-free period, in this case, was 19 months, overall survival period – 60 months. Median follow-up period was 31 months. Patients with positive PD-L1 expression had higher Ki-67 index (58,8% vs. 47,8%, p<0,02), lower median overall survival among patients with G2 leiomyosarcomas (30 months vs 105 months, p=0.043).

Conclusion: Among patients with retroperitoneal leiomyosarcomas PD-L1 positive expression was found in 24% of cases and MSI-low status was found in 2,4% of cases. In patients with grade 2 tumors positive PD-L1 expression is associated with worse overall survival. Positive PD-L1 expression can be considered as prognostic marker and possible basis for immunotherapy in patients with retroperitoneal leiomyosarcomas.



MSI-low



Overall survival in patients with G2 leiomyosarcoma with or without PD-L1 expression

Poster #133 3252978

CTNNB1 MUTATIONS AND AGGRESSIVE BEHAVIOR IN NEUROMUSCULAR CHORISTOMA-ASSOCIATED FIBROMATOSIS

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Objective: Neuromuscular choristoma (NMC) is a rare, developmental malformation that typically arises in the major proximal peripheral nerves, most commonly the sciatic nerve. NMC is strongly associated with development of a peri-lesional desmoid-type fibromatosis (DTF). Previously, we reported that activating *CTNNB1* mutations occur in NMC and NMC-fibromatosis, similar to those seen in sporadic DTF. As *CTNNB1* mutational subtypes have established prognostic and predictive significance in sporadic DTF, we evaluated the frequency of *CTNNB1* mutational subtypes and the clinical outcomes in a series of patients with NMC-fibromatosis.

Methods: With institutional approval, cases coded as neuromuscular choristoma and desmoid-type fibromatosis, with available formalin-fixed, paraffin-embedded (FFPE) tissue were retrieved. Clinical data, radiologic images and pathologic material were reviewed. Archival FFPE tissues, enriched for NMC-fibromatosis, were macro-dissected. Genomic DNA was extracted using the QIAamp® DNA FFPE Tissue kit (QIAGEN, Valencia, CA) and amplified by polymerase chain reaction using primers specific for the region surrounding *CTNNB1* codons 41 and 45, followed by pyrosequencing and mutation analysis.

Results: Seven cases of biopsy-proven NMC-fibromatosis, occurred in 3 females and 4 males (median age at diagnosis: 14 y, range 5 to 51y) with biopsy-proven (N=5) or radiologic diagnosis (N=2) of NMC of the sciatic nerve. In all cases, NMC-fibromatosis arose within the affected nerve territory: involving the soft tissues of the buttock, posterior thigh or popliteal fossa, and cases developed following NMC biopsy (N=5) or spontaneously (N=2). All 7 NMC-fibromatosis contained *CTNNB1* mutations, including 5 p.S45F, 1 p.S45P and 1 p. T41A. In 6 cases with clinical follow-up (mean 3.5 y; range 1-8y), all patients had disease progression, irrespective of initial treatment modality: surgical resection (N=3) cryoablation (N=1), tamoxifen (N=1) or observation (N=1). One patient developed multifocal, metachronous NMC-fibromatosis at spatially-distinct sites along the NMC-affected nerve. Disease stabilization was achieved with adjuvant radiation therapy (N=3), doxorubicin-based chemotherapy (N=1) or receptor tyrosine kinase inhibitor-based therapy (e.g. sorafenib) (N=1).

Conclusion: NMC-fibromatosis frequently harbors *CTNNB1* p.S45X mutations and displays aggressive biologic behavior, requiring adjuvant local or systemic therapy for disease stabilization. As such, and as development of NMC-fibromatosis is frequently precipitated by iatrogenic injury (i.e. biopsy) of the NMC, we now employ a "no-touch" approach for the diagnosis of NMC, and rely on clinical and MR imaging features for both diagnosis and surveillance whenever possible.

Poster #134 3256176

MALIGNANT TRANSFORMATION OF LIPOSCLEROSING MYXOFIBROUS TUMOR: A CASE REPORT

Yoshihiro Araki[1]*; Norio Yamamoto*[1]*; Katsuhiro Hayashi*[1]*; Akihiko Takeuchi*[1]*; Shinji Miwa*[1]*; Kentaro Igarashi*[1]*; Yuta Taniguchi*[1]*; Hirotaka Yonezawa*[1]*; Sei Morinaga*[1]*; Takayuki Nojima*[2]*; Hiroyuki Tsuchiya*[1]

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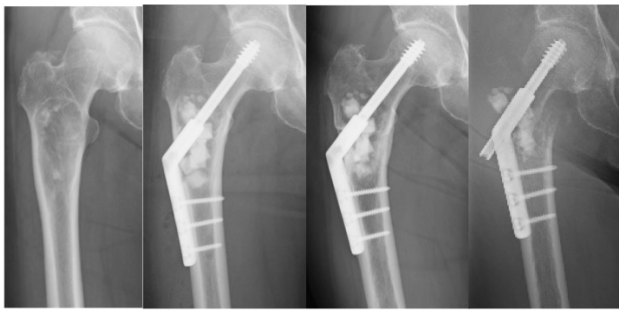
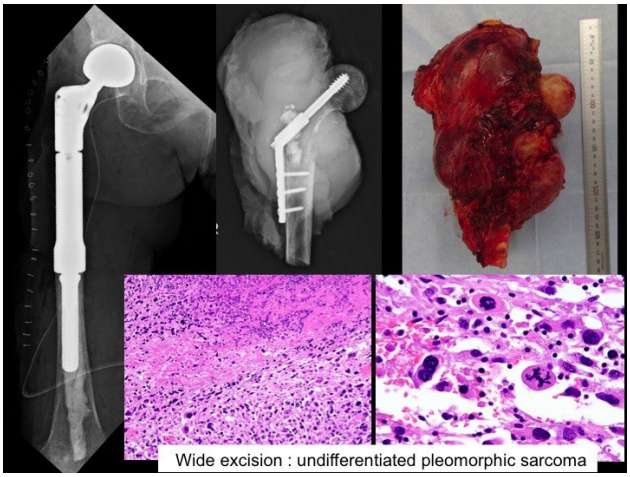
Objective: Liposclerosing myxofibrous tumor (LSMFT) is a benign fibrous-osseous lesion showing various kinds of histology; fibrous lesion, adipocytic lesion, necrosis, degenerative cystic lesion and infarction, other than the histology of fibrous dysplasia. There are few reports about malignant transformation of LSMFT. GNAS point mutation was confirmed uniquely in fibrous dysplasia or LSMFT, but few previous literatures about malignant transformation from fibrous dysplasia or LSMFT, confirmed any GNAS mutations. We describe a case report of malignant transformation of LSMFT verified R201H, one of GNAS mutaions.

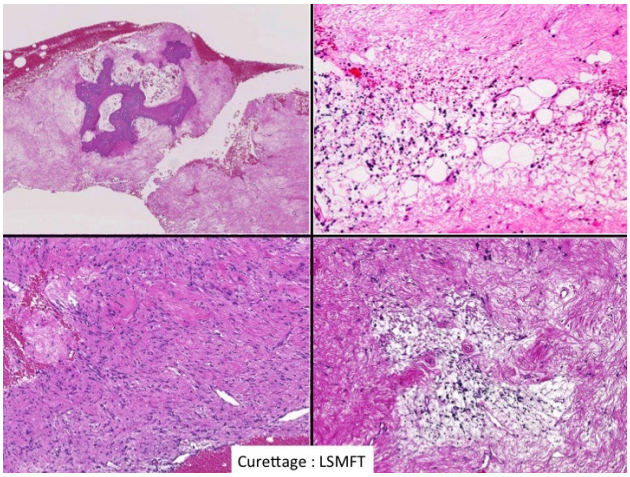
Methods: We retrospectively reviewed the medical records of a 76-year-old woman with bone tumor of the right proximal femur. She underwent curettage, artificial bone graft and internal fixation with plate at previous hospital four years ago. The histology revealed the intra-osseous lipoma by intraoperative frozen section. For 2 and half a year after surgery, she had spent normal daily living without any limitation, and no recurrence or metastases were observed at outpatient clinic. At 3 and half a year after surgery, she noticed swelling and tenderness around the right hip joint. Gradually, the symptom was getting worse and she felt gait disturbance. She consulted a previous doctor again, and recurrence of bone tumor was suspected on MRI and she was referred to our institution. Lytic bone lesion was detected on X-ray, and extraosseous extension from the bone was also observed on MRI. The lesion showed hypointensity on T1 weighted-images and hypo- to iso- intensity on T2 weighted-images. Needle biopsy revealed undifferentiated pleomorphic sarcoma. Both of MDM2 and cdk4 were negative in fluorescence in situ hybridization and other immunohistochemical staining did not show specific differentiation of the lesion. Lung metastases were found by systemic examination. She was advanced age, and showed grade 3 of performance status due to gait disturbance, and chemotherapy was hard to perform. However, she opted to undergo wide excision and reconstruction with tumor prosthesis to improve her daily living. The surgery was done under general anesthesia, and the histology for the operation specimen was as same as that of needle biopsy. She recovered after surgery and was able to transfer from bed to wheel chair by herself.
We lysated the tissues harvested from wide excision specimen and perform PCR. PCR products were tranfected into cloning vector (pTOPO) and purified the plasmid. Sequence was confirmed after GNAS gene amplification in the plasmid by the primer (M13-F).

Results: Curettage specimen did not include the histology of fibrous dysplasia, but was consistent with the histology of intraosseous lipoma with degenerative change and the histology looked like LSMFT. However, we detected the R201H, which was one of GNAS mutaions, from the operation specimen of undifferentiated pleomorphic sarcoma. This would be a proof of malignant transformation from LSMFT.

Conclusion: We described a case of malignant transformation of LSMFT verified R201H, one of GNAS mutaions in the operation specimen.







Poster #135 3239164

AN ANALYSIS OF THE STAGE AT PRESENTATION AND OUTCOMES OF PEDIATRIC PATIENTS WITH OSTEOSARCOMA IN CANADA

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Objective: Osteosarcoma is the most common primary bone malignancy and occurs most frequently in adolescents. Early diagnosis, local and systemic control are critical to the successful management of the disease. Historically, approximately 15% of patients have been reported to present with distant metastatic disease. The 5 year overall survival of these patients has been reported to be 27% to 44%. With advances in imaging technology, early access to expert assessment and improvements in surgical care, an updated analysis is warranted on the presentation, and outcomes of pediatric patients with osteosarcoma. The primary objective of this study is to report on the proportion of patients presenting with metastatic osteosarcoma in Canada, compared to localized disease in the modern era. Secondarily, an analysis of overall patient outcomes, number of surgical interventions and use of adjuvant therapy is undertaken.

Methods: Using the Cancer in Young People in Canada (CYP-C) national database, we completed a retrospective review of pediatric patients presenting with osteosarcoma between 2001 and 2017. Data on a total of 304 patients under 15 years of age were collected. Data extracted included demographic information, location of the primary tumour, tumour histologic sub-types, presence and location of metastasis, number of surgical interventions, use of adjuvant treatment and survival data (including event-free survival, disease-free survival and overall survival). A two-sample t-test was used for normally distributed variables to compare the differences between groups. Mann-Whitney rank sum test was used on non-distributed continuous variables. Fisher exact test and chi square were used for categorical outcomes. Event free (EFS), disease free (DFS) and overall survival (OS) was analyzed using the log-rank test.

Results: The proportion of Canadian patients initially presenting with metastatic disease was 23.0%. The overall 5 year survival for patients presenting with metastatic disease was 37.4%, which is consistent with the historic literature. EFS and OS were significantly decreased in these patients compared to those with local disease at presentation (figure 1, $p<0.0001$, hazard ratio (HR)=3.1 and $p<0.0001$, HR=4.3 respectively). In our population, the median number of operative interventions aimed at disease resection was 1, with a maximum of 7 (table 1). OS was significantly better in patients that underwent 1-2 operations, compared to those undergoing 0 or requiring greater than 2 operations (figure 2, $p<0.0001$). For patients presenting with metastatic disease, the 5 year OS for those undergoing an operative intervention was 44.1% versus 17.6% for those not operated upon (figure 3, $p<0.0001$). A higher proportion of patients with metastatic disease had 3 or more surgical interventions compared to those with local disease (27% vs 16%). For adjuvant therapy, 75% of patients underwent treatment with chemotherapy alone, while 3% received radiation therapy alone, and 10% received both chemotherapy and radiation during their treatment course (table 2). In those patients who received palliative radiotherapy, with or without chemotherapy, outcomes were poor with a median survival of only 3.6 months after starting radiation treatment (figure 4).

Conclusion: In summary, the proportion of pediatric patients presenting with metastatic versus local osteosarcoma in our population is higher than that in the reported literature. The overall outcomes of patients with metastatic disease have not changed over time. Our data reaffirms a role for surgical resection in patients with metastatic disease in the modern era. However, there remains a need to identify new adjuvant treatment strategies to improve the overall prognosis of these patients.

Table 1 - Number of Surgeries Performed per Patient

Number of Surgeries	Total N=304 (%)	Local Disease N=234 (%)	Metastatic Disease N=70 (%)	P value
0	44 (14)	26 (11)	18 (26)	0.0002
1-2	203 (67)	170 (73)	33 (47)	
3	57 (19)	38 (16)	19 (27)	

Table 2 - Number of Patients Receiving Adjuvant Therapy

Adjuvant Treatment	Total N=304 (%)	Local Disease* N=234 (%)	Metastatic Disease N=70 (%)
None	38 (12)	25 (11)	13 (19)
Radiation Alone	9 (3)	<2)	5 (7)
Chemotherapy Alone	227 (75)	183 (78)	44 (63)
Chemotherapy + Radiation	30 (10)	22 (9)	8 (11)

*Cell sizes less than 5 have been suppressed and random rounding is shown within this column as per CYP-C privacy regulations

Figure 1 - Outcomes of patients presenting with localized versus metastatic disease. A - Event free survival. B - Overall survival.

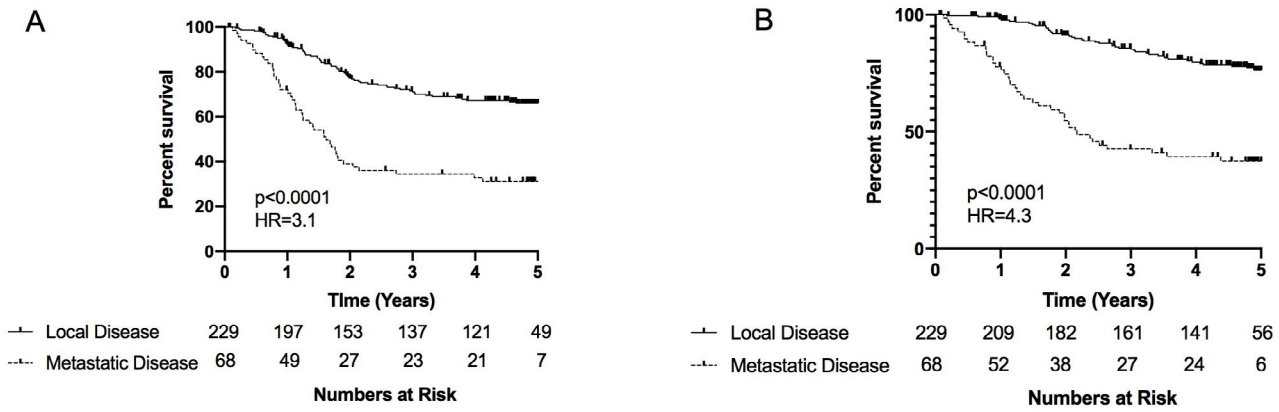


Figure 2 - Overall survival of patients stratified by the number of surgical interventions.

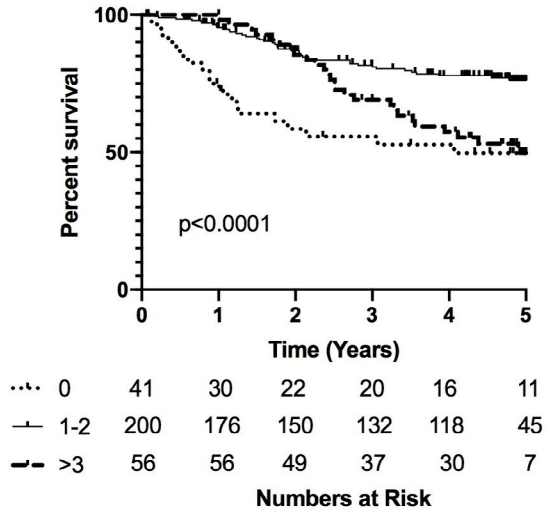


Figure 3 - Overall survival of patients presenting with metastatic disease who had an operative intervention versus those who were not operated upon.

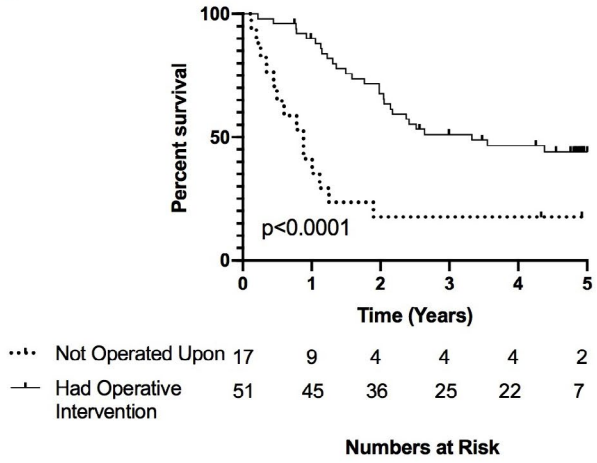
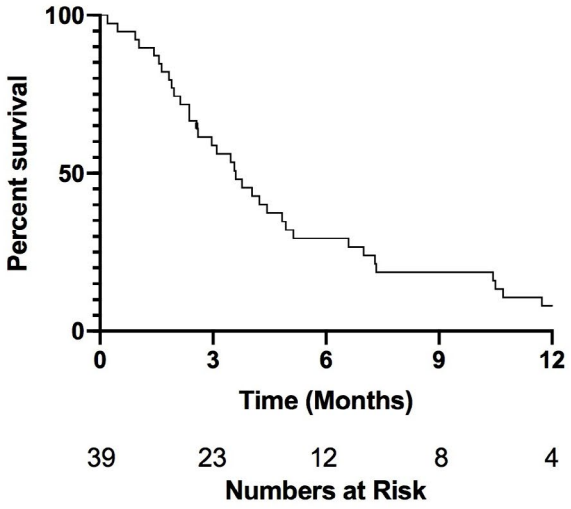


Figure 4 - Overall survival of patients after the initiation of palliative radiation therapy.



Poster #136 3253373

A RETROSPECTIVE STUDY OF GEMCITABINE AND DOCETAXEL FOR RELAPSED OR REFRACTORY PEDIATRIC OSTEOSARCOMA AND SOFT TISSUE SARCOMAS

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Objective: Among pediatric malignancies, osteosarcomas and soft tissue sarcomas have poorer outcomes despite intensive multimodal therapy including chemotherapy, surgery and radiation. Especially relapsed or refractory sarcomas have worse prognosis and definite unmet need. Here, we report the efficacy and toxicity of Gemcitabine and Docetaxel (GD) for the patients with relapsed or refractory osteosarcomas and soft tissue sarcomas who were treated in pediatric ward of our institution.

Methods: We retrospectively reviewed the clinical records of all patients treated with gemcitabine (675-900mg/m^2) intravenously (IV) on Day 1 and Day 8 and docetaxel (75mg-90mg/m^2) IV on Day8, repeated every 3 weeks as an off-lable use at pediatric oncology department in National Cancer Center Hospital. Primary end-point was progression free survival (PFS) at 4months and secondary end-points were overall survival (OS) and disease control rate. Adverse events were evaluated using CTCAE v4.0.

Results: Since September 2012, forty-five patients were treated with GD and 43 patients including 23 patients with osteosarcoma, 12 with Ewing sarcoma family tumors (ESFT) and 8 with other soft tissue sarcomas were eligible for a data analysis. Median age at initiation of GD therapy was 16 (range 6-42) and 13 patients (30 %) were less than 15 years old. Male to female ratio was 1.3. 37 out of 43 patients (86 %) had been treated with more than one regimen for their relapsed or refractory diseases before GD therapy was initiated. The patients received total of 189 courses of chemotherapy (median 3 courses; range, 1-15) and 19 patients (44 %) received more than 4 courses of treatment. 6 out of 23 patients with osteosarcoma (26 %) demonstrated partial response (PR) while none had PR in patients with ESFT and other sarcomas. 15 patients (35 %) had stable disease (SD) in total. Four-month PFS rates were 43, 12.5 and 8.3 % for osteosarcoma, ESFT and other sarcomas, respectively. Disease control rate was the best in osteosarcomas which was 52 %. After GD therapy, 2 patients with osteosarcoma underwent lung metastasectomy and achieved surgical complete response (sCR). One remains free of disease for 5 months after last course of GD administration. The 1-year OS was 30 % in total. Common adverse events included fever and hematologic toxicities. We observed grade 3-4 non-hematologic toxicities in 9 patients (21 %) including febrile neutropenia, pleural effusion and pericardial effusion. No death related to the therapy was seen.

Conclusion: GD showed decent disease control rate for relapsed or refractory osteosarcomas and may be the treatment of choice as a second or third line for these difficult-to-treat disease. Although the treatment outcomes are still dismal, GD therapy was tolerable for most of our pediatric patients. To improve outcome, further investigation using combination therapy with radiation or molecular targeted therapy may be needed.

Poster #137 3255166

EVALUATION OF THE ANTIBODY-DRUG CONJUGATE ABBV-085 TARGETING LRRC15 IN THE PEDIATRIC PRECLINICAL TESTING CONSORTIUM OSTEOSARCOMA IN VIVO MODELS

Jonathan B. Gill[2]*; Michael Roth*[2]*; Douglas Harrison*[2]*; Wendong Zhang*[2]*; Beverly Teicher*[1]*; Stephen Erickson*[3]*; Malcolm Smith*[1]*; Edward A. Kolb*[2]*; Richard Gorlick*[2]

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Objective: Membrane protein leucine-rich repeat containing 15 (LRRC15) is highly expressed on cancer associated fibroblasts in the stromal microenvironment of many solid tumors, including sarcomas. LRRC15 has limited expression in normal tissue and thus may be an attractive target for drug therapy. ABBV-085 is an antibody drug conjugate directed against LRRC15 that contains the tubulin inhibitor monomethyl auristatin E (MMAE). The *in vivo* activity of ABBV-085 was studied in osteosarcoma patient derived xenograft (PDX) models by the Pediatric Preclinical Testing Consortium (PPTC).

Methods: The *in vivo* anticancer effects of ABBV-085 were assessed in a panel of six osteosarcoma PPTC PDX models with varied LRRC15 (OS1, OS9, OS33, OS34-SJ, OS42-SJ, OS60). RNA expression was assessed by RNASeq in all models, and protein expression was assessed utilizing immunohistochemistry in 3 models (OS9, OS33, OS60). ABBV-085 was administered at a dose of 6 mg/kg once per week for 4 consecutive weeks via intraperitoneal injection. A control cohort that received vehicle and an additional control cohort that received an isotype MMAE linked antibody were included in all PDX models. Tumor volumes were measured and responses defined utilizing the PPTC statistical analyses.

Results: PDX models OS1, OS33, OS42-SJ, and OS60 had the highest RNA expression of LRRC15, all with RNA expression >14x that of OS9. Mirroring the RNA expression data, OS33 and OS60 demonstrated a high proportion of tumor and stromal cells strongly expressing the LRRC15 protein, whereas OS9 did not express LRRC15. ABBV-085 significantly inhibited tumor growth in 5/6 osteosarcoma PDX models compared to vehicle control cohorts and induced significant differences in event-free survival (EFS) in 4/6 models compared with the isotype control treated cohorts. Models with higher LRRC15 RNA expression (OS1, OS33, OS42-SJ, OS60) all had significantly longer EFS compared with the isotype control, while no significant difference was seen in EFS in the two models with low LRRC15 RNA expression (OS34-SJ, OS9). ABBV-085 treatment resulted in an objective response in 1/6 models, with OS33 experiencing a maintained complete response. All other models experienced progressive disease with median time to event for treated versus control animals (EFS T/C) ranging from 0.95 for OS-9 to >5.1 for OS-60.

Conclusion: ABBV-085 exhibited significant antitumor activity against the PPTC osteosarcoma PDX models with high expression of LRRC15, demonstrated by prolonged EFS. Additional studies are needed to determine the prevalence of LRRC15 in osteosarcoma patient samples to better determine the potential utility of LRRC15 as a drug target. These data provide proof of principle that LRRC15 may be a potential target for antibody delivered cytotoxic payloads. The role of tubulin targeted drug conjugates is not yet clear in osteosarcoma, though there is preclinical evidence of target-specific effects.

		EFS Evaluation					Tumor Volume Evaluation				Response
Tumor	Grp	KM med	EFS T - C	EFS T/C	p-value exact log-rank	p-value Gehan-Wilcoxon	V_0 mean±SD (cm^3)	V_0 p-value	minRTV mean±SD	minRTV p-value	Median response
OS-1	A	25.2					0.115±0.024		1.580±0.150		PD
	B	72.6	47.4	2.88	p < 0.001	p < 0.001	0.113±0.016	p = 1.000	1.162±0.234	p < 0.001	PD2
	C	32.5	7.3	1.29	p < 0.001	p < 0.001	0.116±0.013	p = 0.762	1.383±0.098	p = 0.004	PD1
	B vs C				p < 0.001	p < 0.001		p = 0.496		p < 0.023	
OS33	A	18.1					0.123±0.012		1.560±0.195		PD
	B	> 84	> 65.9	> 4.65	p < 0.001	p < 0.001	0.122±0.008	p = 0.940	0.026±0.056	p < 0.001	MCR
	C	29.4	11.3	1.62	p < 0.001	p < 0.001	0.125±0.014	p = 0.734	1.269±0.150	p = 0.002	PD1
	B vs C				p < 0.001	p < 0.001		p = 0.705		p < 0.001	
OS-34	A	32.3					0.137±0.024		1.420±0.189		PD
	B	49.9	17.6	1.54	p < 0.001	p < 0.001	0.134±0.012	p = 0.971	1.136±0.113	p = 0.001	PD1
	C	38.8	6.5	1.2	p = 0.030	p = 0.025	0.127±0.021	p = 0.345	1.233±0.121	p = 0.052	PD1
	B vs C				p = 0.111	p = 0.102		p = 0.473		p = 0.063	
OS42	A	20.2					0.131±0.013		1.527±0.283		PD
	B	25	4.8	1.24	p < 0.001	p < 0.001	0.130±0.013	p = 1.000	1.251±0.194	p = 0.035	PD1
	C	21.3	1.1	1.06	p = 0.130	p = 0.226	0.126±0.011	p = 0.472	1.430±0.223	p = 0.393	PD1
	B vs C				p < 0.001	p < 0.001		p = 0.734		p = 0.143	
OS-60	A	16.7					0.141±0.014		1.997±0.228		PD
	B	80.1	63.4	4.79	p < 0.001	p < 0.001	0.131±0.008	p = 0.064	1.022±0.167	p < 0.001	PD2
	D	19.9	3.2	1.19	p = 0.024	p = 0.024	0.147±0.027	p = 0.684	1.634±0.347	p = 0.023	PD1
	B vs D				p < 0.001	p < 0.001		p=0.186		p<0.001	
OS-9	A	24.7					0.133±0.023		1.549±0.316		PD
	B	23.6	-1.2	0.95	p = 0.307	p = 0.447	0.130±0.026	p = 0.963	1.687±0.389	p = 0.673	PD1
	C	23.4	-1.4	0.94	p = 0.265	p = 0.631	0.125±0.028	p = 0.481	1.684±0.268	p = 0.370	PD1
	B vs C				p = 0.864	p = 0.827		p = 0.627		p = 0.796	

A: Control

B: ABBV-085 6mg/kg

C: Isotype-MMAE-antibody 6mg/kg

D: Isotype-MMAE-antibody 12mg/kg

Poster #138 3255557

SALVAGE CHEMOTHERAPY USING IRINOTECAN AND TEMOZOLOMIDE IN PAEDIATRIC, AYA AND ADULT POPULATIONS WITH RELAPSED EWING SARCOMA

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Objective: Irinotecan and temozolomide (IT) is a widely used regimen for relapsed Ewing Sarcoma (ES), although studies are largely limited to the paediatric population. We aimed to compare the tolerability and efficacy of IT between paediatric and adult patients.

Methods: We retrospectively reviewed paediatric (< 18 years), AYA and adult patients treated with salvage IT chemotherapy at two institutions. Toxicities were graded according to CTCAE v.4.03 and compared using the Chi Square test. Responses were interpreted by Response Evaluation Criteria in Solid Tumors (RECIST). The Kaplan-Meyer method was used to estimate progression free survival (PFS); survival comparisons were carried out by the Log-rank test.

Results: Fifty-three patients were included (n=16 paediatric; N=37 adult). Median age was 20 (range, 5 – 45 years). All patients had prior VAC-IE. Fifty-six percent (*n* = 20) of adults and 82% (*n*=14) of paediatric patients received IT as second-line (*p* =0.07). There was no difference in ≥grade 3/4 haematological toxicity between paediatric and adult patients (31% vs. 35% respectively; *p*=0.76) . The frequency of diarrhoea of any grade was similar (38% in each group). Of 43 patients assessable for response, 12 (28%) had objective response (1 CR, 11 PR), 19 (44%) had disease progression and 12 (28%) had stable disease. Objective response rate did not differ between the two groups (36% in paediatrics vs. 25% in adults; *p*=0.47). Median PFS was superior in paediatrics vs. adults (7.4 vs. 2.1 months, *p* = 0.001). Superior PFS for the paediatric population was observed in both, the second-line (6.2 vs. 2.2 months; *p*=0.060) and ≥ third-line setting (7.4 vs. 1.2 months, *p*=0.014).

Conclusion: IT is an effective salvage regimen for ES, with favourable toxicity and equally observed objective responses in paediatric and adult populations. The observed superior PFS for the paediatric cohort requires further confirmation in a larger prospective study.

Poster #139 3255563

HIGH ENGRAFTMENT RATE OF PEDIATRIC AND YOUNG ADULT BONE AND SOFT-TISSUE SARCOMA PATIENT-DERIVED XENOGRAFTS

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Objective: Therapy regimens for most sarcomas have changed minimally in the past few decades, and outcomes for metastatic and recurrent/refractory sarcoma patients remain dismal. Young adults with sarcomas often fare less favorably than their pediatric counterparts. The vast biological heterogeneity among the dozens of sarcoma subtypes further hinders the development of novel therapies. Improved tools to study the biology and therapy of sarcomas are desperately needed. Commonly studied sarcoma cell lines are compromised by genetic and phenotypic drift that occurs during the culture process. Patient-derived xenograft (PDX) models resolve this shortcoming by providing a minimally selective *in vivo* system to expand human tumor tissue. This approach also preserves the broad genomic and biological heterogeneity seen within tumor types which is largely absent in transgenic tumor models.

Methods: After obtaining informed consent, tissue was collected from patients at Cincinnati Children's Hospital Medical Center (CCHMC) undergoing tumor biopsy or resection as part of routine care, using only excess tissue not required pathology, biobanking, or clinical trial protocols. Tissue was collected in RPMI media supplemented with antibiotics and maintained on ice and immediately transferred to research once released by Pathology. All transplantation studies were performed in immunocompromised mice including NSG, NRG, and NSGS strains (Jackson Labs). In general, two mice were implanted with tumor tissue fragments: one mouse with two subcutaneous xenografts on each flank and a second mouse with a single intramuscular injection of tumor. Once established, all tumors were serially passaged to at least a second generation (F2) in mice to ensure the stability of the PDX model and expand the amount of tumor tissue for future study. PDX tissues at each generation were characterized by standard histopathology, genomics, and/or gene expression and cryopreserved to establish a sarcoma PDX repository.

Results: A total of 41 tissues from 37 sarcoma patients were implanted from July 2016 to March 2019. Primary and metastatic tumor tissue was obtained from the head & neck, trunk, and extremity locations. Specimens were acquired by a variety of methods including surgical resection (n=21), percutaneous image guided needle biopsy (n=15), bone marrow aspirate/core biopsy (n=2), or pleurocentesis/paracentesis (n=3). Patient ages ranged from 2 to 46 years with a median of 18.6 years at the time of biopsy. Seventeen patients were 18 years or older. Among 33 tumors that completed observation, 24 (73%) successfully engrafted including 7 of 7 rhabdomyosarcomas, 6 of 9 Ewing sarcomas, 5 of 6 osteosarcomas, 2 of 2 malignant peripheral nerve sheath tumors, 2 of 3 malignant rhabdoid tumors, 1 of 1 synovial sarcoma, and 1 of 1 desmoplastic small round cell tumor. All established F1 PDX tumors were re-transplanted and successfully established F2 PDX models. The time to tumor establishment ranged from 25 to 303 days. One-half of engrafted tumors had no prior exposure to anti-cancer therapy. Prior radiation and tumors characterized by indolent growth were associated with engraftment failure. H&E stains of rhabdomyosarcoma PDX tissues demonstrated recapitulation of unique histologic features found in the primary specimen (Figure 1).

Conclusion: A multi-disciplinary team of oncologists, surgeons, interventional radiologists, pathologists, and basic investigators developed a concerted protocol to deliver extraneous tumor tissue to the research laboratory for mouse implantation. Over 32 months, a broad portfolio of pediatric and young adult sarcoma investigational models was developed. A high rate of engraftment was achieved despite the heterogeneous group of tumor diagnoses, diverse anatomic locations, wide variety of surgical techniques and proceduralists, and the broad age range including many young adults.

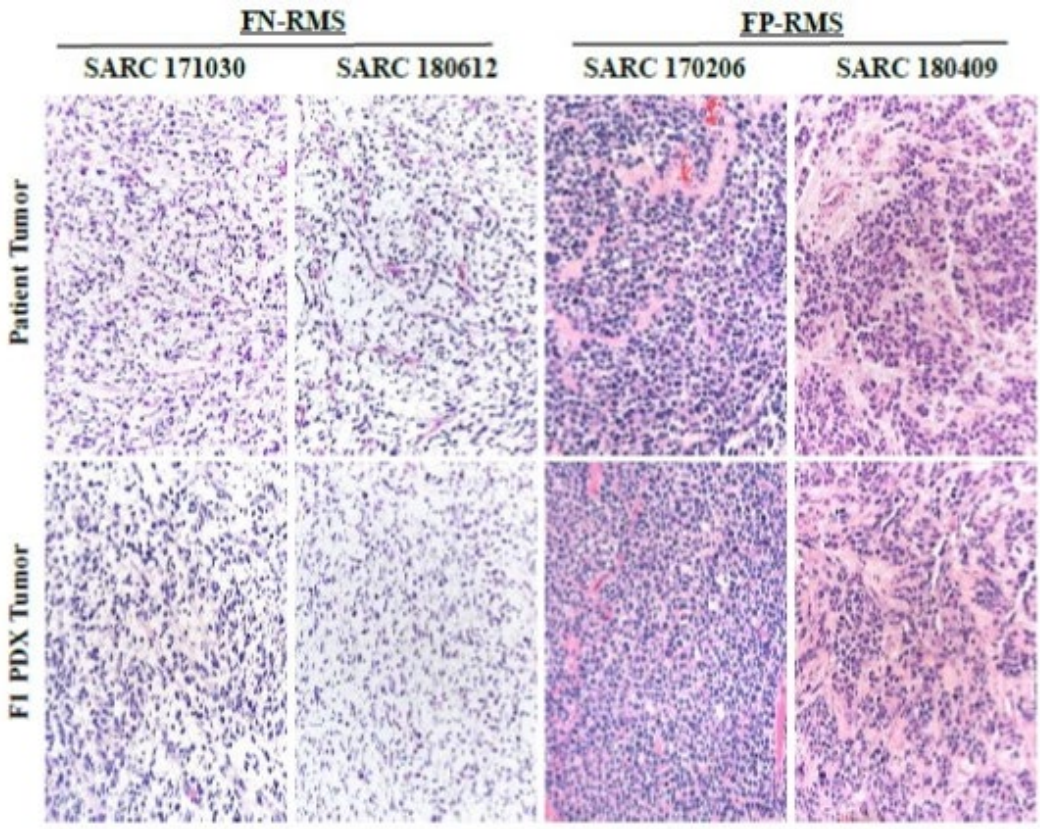

Figure 1. Preservation of hallmark histological features between paired patient and PDX rhabdomyosarcomas. H&E stains demonstrated that histopathological findings characteristic of the original tumor were maintained in PDX specimens. Among four rhabdomyosarcoma patient + PDX tumor pairs, both fusion-negative rhabdomyosarcoma (FN-RMS) tumors retained their classic embryonal tumor histologies of small cells in a loose myxoid pattern. Moreover, two fusion-positive rhabdomyosarcoma (FP-RMS) tumors demonstrated a uniform small round blue cell morphology. One of these patient tumors (SARC 170206) had a more cellular and dense morphology which was reflected in the PDX model. A second tumor with a substantial stromal component also showed a similar stromal component in the resulting PDX model.

Poster #140 3254269

PRESERVING THE PHYSIS IN VERY YOUNG PEDIATRIC PATIENTS WITH LOWER EXTREMITY EWING SARCOMA

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Objective: In very young patients with primary bone sarcomas arising adjacent to the physis, the optimal method of resection and reconstruction remains controversial. While surgical resection with negative margins is the standard of care, what constitutes an adequate surgical margin is poorly defined. We present a case series of skeletally immature patients with Ewing sarcomas of the femur and tibia in which close surgical margins were utilized to preserve the adjacent physis. The reconstruction was accomplished with intercalary fixation of autograft or allograft.

Methods: We retrospectively reviewed the records of three patients with primary bone sarcomas (age 2-8 years, at diagnosis) treated with chemotherapy and physeal sparing surgical resection and intercalary reconstruction. Patients were followed for a minimum of 61 months (range 61-127), and monitored for local recurrence, distant metastasis, functional outcomes, leg length discrepancy, physeal arrest, and avascular necrosis of the femoral head. The closest surgical margins ranged from 1.5 to 9 mm.

Results: Two of three patients were alive at last follow up. One patient developed lung metastases at 37 months post-operatively and passed away three years later. There were no instances of local recurrence. All achieved union of their host-graft junction sites, and there was no evidence of physeal arrest at their most recent follow-up. For those patients who underwent resections near the hip, there were no cases of avascular necrosis of the femoral head. All patients had leg length discrepancies involving overgrowth of the operative extremity. Two patients required additional surgery to repair broken hardware. One patient had a nondisplaced fracture of his autograft successfully treated in a cast. All patients had good or excellent function at their most recent office visit.

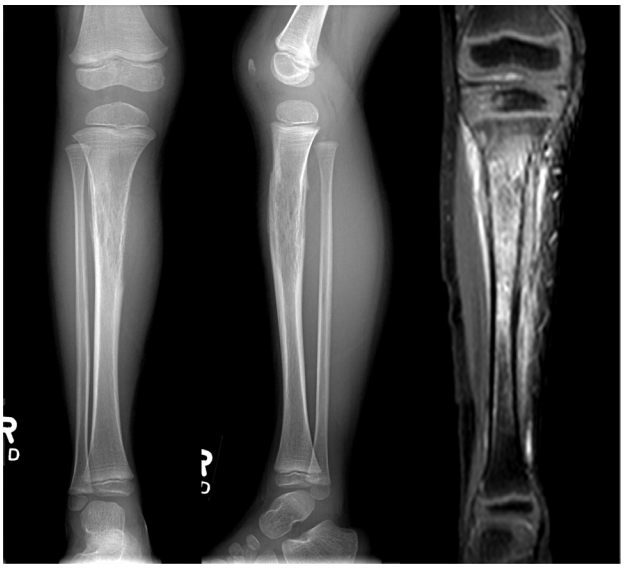
Conclusion: In this series, utilization of close surgical margins sparing the physis allowed significant longitudinal growth and good to excellent function of the extremity. With a decade of follow up, there has been no evidence of local recurrence.

Patient and Operative Information

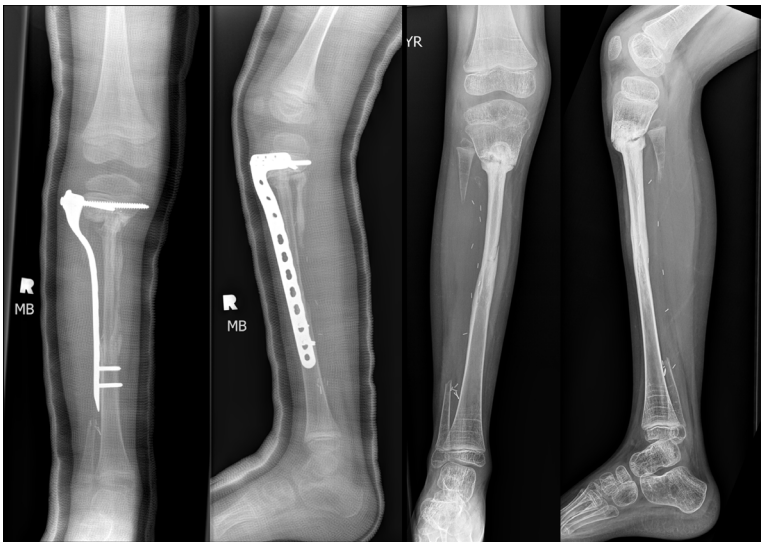
Patient	Age at Dx (yrs)	Length of F/U (mos)	Closest Resection Margin (mm)	Graft Type	Anatomic Location
1	2	127	1.5	Vascularized fibula autograft	Left femur
2	4	61	9	Allograft	Right tibia
3	8	109	1.5	Vascularized fibula autograft + allograft	Right proximal femur

Patient Surgical Outcomes

Patient	Local Recurrence	Limb Length Discrepancy	AVN Hip	Complications	Current Status
1	No	1.5cm long	No	None	Living
2	No	3cm long	N/A	2 fractures treated with cast and revision ORIF	Deceased due to pulmonary metastatic disease
3	No	1.5cm long	No	Revision ORIF x 1	Living



The anteroposterior and lateral radiographs of the right tibia demonstrate a diaphyseal lucent lesion of the right proximal tibia in a 4-year-old male with Ewing sarcoma. A coronal post-contrast T1-weighted MR image demonstrates the proximity of the intramedullary involvement to the proximal tibial physis.



Postoperative radiographs demonstrate an intercalary resection with vascularized fibula reconstruction. The AP and lateral radiographs at 61 months post-operatively show interval evidence of hardware removal, growth at the proximal physis, and hypertrophy of the vascularized fibula autograft.

Poster #141 3256327

ENUMERATION OF CELL SURFACE VIMENTIN POSITIVE CELLS AS A METHOD OF DETECTING TUMOR CELLS IN PEDIATRIC PATIENTS WITH SARCOMA

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Objective: Enumeration of cell surface vimentin (CSV) positive cells detected in peripheral blood has been previously identified as a method of identifying circulating tumor cells (CTC). Unlike carcinomas, sarcomas lack epithelial markers, making methodologies that rely on these markers impractical for sarcoma patients. We have conducted a study to evaluate the utility of enumerating CSV positive cells in detecting CTCs in pediatric solid tumor patients.

Methods: The study enrolled patients with solid tumors younger than 21 years and survivors of childhood solid tumors of any age. Survivors were 5 years off therapy with no evidence of disease. Up to 10 mL of blood was collected at time of initial diagnosis, relapse/disease progression, or during therapy. To account for blood volume variability, all CTC enumerations were standardized to the number of cells in 6 mL of blood. Leukocytes were removed using a human CD45 depletion kit (Stemcell Technologies). The remaining cells were then labeled with 84-1 cell antibody that targets CSV and then isolated using IgG binding microbead system (Miltenyi). Cells were enumerated using confocal microscopy visualization. The number of $CSV^{+}CD45^{-}$ cells was compared between cancer patients and survivors using rank sum test test. The correlation between timing of last chemotherapy administration to time of blood collection with number of CSV positive cells was examined using the Spearman test.

Results: We analyzed data from 49 sarcoma patients (25 osteosarcoma, 11 rhabdomyosarcoma, 7 Ewing sarcoma, 6 other sarcoma) who had blood samples collected before start of therapy and 17 survivors. An additional sample was collected in 11 of the 45 patients after receiving therapy at the time of next disease evaluation. The number of CSV^{+} cells in peripheral blood of patients was significantly increased ($p=<0.001$) in the sarcoma cohort (mean CTC number, 4.51 ± 6.58) compared to survivors (mean CTC number, 0.35 ± 0.86). No significant difference was detected in number of CSV positive cells according to sarcoma type. Using a cut off of 3 cells (negative test <3 and positive test ≥ 3) and assuming samples from survivors as true negatives and those from sarcoma patients with clinically detectable metastasis as true positives, the specificity was 94% (95% CI, 69-100%) and sensitivity was 37% (95% CI, 23-52%). We found a significantly higher number of CSV positive cells in patients with recurrent disease (n=16) vs. refractory disease (n=20) ($p=0.02$); patients with refractory disease often had samples drawn at time of recovery from last chemotherapy. The median time to chemotherapy for the refractory group was 24 days versus 208.5 days for the recurrent group. We found a significant positive correlation between CSV positivity and time between last chemotherapy and time of sample collection ($p=0.0014$). The number of patients collected closely to time from therapy may be partially responsible for the lower sensitivity, although this is an inherent challenge in CTC tests that target the presence of rare cells. This issue is compounded in pediatrics due to low blood collection volumes. No significant correlation with presence of localized vs. metastatic disease was seen. Additionally, the sample size that had an early on therapy sample drawn was too small to draw any correlation with change in number of CTCs and response to the therapy. The median change in number of identified CSV positive cells was 4.

Conclusion: The number of CSV positive cells is significantly higher in active pediatric sarcoma patients compared to survivors of pediatric solid tumors. Our study provides a promising novel methodology for enumeration of CTCs in patients with pediatric sarcomas. Future studies will be needed to fully delineate the utility of CSV based CTC enumeration in prognostic profiling and relapse surveillance.

Poster #142 3227605

IDENTIFYING A NEED AND KNOWLEDGE GAP OF OSTEOPATHIC MEDICINE FOR PEDIATRIC SARCOMA PATIENTS

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Objective: Pediatric patients receiving chemotherapy often struggle with detrimental side effects including constipation, nausea, neuropathy, and decreased quality of life. As we continue to make great strides in medications to help minimize chemotherapy side effects, there remains a need for additional adjunctive supportive care. Since the advent of osteopathic medicine in the 1890's, this adjunctive therapy has been implemented successfully in both adult and pediatric populations for a myriad of illnesses. To date, there has been no literature on the need for osteopathic manipulative treatments (OMT) in oncology, specifically within the sarcoma field. Additionally, there have been no studies examining practitioner knowledge and implementation of osteopathic medicine in the pediatric oncology population. The objective of this study was to investigate a knowledge gap and potential need for osteopathic medicine in pediatric oncology with a focus on pediatric sarcoma.

Methods: Sixty-three total pediatric oncology clinicians, patients, and caregivers at Nationwide Children's Hospital were approached for participation. Of those approached, 20 oncology clinicians, 20 patients, and 20 caregivers completed the survey. Following a description and video of OMT, participants completed quantitative surveys in REDcap and 1:1 semi-structured qualitative interviews. Clinicians were asked about their personal knowledge of OMT, their experiences with difficult to control chemotherapy side effects, and hesitations or barriers regarding OMT utilization for non-pharmacologic symptom control. Interviews were audio-recorded, transcribed, and independently coded by two investigators to determine consensus thematic content. Descriptive statistics were used to summarize quantitative data.

Results: We surveyed 20 pediatric oncology patients (12 sarcoma), 20 caregivers of pediatric oncology patients (8 sarcoma), and 20 oncology clinicians, including 15 attending physicians and 5 nurse practitioners (4 sarcoma specialists), with a median of 6.5 years of clinical practice (range: 1-24 years). All attending physicians were allopathic trained pediatric oncologists and had varying degrees of knowledge of osteopathic medicine. No provider reported they knew "a lot" about OMT. All clinicians supported further research to study the benefits of OMT, with 100% reporting a desire to have OMT available as a supportive care option. Clinicians and caregivers of sarcoma patients shared a common theme of frustration secondary to uncontrolled symptoms requiring multiple failed medication regimens. Additional major themes shared by all 3 cohorts included 1) frustration with current available treatments for managing chemotherapy side effects such as nausea, neuropathy, and constipation, 2) attractiveness of OMT as a non-invasive, home intervention, with low-risk and high reward, and 3) minimal hesitation for incorporating OMT into supportive care plans.

Conclusion: Pediatric oncology clinicians reported a need for better management of chemotherapy-associated side effects, specifically with regard to sarcoma therapy regimens, and an openness to non-pharmacological therapies, including OMT. These findings support the further need to investigate the safety, feasibility, and efficacy of OMT in the pediatric oncology clinical setting, with focus on children receiving therapy to treat sarcoma.

Poster #143 3253042

OFFERING GNRH AGONISTS FOR FERTILITY PRESERVATION IN FEMALE ADOLESCENT & YOUNG ADULT SARCOMA PATIENTS: A NEW STANDARD OF CARE?

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Objective: Female adolescent and young adult (FAYA) oncology patients are faced with difficult decisions regarding fertility. Thanks to advances in cancer therapy, the majority of FAYA diagnosed with cancer will become long term survivors. Currently, there are nearly 370,000 FAYA cancer survivors in the U.S. Although rare, only about 1% of all malignancies in the U.S., sarcomas account for roughly 10% of all invasive cancers diagnosed in this age group. Infertility caused by chemotherapy causes psychosocial distress negatively impacting these survivors' relationships, including reduced likelihood of marriage and greater likelihood of divorce. Some studies suggest the potential loss of fertility can be as painful as the cancer diagnosis itself and often an unsatisfied desire for information on fertility preservation (FP) compounds this distress. Conversely, pursuit of FP has been associated with improved quality of life and less regret in survivors. Our practice is to refer all FAYA cancer patients to a fertility specialist for detailed discussion of available options for FP. Such options include: GnRH-a, ova and embryo cryopreservation and ovarian tissue cryopreservation. Most cryopreservation options require ovarian stimulation (2-6 weeks) thus delaying initiation of cancer treatment. GnRH-a does not require delay, is non-invasive, has fewer side effects and is lower in costs.

Methods: The EMR was queried to identify FAYA patients treated by the Pediatric Oncology service at Rush University Medical Center from 2008-2019. Charts were reviewed and data collected. Forty post-pubertal FAYA patients were identified each of whom was provided available options for FP. Further analysis was undertaken to determine how many chose to pursue GnRH-a therapy.

Results: Forty post-pubertal FAYA cancer patients from 10-40 years old were identified. Twenty-nine of these patients (72.5%) chose GnRH-a therapy before and/or during adjuvant chemotherapy between 2008-2019. Of the 40 patients, 19 (47.5%) were sarcoma patients. Interestingly, an even higher percentage of the FAYA sarcoma patients, 17 of the 19 (89.5%), opted for GnRH-a.

Conclusion: Studies of FAYA cancer survivors show that lack of knowledge about options for FP, distress at the time of diagnosis, fear of treatment delays and cost concerns reduced pursuit of FP. While the American Society of Clinical Oncology issued updated guidelines in 2018 recommending providers discuss FP with all patients of reproductive age considering treatment with risks of iatrogenic infertility, compliance with these recommendations is lacking. Additionally, data on GnRH-a are conflicting. Live birth rate data is the best marker of fertility, but few studies have included sufficient patients or length of follow-up. As such, some have suggested GnRH-a only be offered when proven FP methods cannot be used. However, our data suggests the contrary. When given all FP options, a strong majority of FAYA patients (72.5%) and an overwhelming majority with sarcoma (89.5%) chose GnRH-a. This choice was made despite knowledge of the experimental nature of GnRH-a therapy, unproven efficacy, unknown chemotherapy interactions and inability to guarantee fertility. Given advances in cancer therapy and resulting increase in survivors, it is more paramount than ever to consider the futures of our FAYA patients. The impact infertility can have on survivors suggests FP is one of the most important factors to consider. Providing complete information of available options for FP, including GnRH-a, should be strongly considered given our results. It is possible that offering GnRH-a empowers these patients to decide for their futures at a point when they have control of so little. Finally, it can not be overstated how significant it may be for these patients to know their future fertility is being seriously considered by the medical team, thereby, encouraging them to not only consider the likelihood of their own futures, but giving them the power to plan for them.

Poster #144 3256229

EVALUATION OF THE TPO-RECEPTOR AGONIST ELTROMBOPAG IN THE PEDIATRIC PRECLINICAL TESTING CONSORTIUM OSTEOSARCOMA IN VIVO MODELS

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Objective: Eltrombopag (EP) is a small molecule, thrombopoietin receptor (TPO-R) agonist indicated for the treatment of patients with chronic immune thrombocytopenia and severe aplastic anemia. EP is a polyvalent cation chelator and inhibits leukemia cell proliferation via depletion of intracellular iron. Recent studies show EP inhibits the proliferation of osteosarcoma cells lines via depletion of polyvalent cations. The *in vivo* effects of EP were studied in osteosarcoma patient derived xenograft models by the Pediatric Preclinical Testing Consortium (PPTC).

Methods: The *in vivo* anticancer effects of EP were assessed in a panel of six osteosarcoma PPTC PDX models with limited *MPL* mRNA expression (OS2, OS9, OS31, OS33, OS36, OS60). EP was administered at an oral dose of 5 mg/kg/day given for 5 days each week with planned treatment period of 4 weeks. High dose EP (50mg/kg/day) was also tested in 2 PDX models (OS2, OS9) on the same schedule. A control cohort that received vehicle was included for each PDX model. Tumor volumes were measured and responses defined utilizing the PPTC statistical analyses.

Results: EP at 5 mg/kg failed to inhibit tumor growth or induce significant differences in event-free survival (EFS) in any of the 6 osteosarcoma PDX models. At the higher dose of 50 mg/kg a significant prolongation in time to event in the EP-treated group was observed, but the effect was small with the ratio of the median time to event for treated versus control animals (EFS T/C) being only 1.2 in the 2 OS PDX models tested. No objective responses were observed with EP at either dose, with all models demonstrating progressive disease.

Conclusion: EP did not exhibit significant antitumor activity against the PPTC osteosarcoma PDX panel. However, EP also did not enhance tumor growth. EP's lack of anti-tumor activity against the OS PDX models suggests leukemia and osteosarcoma cells likely have different dependencies on intracellular polyvalent cations. Given EPs effect on stimulating platelet production, and the demonstration that EP does not stimulate *in vivo* growth of osteosarcoma, EP may be considered for further study in patients with osteosarcoma as a supportive care agent in supporting platelet recovery.

Table 1: Osteosarcoma PDX model response to eltrombopag

Model	KM med (days)	EFS T - C (days)	EFS T/C	p-value Gehan-Wilcoxon	minRTV mean±SD	minRTV p-value	Objective Response Measure
				5 mg/kg			
OS-2	26.0	0.9	1.03	p = 0.172	1.134±0.091	p = 0.631	PD1
OS-9	23.0	1.5	1.07	p = 0.881	1.686±0.461	p = 0.739	PD1
OS-31	16.1	0.6	1.04	p = 0.407	1.774±0.188	p = 0.011	PD1
OS-33	21.1	2.2	1.12	p = 0.109	1.472±0.236	p = 0.123	PD1
OS-36	18.1	2.8	1.18	p = 0.170	2.019±0.352	p = 0.684	PD1
OS-60-SJ	34.1	0.0	1.00	p = 0.452	1.228±0.113	p = 0.353	PD1
				50 mg/kg			
OS-2	24.9	3.7	1.2	p = 0.015	1.403±0.241	p = 0.529	PD1
OS-9	20.5	3.8	1.2	p = 0.014	1.752±0.197	p = 0.143	PD1

Poster #145 3229100

CLINICAL FEATURES AND OUTCOMES OF PRIMARY BONE AND SOFT TISSUE SARCOMAS IN ADOLESCENTS AND YOUNG ADULTS

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Objective: This study aimed to investigate the clinical outcomes of adolescents and young adults with bone and soft tissue sarcomas.

Methods: Records of seven male and six female patients aged 17–39 years with bone or soft tissue sarcoma were reviewed retrospectively; data on histology, size, location, grade/stage, treatment, recurrence, metastasis, and prognosis were retrieved. Five-year survival rates were estimated using the Kaplan-Meier method and were compared according to age, sarcoma type, histological grade, and location. Seven and six patients had bone and soft tissue sarcomas, respectively.

Results: In terms of histology, patients with bone sarcomas included four with osteosarcoma, two with chondrosarcoma, and one with Ewing sarcoma of the bone. As for those with soft tissue sarcomas, three had liposarcoma, two had synovial sarcoma, and one had Ewing sarcoma and leiomyosarcoma. The five-year survival rate of all patients was 57.1%, with no significant difference between younger versus older patients or between patients with soft tissue versus bone sarcomas. However, patients with high-grade sarcomas had poorer survival than those with low-grade tumors; moreover, those with trunk-located tumors had poorer survival than those with tumors in the extremities.

Conclusion: Adolescents and young adults with high-grade or trunk-located sarcomas require more aggressive treatment.

Poster #146 3254677

FACTORS INFLUENCING SARCOMA ACT EFFICACY

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Objective: Sarcoma is a heterogeneous group of cancers with over 50 subtypes. Survival rates have remained comparatively stagnant in recent decades and treatment strategies such as immunotherapy are largely underutilized. Adoptive cell transfer therapy (ACT) is a relatively non-invasive immunotherapy approach wherein a patient's immune cells are externally isolated, expanded and re-administered. While some cases show positive outcomes, it is unknown why certain patients do not have long-lasting results and some do not respond at all. We have found that a subset of Undifferentiated Pleomorphic Sarcoma (UPS), Myxofibrosarcoma (MFS) and Osteosarcoma (OSA) cases harbour tumour-infiltrating lymphocytes (TILs) that are associated with good prognostic outcome for UPS and OSA. Through RNA-sequencing, a list of differentially-expressed genes between UPS cases with and without a positive prognosis was determined. With this discovery, we hypothesize that there are case-specific tumour characteristics and genes that may indicate ACT efficacy. Our aims are to create a case-specific system to investigate the variability in tumour-immune reactivity, characterize this activity and to validate any possible functional ACT biomarkers.

Methods: More than 190 sarcoma tumour specimens from patients undergoing open biopsy or surgical resection without pre-operative adjuvant treatment have been collected for the isolation of both tumour cells and the respective TILs. Various dissociation and tumour culturing methods were optimized for each case. After stable populations of corresponding tumour and TILs were grown, these two components were co-cultured. Indicators of cell activity and toxicity were evaluated with an ELISA. Expression levels of the UPS discriminatory genes were investigated in cultured tumour cells by qPCR.

Results: Due to the intra and inter-subtype heterogeneity of sarcoma, optimal culturing conditions were variable. We determined that culturing methods and materials influence cell morphology (Figure 1), therefore techniques were optimized on a case-specific basis. As shown in Table 1, 16 of the 31 cases resulted in a sucessful tumour culture. Preliminary experiments demonstrate that when co-cultured *in vitro* to reflect ACT therapy, tumour cells and autologous TILs are reactive (Figure 2). This was measured using ELISAs for interferon-gamma, an indicator of TIL activity. Currently we are investigating the relative expression levels of UPS discriminatory genes in cultured tumour cells by qPCR. Further, we are assessing the concentration of Granzyme B, an indicator of cytotoxicity, in the supernatant of the co-cultures.

Conclusion: A subset of resected patient samples are capable of forming successful tumour cell cultures. Initial experiments suggest that autologous TILs are active in the presence of tumour cells. Future assays will guide our studies to determine which cases have more or less tumour-TIL reactivity. Genetic analysis of more reactive cases will occur with the goal of finding a functional ACT biomarker.

Table 1. Tumour Cell Culturing

Sarcoma Subtype	Number of Cases Attempted to Culture	Number of Successful Cultures
Undifferentiated Pleomorphic Sarcoma	7	5
Myxofibrosarcoma	8	4
Leiomyosarcoma	4	1
Liposarcoma	2	1
Osteosarcoma	3	1
Other or Unknown	7	4

Table 1. A summary of sarcoma cases that have attempted to be cultured by subtype.

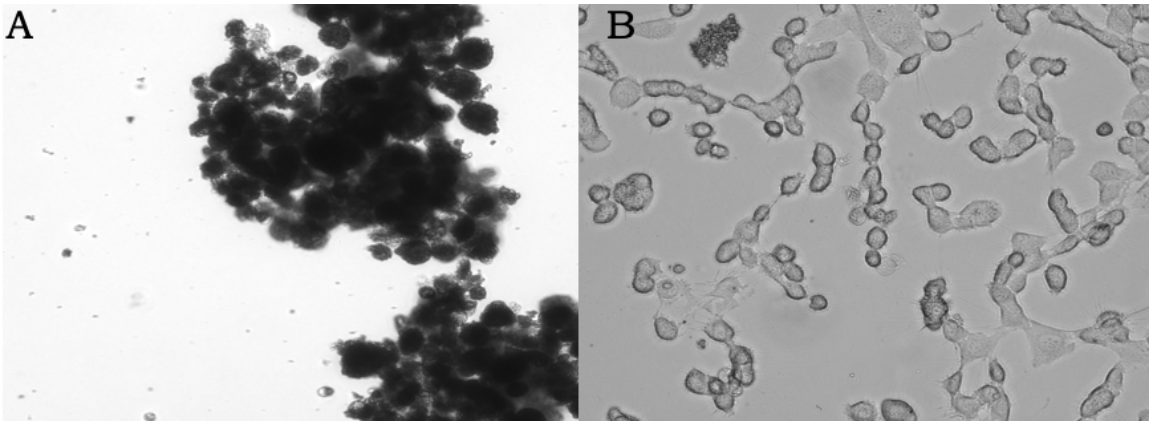

Figure 1. 2 myxofibrosarcoma (MFS, sample 166) sub-cultures 72 hours after being plated in A) suspension or B) adherent media. The patient sample was preserved in liquid nitrogen and dissociated by tumour fragment method before sub-culturing.

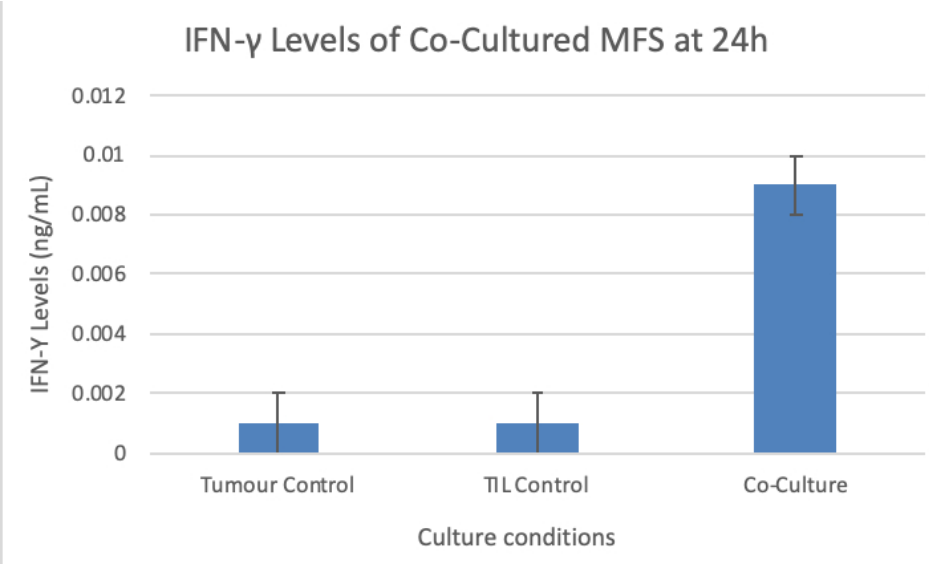

Figure 2. A myxofibrosarcoma (MFS, sample 11) was cultured and then incubated with an autologous TIL population. The supernatant was analyzed for IFNγ levels using an ELISA kit after 24 hours in culture.

Poster #147 3255443

DISCOVERY OF TARGETED EXPRESSION DATA FOR NOVEL ANTIBODY-BASED AND CHIMERIC ANTIGEN RECEPTOR- BASED THERAPEUTICS IN SOFT TISSUE SARCOMAS USING RNA-SEQ: CLINICAL IMPLICATIONS

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Objective: Recent failure of large phase 3 trials and paucity of oncogenic drivers hamper developmental therapeutics in sarcomas. Antibody-based therapeutics, like drug conjugates (ADCs) which combine specific antibodies with cytotoxic or radiopharmaceutical payloads and chimeric antigen receptor- based therapeutics, have emerged as a promising strategy for targeted anti-cancer drug delivery. The efficacy of these novel therapies is highly dependent on the expression of the antibody target and are relevant for sarcomas lacking clear oncogenic drivers. We analyzed the expression of targets currently in clinical trials in sarcoma subtypes for future ADC and CAR drug development.

Methods: We used RNA sequencing data from the Cancer Genome Atlas (TCGA) to analyze the expression of ADC targets 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). We searched published literature and clinicaltrial.gov database for ADC, bi-specific antibodies, immunotoxins, radioimmunoconjugates (radiolabelled antibodies) and chimeric antigen receptors that are in clinical trials.

Results: CD70 expression was significantly higher in DDLPS, UPS, and MFS than in SS ($p<0.001$, $p<0.001$ and $p<0.05$ respectively) and STLMS ($p<0.001$, $p<0.001$ and $p<0.05$ respectively). CDH3 expression was greater in STLMS and ULMS than in UPS ($p<0.001$), MFS ($p<0.001$), and DDLPS ($p<0.001$). 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 ($p<0.05$). GPNMB was highly expressed in most sarcomas, with the exception of SS. LRRC15 also appeared to be a relevant target, especially in UPS. MSLN expression was relatively low except in SS and MPNST. Interestingly, PDGFRA was also highly expressed in most sarcomas with the exception of ULMS and STLMS. TNFRSF8 seems to be the most appropriate in DDLPS, as well as in MFS. AXL was expressed especially in MFS and STLMS. ADCs targeting these are currently in development. MMAE, MMAF (auristatin) are cytotoxins.

Conclusion: Sarcoma subtypes express multiple target genes relevant for ADCs, CAR's, and other cell surface targeting agents, warranting further pre-clinical and clinical validation and evaluation. These targets may also be relevant in development of novel antibody-based and chimeric antigen receptor- based therapeutics.

Poster #148 3255480

EVALUATING THE POTENTIAL OF TUMOUR INFILTRATING LYMPHOCYTES FOR THE TREATMENT OF ADULT SARCOMA

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Objective: For sarcoma, due to their heterogeneity, conventional chemotherapy and molecular targeted therapies have varying effects across individuals and subtypes. These methods often only provide short-term disease control and so, more effective treatments are urgently needed. Recent advances in immunotherapy strategies such as checkpoint inhibition or adoptive T-cell therapy (ACT) show potential towards providing a more personalized treatment for sarcoma patients, which could increase treatment efficacy. We hypothesize that some sarcoma subtypes contain tumor infiltrating lymphocytes (TILs) in the tumor microenvironment and that these TILs can be isolated and applied towards ACT. Our aims are to investigate the availability and viability of TILs from sarcoma tissue fragments, characterize the TILs, and assess the cytotoxicity of the TILs through functional assays.

Methods: We collected 190+ sarcoma tumor specimens from patients undergoing open biopsy or surgical resection without pre-operative adjuvant treatment in order to isolate TILs. We compared different methods of TIL expansion and optimized a protocol specifically for efficacy in culturing TILs from sarcoma. The expanded TIL populations were characterized by flow cytometry analysis using CD3, CD4, CD8, CD14, CD19 and CD56 markers. The TIL populations were non-specifically stimulated to establish TIL reactivity and TILs were co-cultured with autologous and allogenic tumour cells to establish TIL specificity.

Results: Through 87 cases, we found that the tumor fragment method was much easier to execute and yielded a more homogenous cell population (Table 1). Additionally, there were relatively lower TIL yield from sarcoma compared to previous studies done on epithelial-based cancers, such as melanoma and ovarian cancer. Since we observed intratumoural differences in TIL growth, the modified protocol pools populations with similar growth densities to provide the higher cell counts needed for further experiments and also to reach a clinically significant amount for ACT (Figure 1). The flow cytometry results of 38 characterized cases show TIL cultures exhibiting varying ratios of $CD4^+$ to $CD8^+$ T-cells, both intratumoural and intertumoural (Figure 2a). There also seems to be a population of $CD56^+$ cells that hinders the growth of $CD3^+$ T-cells (Figure 2b). Upon non-specific stimulation of 25 cases, through IFNg ELISA, TIL populations show reactivity, indicating a viable and functional population (Figure 3). Our preliminary results from tumour-TIL co-cultures show specific reactivity to autologous tumour cells through increase levels of IFNg and granzyme B.

Conclusion: With our modified protocol, 87 sarcoma cases have been cultured *in vitro* and TILs were successfully collected from over 40% of those cases. The final yield and growth density of TIL populations have minimal association to the PDL1 expression levels of tumour cells. Thus, we are looking into other molecular markers that could potentially indicate better TIL growth *in vitro*. Currently, by RT-qPCR, we are analyzing expression levels of chemokines involved in lymphocyte recruitment (CXCL9, CXCL10, CCL4, CCL5) among the cultured cases. TIL populations from 38 cases have been characterized with flow cytometry and demonstrated variable ratios of $CD4^+$ and $CD8^+$ TILs. TILs from 25 cases have also shown reactivity and autologous tumour specificity. These initial studies will enable us to move forward with evaluating the potential of TIL-based ACT for patients with sarcoma.

Subtype breakdown of cultured cases

Subtype	# of Cases Cultured
Liposarcoma	16
Leiomyosarcoma	11
Myxofibrosarcoma	22
UPS	21
Osteosarcoma	16
Other	1
Total	87

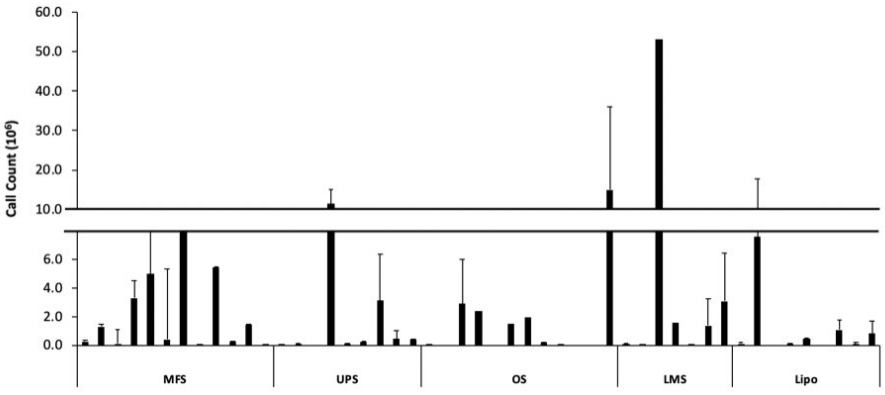

Figure 1. Cell Counts of Pooled Populations.

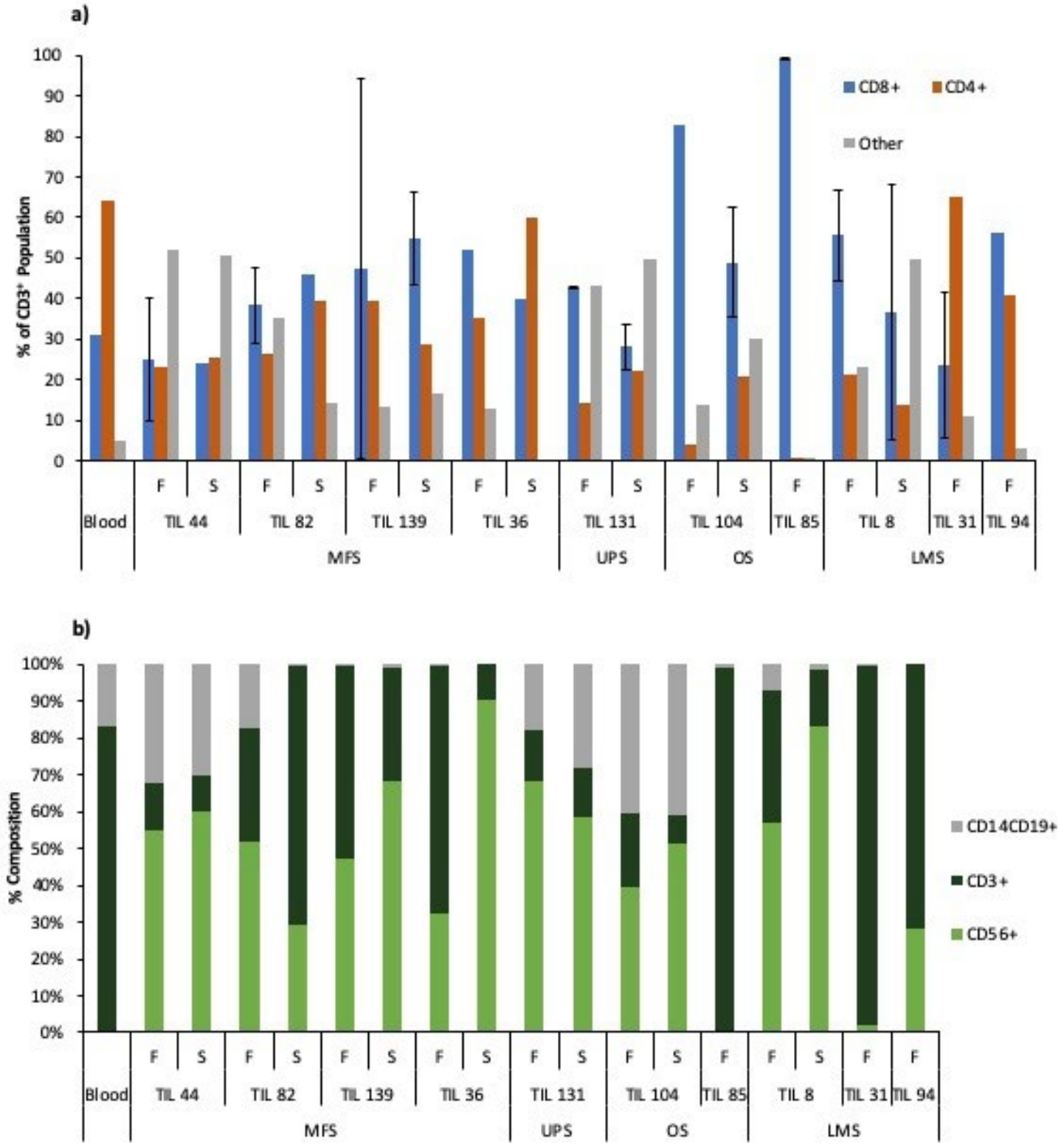

Figure 2. TIL composition of selected cases. a) Proportion of CD4+ and CD8+ TILs in the CD3+ population of selected cases. b) Composition of expanded TIL composition of selected cases.

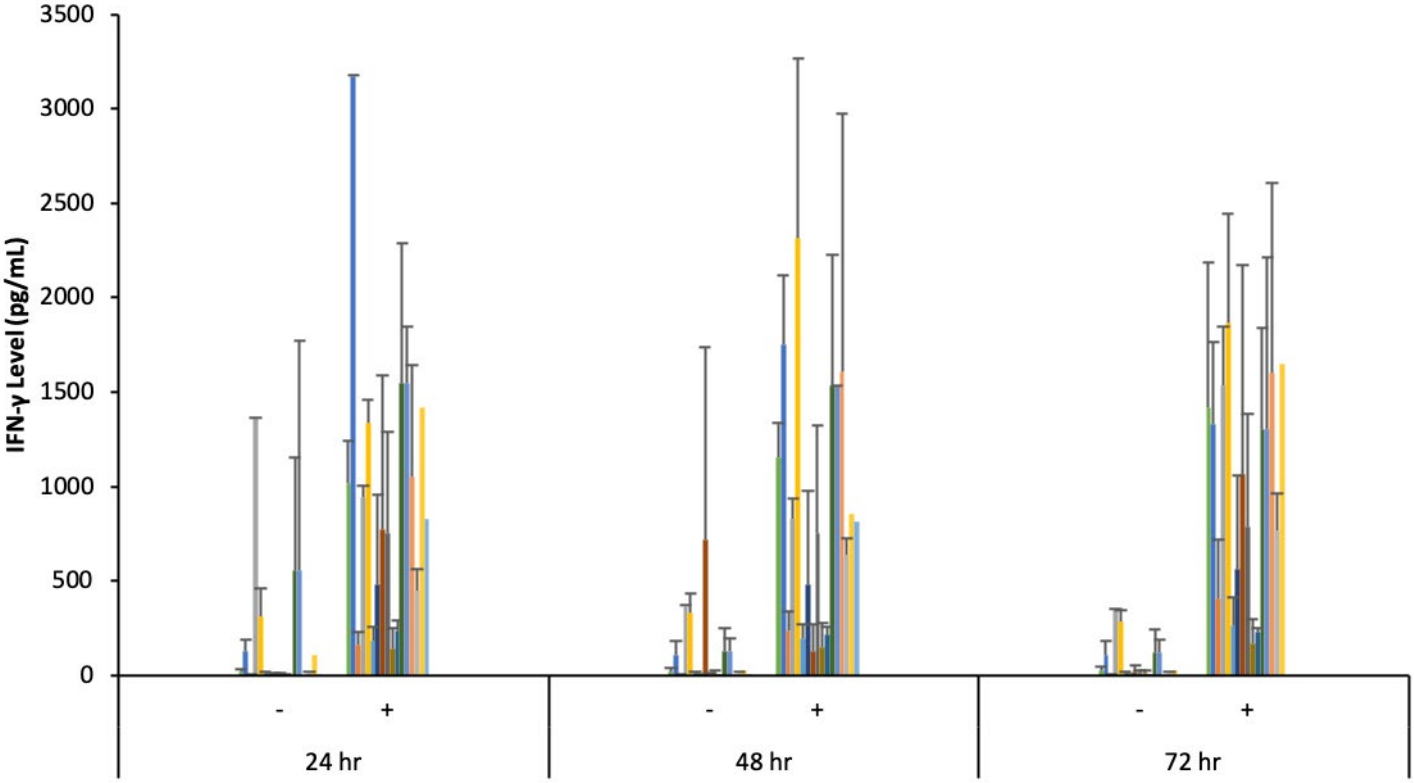

Figure 3. IFN-γ levels of all analyzed cases at various time points.

Poster #149 3256028

PREVALENCE OF GERMLINE VARIANTS AS DETERMINED BY EXPANDED MULTIGENE PANELS IN PATIENTS WITH SOFT TISSUE SARCOMA

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Objective: Soft tissue sarcomas (STS) typically present as sporadic tumors with only a small percentage thought to be associated with inherited genetic syndromes. However, several factors point to a strong genetic component as STS disproportionately affects younger patients and STS survivors carry an increased lifetime risk of developing a second primary malignancy. Little is known about the true frequency of germline mutations that may drive STS tumorigenesis. Objective: The objective of this study was to characterize the prevalence of clinically actionable germline variants (defined as pathogenic or likely pathogenic) among patients with localized STS.

Methods: This is a retrospective review of a cohort of 32 consecutive patients with a diagnosis of STS seen at a single, high-volume sarcoma surgical oncology program and referred for genetic counseling and testing over a 6-month period from October 2018 to April 2019.

Main Outcome Measure: Identification of a clinically actionable germline variant.

Results: Of the 32 patients with STS, 31 (97%) were seen by a genetic counselor and genetic testing was performed in 30 (94%). Four (13%) has a personal history of a second primary cancer. Of the 30 patients with genetic testing results, 8 patients (27%) had a clinically actionable genetic variant in the following genes: *CHEK2* (n=2, 7%), *BRCA2* (n=1, 3%), *PMS2* (n=1, 3%), *MUTYH* (n=3, 10%), and *WRN* (n=1, 1%). Of the 8 patients with a clinically actionable variant, 1 (12%) had a personal history of a non-STS cancer (*CHEK2* gene; breast cancer), 2 (25%) had at least one first-degree relative with a history of any cancers, 6 (75%) had any-degree relative with a history of any cancer, 1 (13%) had no relative with cancer, 1 (13%) patient was adopted and unable to provide a family history.

Conclusion: Clinically actionable variants were identified in 27% of patients with STS who underwent genetic testing. Family history is not predictive for who will harbor a germline mutation. The detection rate of germline mutations in sarcoma is similar to other cancers (ovarian/pancreas) where we perform genetic evaluation on all and should be considered in all STS patients.

Poster #150 3256473

GSTP1 EXPRESSION IS PREDICTIVE OF SARCOMA RESPONSE TO DOXORUBICIN BASED CHEMOTHERAPY

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Objective: Doxorubicin is a key component of systemic therapy for both bone and soft tissue sarcomas. It is used in a variety of settings - neo-adjuvant and adjuvant therapy for selected high risk soft tissue sarcomas and most Ewings sarcoma and osteosarcoma cases, as well as treatment of advanced sarcomas. While doxorubicin is one of our most active chemotherapy agents in general, responses are not universal, and there is currently no way to predict which tumors will respond to treatment. Our objective is to identify potential biomarkers that predict response to doxorubicin-based chemotherapy.

Methods: With appropriate institutional review board approval, we identified a cohort of patients with bone or soft tissue sarcoma who had been treated wtih doxorubicin or liposomal doxorubicin at our institution from 2010 to present. From among these patients, we identified those with archived pathology samples remaining after their diagnostic workup. Literature review was undertaken, and we identified eleven genes that had been associated with sarcoma or other cancer response to doxorubicin. Tissue slides for each patient in our cohort were tested with immunohistochemical stains for each of eleven potential biomarkers, and expression levels (as percent of cells positive and H-score) were tested for correlation to tumor response. Univariate analysis was done for each of the biomarkers, testing expression impact on RECIST response. Multivariate analysis, factoring in patient age, metastatic vs localized stage, and single-agent vs combination doxorubicin therapy, was done, assessing relationship biomarker expression to best percent change in tumor size.

Results: On univariate analysis, GSTP1 expression, as percent of cells positive for the stain, is the only biomarker that was correlated with response at a significance level of $p < 0.05$ (0.042) - lower expression correlated with higher likelihood of response. On multivariate analysis, using linear regression, GSTP1 percent positive was correlated with percent change in tumor size ($p = 0.0316$).

Conclusion: GSTP1 is an enzyme that decreases oxidative damage in cells by conjugation of toxic compounds to glutathione. Higher GSTP1 expression has been correlated with relative docetaxel resistance in triple negative breast cancer patients, and GSTP1 has been correlated with chemoresistance in other cancers as well. Osteosarcoma cells modified to overexpress GSTP1 were relatively resistant to chemotherapy. This is the first report we are aware of demonstrating an association of clinical outcomes with GSTP1 expression in sarcoma patients.

Poster #151 3219544

IN SITU CRYO-ABLATION OF DESMOID TUMORS ASSISTED BY 3D MODELLING AND NAVIGATION BY O ARM

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Objective: Aggressive fibromatosis, is a rare, locally invasive, non-metastasizing condition. The natural history of desmoid tumors is variable and includes periods of indolence, growth, and regression.

Reasons for treatment and how? Volumetric progression, Symptoms worsening & Cosmetic disturbance. Large en-bloc surgery is no longer regarded as the cornerstone treatment. Rate of relapse after surgery exceeds 60% in larger series. Shift to a more conservative approach, the 'wait-and-see' policy was adopted during last years. Other forms of treatment include: radiation, systemic therapy, and neoadjuvant radiation with or without chemotherapy. neither approach has emerged as optimal or definitive, and each is associated with high recurrence rates or complications from the treatment itself.

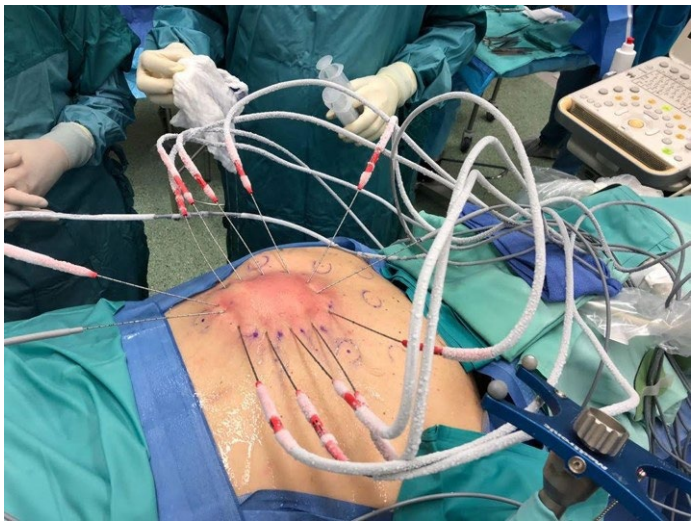
In situ cryotherapy is a minimal invasive procedure that can decrease tumor size by apoptosis. cryotherapy is a safe procedure the does not damage collagenous structures surrounding the tumor. During the procedure, the ice ball in the tumor can be monitored using imaging studies such as CT or ultrasonography. The proper position and the number of needles is crucial in order to ideally cover and surround the tumor mass. By 3D modelling and planning this goal can be achieved. The most effective trajectory can be determined and vital organs (nerves, blood vessels and other structures) can be protected. Using the O arm navigated system, real time positioning and monitoring is possible.

Methods: 11 patients with histolocally confirmed extra abdominal desmoid tumor with progression of tumor mass on imaging and severe functional disturbance were treated with in situ cryosurgery. All patients were scanned by MRI and CT prior the procedure. Segmentation of the tumor and surrounding structures was perform into 3D surface models. Then by extrapolating the "kill zone" of each cryotherapy needle we placed the needle in to the tumor. All procedures took place at the operating theater under general anesthesia. According to previous planning, several isolated cryo needles (Galil medical ice-rod plus, Israel) were inserted into the tumor mass under O arm navigated guidance. Then cryotherapy protocol was activated which includes 10 minutes freezing, 5 minutes active thawing and repeated 10 minutes freezing. During freezing cycles, a scan by the O arm was done in order to monitor the "ice ball" in the tumor.

Results: 10 tumors progression has stopped. 2 patients underwent repeated ablation do to relative tumor growth. in 6 patients (54.5%) – there was average of 53% reduction in tumor volume within 6 months. In 2 patients the tumor disappeared completely. In 3 patients the tumor as stopped growing but no reduction was noted. One patient the tumor is growing (close to brachial plexus) and One patient data collection is missing (Russia). Quality of life - SF 36 - physical health, emotional health and pain was significantly improved.

Conclusion: In situ cryo-surgery in a safe procedure and effective in stabilizing tumor mass in desmoid tumors. In 90% of the patients we were able to stop tumor growth and improve quality of life. By 3D modelling correct positioning of cryo needles can be optimal and safer for the patients.

Navigation using the O arm is effective and easy to use



Poster #152 3228336

THERAPEUTIC IMPLICATION OF GENOIC LANDSCAPE OF ADULT METASTATIC SARCOMA

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Objective: This study is to investigate therapeutic potential of integrated genome and transcriptome profiling of metastatic sarcoma, a rare but extremely heterogeneous group of aggressive mesenchymal malignancies with few systemic therapeutic options.

Methods: 43 adult patients with advanced or metastatic non-GIST sarcomas of various histology subtypes who were enrolled into the Personalized OncoGenomics Program at BC Cancer were included in this study. Fresh tumor tissues along with blood samples underwent whole genome and transcriptome sequencing.

Results: The most frequent genomic alterations in this cohort are large-scale structural variation (SV) and somatic copy number variation (CNV). Outlier RNA expression as well as somatic CNVs, SVs, and small mutations together suggest the presence of one or more potential therapeutic targets in the majority of patients in our cohort. Point mutations or deletions in known targetable cancer genes are rare; for example, tuberous sclerosis complex 2 (TSC2) provides a rationale for targeting the mammalian target of rapamycin (mTOR) pathway, resulting in a few patients with exceptional clinical benefit from everolimus. In addition, we observed recurrent 17p11-p12 amplifications, which appear to be a sarcoma specific event. This may suggest that this region harbors an oncogene(s) that is significant for sarcoma tumorigenesis. Furthermore, some sarcoma tumors carrying a distinct mutational signature suggestive of homologous recombination deficiency appear to demonstrate sensitivity to double strand DNA damaging agents.

Conclusion: Integrated large-scale genomic analysis may provide insights into potential therapeutic targets as well as novel biological features of metastatic sarcomas that could fuel future experimental and clinical research and help design biomarker driven basket clinical trials for novel therapeutic strategies.

Table 2 Cases derived clinical benefit from POG-directed therapy

Case	Age at diagnosis/ Gender	Diagnosis	Previous Systemic Treatments	Genetic Aberrance by POG	POG-directed Therapy	Best Response/ Duration of Response
1	62 male	Renal epithelioid angiomyolipoma	Doxorubicin Ifosfamide Docetaxel Gemcitabine	TSC2 mutation	Everolimus 3 cycles ongoing (Compassionate access)	PR 15 months with Continuing response
2	57 female	Undifferentiated round cell sarcoma	Ifosfamide Etoposide Cyclophosphamide Doxorubicin Vincristine	2 copy loss of TSC2	Everolimus 12 cycles (Compassionate access)	PR Over 1 year (died of unrelated cause)
3	31 female	Dedifferentiated liposarcoma	Regorafenib, Docetaxel/ Gemcitabine Doxorubicin	Amplification of MDM2 and CDK4	Combination MDM2 and CDK4 inhibitors 14 cycles (Phase I study)	PR 1 year
4	44 female	Undifferentiated endometrial sarcoma	Docetaxel Gemcitabine Doxorubicin	Gene signature 3 corresponding with high HRD score	Ifosfamide 6 cycles (Standard of care)	PR 4.5months
5	55 female	Uterine leiomyosarcoma	Doxorubicin Docetaxel Gemcitabine	Gene signature 3 corresponding with high HRD score	Ifosfamide 6 cycles (Standard of care)	PR 4.5 months
6	53 male	Non-gynecological leiomyosarcoma	Docetaxel Gemcitabine	Gene signature 3 corresponding with high HRD score	Prexasertib (Phase I study) 9 cycles	SD 6 months
7	77 male	Undifferentiated pleomorphic sarcoma	Doxorubicin	High percentile expression of PDGFRs	Sunitinib 6 cycles (Compassionate access)	PR 6 months
8	59 male	Non-gynecological leiomyosarcoma	Docetaxel/ Gemcitabine Doxorubicin	High percentile expression of FLT3 and CSF1R	Sunitinib 6 cycles (Compassionate access)	SD 6months
				High IIS score from CYBERSORT	PDL1 antibody 10cycles (Phase 1 study)	SD 8 months

Case series of patients who derived clinical benefit from POG-directed therapy

Figure 3 Hierarchical clustering of 43 metastatic sarcomas according to genomic instability characteristics.

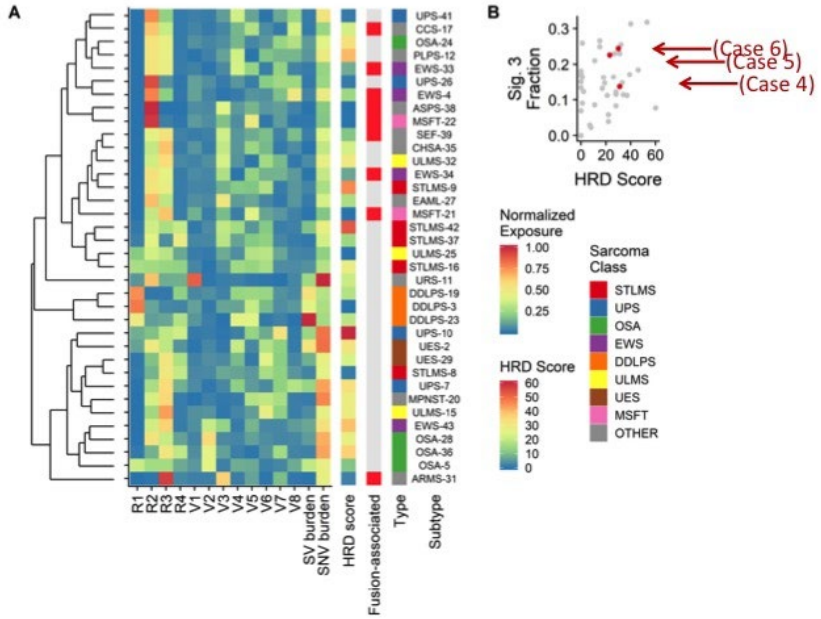

Figure 3. Hierarchical clustering of 43 metastatic sarcomas according to genomic instability characteristics.
(A) Structural variant mutation signatures (R1-R4) and single nucleotide variant mutation signatures (V1-V8) were deciphered *de novo* from metastatic sarcomas. Hierarchical clustering distinguished clusters of fusion-associated sarcomas, as well as osteosarcomas, de-differentiated liposarcomas, and leiyomyosarcomas.
(B) Three sarcoma cases (labelled in red) with elevated homologous recombination deficiency (HRD) score and/or the HRD-associated Signature 3 demonstrated response to double-strand DNA damaging chemotherapy.
(C) Mutation signatures deciphered *de* novo from sarcomas were compared against 30 canonical signatures from the Catalogue of Somatic Mutations in Cancer (COSMIC) using the cosine similarity metric. Signatures which map most closely to a COSMIC signature are highlighted.

Figure 4 Immune infiltration scores (IIS) of 43 metastatic sarcomas

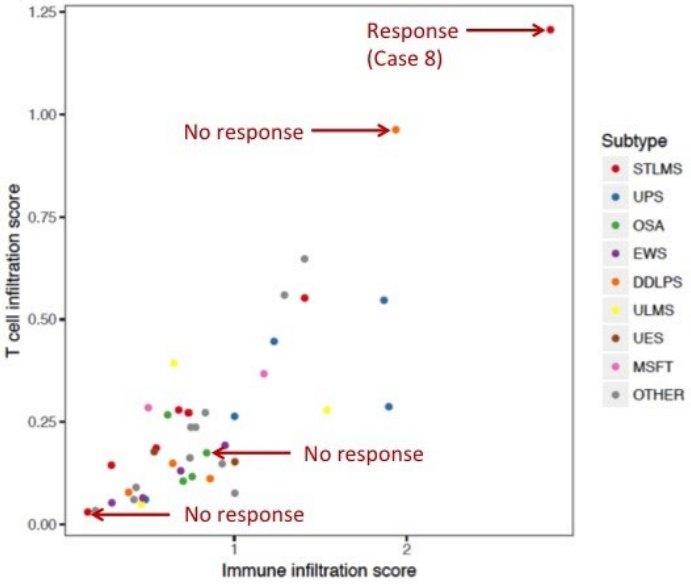

Figure 4. Immune infiltration scores of 43 metastatic sarcomas
Immune infiltration scores determined using CIBERSORT for all sarcoma samples demonstrate evidence for immune infiltration in a subset of samples. T cell infiltration score is the sum of all T cell subtypes excluding regulatory T cells, which are negative modulators. Immune infiltration score is the sum of scores for all 22 immune cell types profiled. STLMS, Non-gynecologic leiomyosarcoma; UPS, Undifferentiated pleomorphic sarcoma; OSA, Osteosarcoma; EWS, Ewing sarcoma; DDLPS, Dedifferentiated liposarcoma; ULMS, gynecologic leiomyosarcoma; UES, Undifferentiated endometrial sarcoma; MSFT, Malignant Solitary fibrous tumor; OTHER, all other subtypes encompassing URS, PLPS, MLPS, CCS, MPNST, EAML, ARMS, SS, CHSA, ASPS and SEF; abbreviations as in Figure 1.

Poster #153 3245758

EXPLORATORY ANALYSIS OF HYBRID-CAPTURE BASED NEXT-GENERATION SEQUENCING CONFIRMS SUCCINATE DEHYDROGENASE DEFICIENCY AS THE SOLITARY GENOMIC DRIVER IN PARAGANGLIOMA, PHEOCHROMOCYTOMA, AND GIST

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Objective: The succinate dehydrogenase (SDH) complex (succinate-coenzyme Q reductase or mitochondrial complex II) is an integral component in both the tricarboxylic acid (TCA) cycle and electron transport chain. Malignant neoplasms exhibiting dysfunction of SDH (SDH-deficiency, or dSDHx) via mutation in any of the four subunits, *SDHA*, *SDHB*, *SDHC*, and *SDHD* (i.e. *SDHx*), accumulate mitochondrial succinate, inducing a phenomenon of pseudohypoxia, which is distinctively oncogenic for subtypes of GIST, paraganglioma (PGL), and pheochromocytoma (Pheo). In this exploratory study, we analyzed next-generation sequencing data from a large pan-tumor cohort to discover the incidence of dSDHx and stratify potentially targetable alterations and biomarkers within this cohort.

Methods: Comprehensive genomic profiling was performed using a CLIA-approved CAP-accredited hybrid-capture based next-generation sequencing assay interrogating at least 295 genes by DNA-seq. A pan-cancer database of 264,331 routine clinical specimens was queried for *SDHx* mutation and stratified into SDHx-mutant and dSDHx, defined as either *SDHx* loss of function (LOF) mutation under loss of heterozygosity (LOH) or homozygous copy number loss of *SDHx*. Odds ratio (OR) was calculated using the Fisher's exact test and false discovery rate (FDR) was assessed using the Benjamini-Hochberg method.

Results: Of 1179 (0.45%) SDHx-mutant specimens, alterations in *SDHA*, *SDHB*, *SDHC*, and *SDHD* comprised 65.0%, 15.5%, 13.1%, and 6.3%, respectively. The only diseases enriched (FDR P<0.001) within this cohort compared to all other diseases were PGL, Pheo, and GIST (OR=88.8, 24.9 & 6.1, respectively). 204 (17.3%) were dSDHx, of which alterations in *SDHA*, *SDHB*, *SDHC*, and *SDHD* comprised 44.9%, 35.6%, 9.3%, and 10.2%, respectively. The dSDHx cohort was 52.9% male with a median age of 56 (range 4-86). Diseases enriched (FDR P<0.001) with dSDHx were PGL, Pheo, and GIST (OR=586.6, 128.5 & 24.6, respectively). dSDHx was also significantly enriched (FDR P<0.001) within SDHx-mutant PGL, Pheo, and GIST (OR=97.5, 34.7 & 8.5, respectively). There was no positional bias of the dSDHx alterations within the *SDHx* genes or compared to SDHx-mutants. dSDHx specimens were mutually exclusive with *CDKN2A/B* homozygous loss (OR=0.07), and significantly enriched with *TERT* promotor (OR=9.21) alterations (FDR P<0.01). dSDHx GIST were mutaually exlusive with *KIT* activating (OR=0.04) alterations. Of the dSDHx PGL, Pheo, and GIST specimens, 0 had other potentially targetable driver alterations, 0 were TMB-high, 0 were MSI, and 0 had significant genomic LOH.

Conclusion: Using a pan-cancer dataset, we demonstrated that dSDHx is a defining genomic feature of a distinct subtypes of GIST, PGL, and Pheo lacking targetable driver alterations or biomarkers suggestive of response to checkpoint inhibitors. Across diseases, these data indicate that most inactivating *SDHx* alterations are heterozygous, implying they are typically passenger alterations; however, the frequency of biallelic *SDHx* LOF in PGL, Pheo, and GIST suggests dSDHx as a distinct oncogenic driver. This emphasizes the need for novel therapeutic approaches to target dSDHx in PGL, Pheo, and GIST and highlights the importance of molecular stratification of these diseases.

Poster #154 3254176

USING A CROSS-SPECIES PRECISION MEDICINE PIPELINE TO IDENTIFY PROMISING NEW THERAPIES FOR OSTEOSARCOMAS

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Objective: Osteosarcoma is the most common primary bone cancer in children with more than 1,500 cases per year, but has seen almost no therapeutic advances over the past three decades. Osteosarcoma is one of the only types of cancer for which the prognosis given today is nearly identical to the prognosis given three decades ago. One of the barriers to studying osteosarcoma is the lack of access to large numbers of patients. There is a significant clinical need to identify new therapies to treat osteosarcoma yet small numbers of patients limit our abilities to make discoveries. To address this need, we are developing a novel mouse to dog to human cross-species pipeline that allows us to identify and validate personalized therapies for osteosarcoma patients at high risk or metastatic disease. Pet dogs are a useful comparative model to study osteosarcoma because sarcomas are common in dogs, and disease progression occurs more rapidly. We can take advantage of these features to pursue and identify new treatments for canine osteosarcoma, since human treatments and clinical trials are costly and slow.

Methods: The pipeline begins with the creation of patient-derived xenografts and matched patient-derived cell lines. From here, the cell lines are in a 2,100 compound high throughput drug screening to identify top drug candidates. Top candidates are validated *in vivo* using the patient-derived xenografts. Whole exome sequencing of patient tumors and patient-derived models enables identification of potential driver mutations and mechanisms of therapy sensitivity or resistance.

Results: A total of twelve canine and one human osteosarcoma patient-derived xenografts were developed in SCID-beige mouse avatars. Two osteosarcoma cell lines were made from a human patient and a canine patient, 173X and D418, respectively. High throughput drug screening identified drugs killing over 90% of cells, with a strong correlation (r=0.747) between human and dog. Top drug candidates were identified and selected for *in vivo* testing in the osteosarcoma bearing mice. *In vivo* testing showed proteasome inhibitors, CRM1 inhibitors and HSP pathway therapies as promising targets. A ten-dog pilot trial of adding the proteasome inhibitor, bortezomib, to standard therapy is currently underway.

Conclusion: Our novel cross-species pipeline is showing promise as a rapid means of screening and validating new candidate drugs as therapy for osteosarcoma. Evaluation of our lead targets – proteasome inhibitors, CRM1 inhibitors, and HSP pathway therapies – is underway.

Poster #155 3255682

EWS-FUSION PARTNERS IN SARCOMA AS REVEALED BY "REAL WORLD" GENOMIC SEQUENCING: CLINICAL IMPLICATIONS

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Objective: Soft tissue sarcomas and bone cancers continue to have a poor prognosis in relapsed refractory patients. The EWSR1 gene is a component for many sarcomas once it translocates and fuses with other essential genes. Clinical next-generation sequencing opens up opportunities for matched therapies. Identifying the different translocations as it pertains to disease types and the frequency of the alterations can help guide therapy, and improve treatment options as more targeted therapies come to the clinic. Our objective was to catalog EWS partners among diverse sarcomas, review outcomes of targeted therapy of these sarcomas, and discuss developing EWSR1 targeted treatment.

Methods: We analyzed EWS partner fusion events in the AACR project Genomics Evidence Neoplasia Information Exchange (GENIE) database. The GENIE registry contains CLIA-/ISO-certified genomic data. We also reviewed sarcoma patient data with fusions that were matched to clinical trials in a large clinical trials unit.

Results: Among the 115 patients, the most commonly occurring recurrent fusions were Ewing's sarcoma harboring EWS-FLI1 (N=50, 43%) and DSRCT harboring EWS-WT1 (N=32, 28%). Other recurrent translocations include Clear Cell Sarcomas with EWS-ATF1 (N=5, 4%), Sarcomas NOS with EWS-ATF1 (N=2, 2%), Sclerosing Epithelioid Fibrosarcoma with EWS:CREB3L1 (N=3, 3%), Ewing Sarcoma EWS-ERG (N=5, 4%), Extraskeletal Myxoid Chondrosarcomas with EWS:NR4A3 (N=3, 3%) and Myxoid Chondrosarcoma with EWS:NR4A3 (N=2, 2%).

Clinical responses included one patient each with clear cell sarcoma EWSR1-CREBL1 fusion (c-MET + VEGF; partial response per RECIST for 1.5 years), Ewing's Sarcoma with EWS-FLI fusion (IGF1R+mTOR; CR after 14months), osteosarcoma with EWS- ATF1 (VEGF; PR for > 1 yr), EWSR1-CREB3L1 (VEGF+mTOR; SD > 9 mo), EWSR1-CREBL1 fusion osteosarcoma (Alpha-particle Ra223; partial metabolic response), and EWS-WT1 DSRCT (Y90 therapy; partial metabolic response).

Conclusion: With the advent of CRISPR and other nascent gene therapy approaches that have reached the clinic to treat genetic errors, the EWSR1-related translocations might all become targetable in the next decade. Inclusion of such rare tumors in targeted therapy basket/umbrella trials with a national registry is warranted. Further studies of the prevalences well as an improved understanding of the molecular mechanisms of response and resistance of EWSR1-related translocations, across the full repertoire of sarcoma subtypes, will aid in defining the study population that might benefit from such therapies.

Poster #156 3229444

SAFETY AND FEASIBILITY OF CIVO PHASE 0 PLATFORM FOR SIMULTANEOUS EVALUATION OF MULTIPLE DRUGS AND DRUG COMBINATIONS IN THE TUMOR MICROENVIRONMENT OF SOFT TISSUE SARCOMA PATIENTS

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Objective: Background: The high failure rate of investigational anti-cancer agents in the clinic suggests that current translational models of cancer frequently do not predict drug efficacy. The complexities of human solid tumors (genetics, microenvironment, heterogeneity) are not accurately modeled in mice. Genomic approaches to precision medicine have not completely addressed this issue. Better, more functional, and personalized approaches for understanding drug activities in the context of authentic tumors are needed. To address this need, the (Comparative In Vivo Oncology) CIVO® microinjection platform was designed specifically for intratumoral microdosing studies wherein multiple therapeutic agents, injected singly or in combination, are simultaneously evaluated and compared, directly within a patient's own tumor in situ. Biomarker and molecular analyses on the excised tissue enable assessment of localized tumor and tumor microenvironment (TME) responses to the injected drugs without exposing patients to systemic toxicities. This approach was evaluated in a multi-site feasibility study in patients with soft tissue sarcoma.

Questions/Purpose: The primary outcome measure was the quantification of fraction of cells positive for apoptosis and drug target engagement biomarkers around injected drugs. The secondary outcome measures included the number of patients with adverse events related to pain.

Methods: This was a single arm, pilot study designed to test the feasibility of using the CIVO system in patients with soft tissue sarcoma accessible for percutaneous injection. Subjects who were scheduled for surgical biopsy or tumor resection surgery were injected one to three days prior to surgery using the CIVO device. Minute volumes (up to 8.3 microliters) of saline (negative control) or microdoses of anti-cancer agents were percutaneously injected in a columnar fashion through each of 8 needles into a single enlarged solid tumor. Following the patient's biopsy surgery or tumor resection surgery, the injected portion and a small uninjected portion were used to determine each in situ drug response in the tumor. None of the data from this evaluation was used to make clinical decisions. Participants were followed for adverse events up to 28 days after microinjection. Thirteen patients with soft tissue sarcoma were prospectively enrolled. Inclusion criteria included accessibility for injection with no impact on surgical resection, and exclusion criteria included tumors under 3 cm in any dimension. This trial is registered at ClinicalTrials.gov (NCT03056599).

Results: The study's primary objective was met, establishing the feasibility and safety of the CIVO platform. Device-related AEs were limited to transient Grade 1 non-serious events. Consistent with historical data, doxorubicin induced localized increases in markers for DNA damage, apoptosis, and immune cell infiltration in several patients, whereas gemcitabine did not induce any observable responses. Importantly, CIVO identified doxorubicin resistance in a patient that had previously failed anthracycline-based therapy. CIVO analysis also revealed potential mechanisms of resistance to systemic therapy, including PDGF and MAPK pathway upregulation.

Conclusion: CIVO enables safe and thorough characterization of drug mechanisms of action and the impact within a naturally occurring tumor. This study positions CIVO as a powerful research tool for translational oncology, via Phase 0 investigation of drug candidates, bridging the knowledge gap between cancer biology and clinical response.

Poster #157 3230261

DIFFERENCES IN RESPONSE WITH PEMBROLIZUMAB IN UNDIFFERENTIATED PLEOMORPHIC SARCOMA BASED ON PROSPECTIVE KNOWLEDGE OF PDL-1 EXPRESSION

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Objective: This is a retrospective review of experiences at University of Kansas Cancer Center with off-label pembrolizumab in patients with metastatic undifferentiated pleomorphic sarcoma based on varying degrees of PDL-1 expression, determined prior to starting immunotherapy.

Methods: PDL-1 expression was carried out via immunohistochemistry on primary tumor cells, not metastatic site, using DAKO PD-L1 IHC 22C3 pharmDX (image 1). These results were known to patient and provider prior to implementing off-label pembrolizumab.

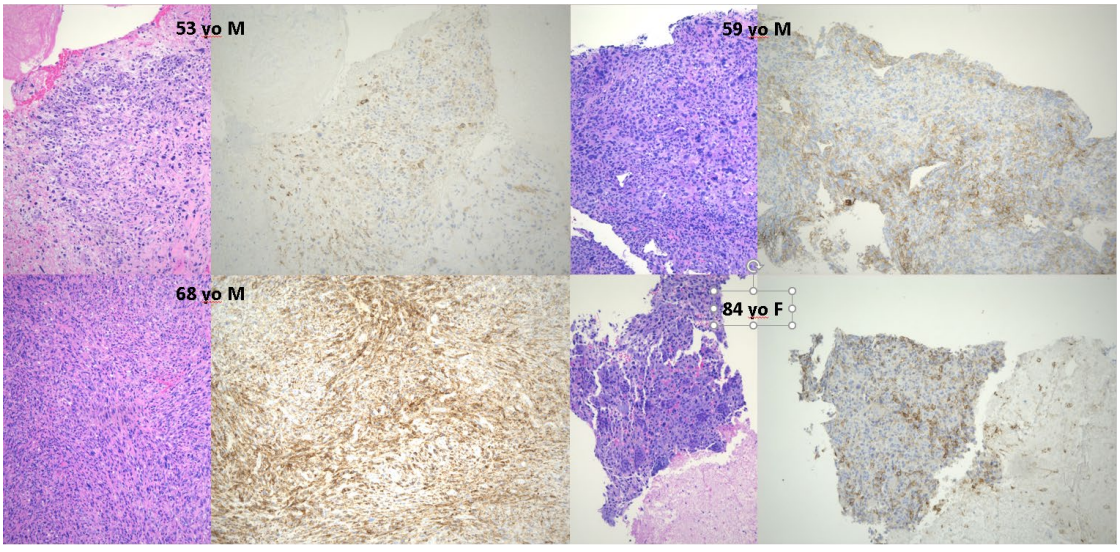
Results: Results varied, and they tended to follow PDL-1 expression (Table). The two gentlemen with >20cm thigh sarcomas both rapidly progressed on immunotherapy; they also happened to have low PDL-1 expression. A representative comparison (image 2) in the 59 year old with PDL-1 expression of 15% showed rapidly progressive disease in lungs/pleura after just 3 cycles of pembrolizumab. On the other hand, the 68 year old male with PDL-1 expression of 80% has had a nice partial response quickly (image 3).
Immunotherapy was well tolerated in all five patients. The symptoms encountered while on treatment were either grade 1 adverse events (i.e. asymptomatic rash) or due to rapidly progressive disease. It was generally much better tolerated than conventional standard-of-care doxorubicin-based chemotherapy, especially in the age range explored.

Conclusion: The numbers of patients with metastatic undifferentiated pleomorphic sarcoma treated with off-label pembrolizumab at University of Kansas Cancer Center are obviously much too small to make any grand conclusions. Much like the non-small-cell lung cancer population, it appears as if PDL-1 expression >50% lends a better chance at prolonged responses. The two gentlemen with >20cm thigh sarcomas both rapidly progressed on immunotherapy; they also happened to have low PDL-1 expression. We anxiously await the ongoing response evaluation of the man with multiple bone metastases on immunotherapy in a "neoadjuvant" fashion, as he is not sure if he will ever consent to the definitive amputation of that right leg. As a center, we are now checking PDL-1 expression via IHC on all undifferentiated pleomorphic sarcomas, even though there is no published correlation between response to immunotherapy in sarcoma and expression of PDL-1 via IHC. After the experiences with these first four patients, we are more likely to push for off-label use of immunotherapy (even up front, before conventional chemotherapy) if the patient's sarcoma expresses high levels of PDL-1 (defined by >50% cells). Although a different scenario, neoadjuvant use of immunotherapy in non-metastatic resectable undifferentiated pleomorphic sarcomas is being explored in an ongoing phase II trial by Dr Roland and her team at MD Anderson. Certainly, evolving data using neoadjuvant immunotherapy in other tumor types looks promising. The hope is that we can start piecing together all of these rather small experiences to get better understanding of how best to utilize immunotherapy in undifferentiated pleomorphic sarcomas. Based on SARC 028 and subsequent expansion cohorts presented at ASCO 2019, we are not as enthusiastic in liposarcomas. We would hesitate in exploring off-label immunotherapy use in sarcomas that do not express high levels of PDL-1, with the exception being alveolar soft part sarcoma. The ongoing DART trial, using dual immunotherapy in rare tumors, now has a new cohort specifically for PDL-1 amplified tumors not otherwise specified; we will be looking at enrolling in that trial for these sarcomas that do not otherwise have a cohort available.

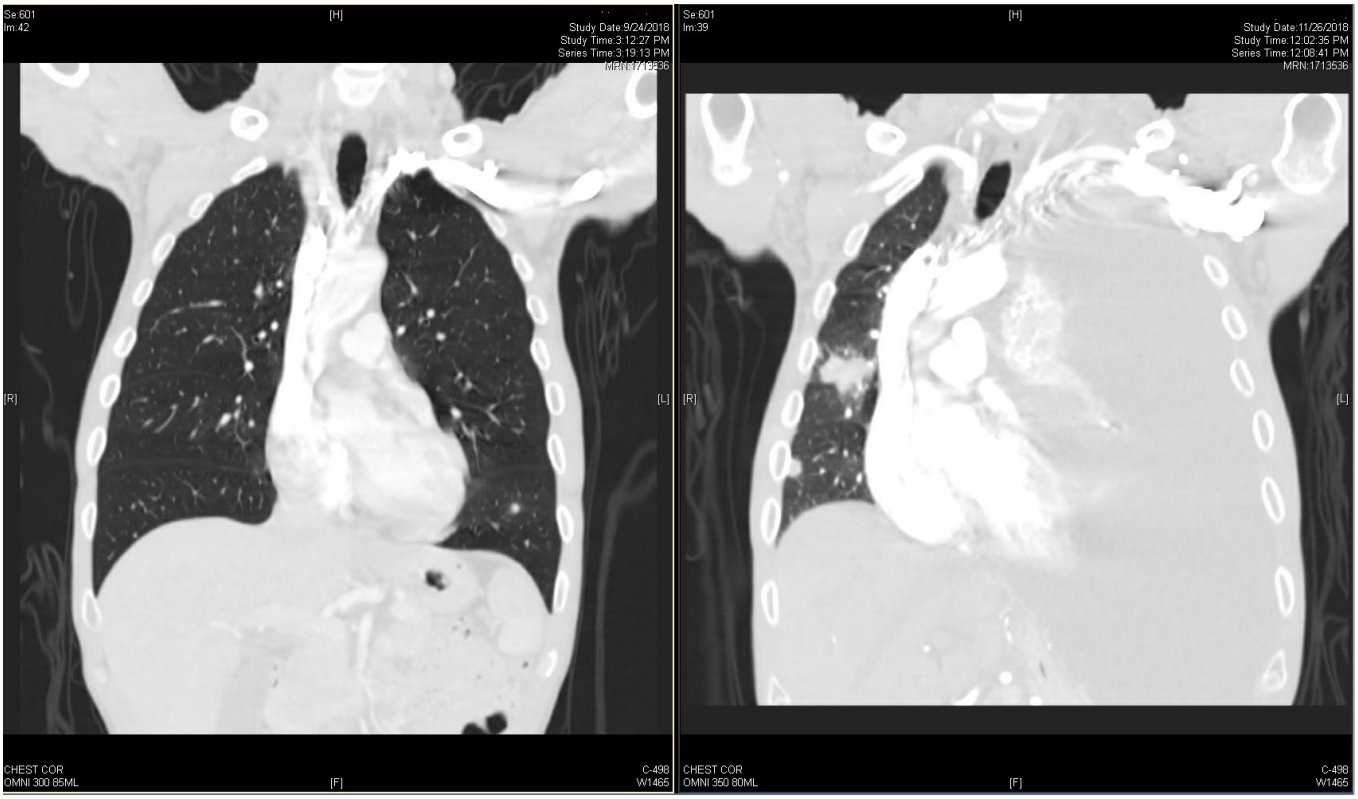
Differing responses in metastatic undifferentiated pleomorphic sarcoma tried on pembrolizumab

Age	Sex	Primary site	Size	*PDL-1	Local treatment	Metastatic at diagnosis	Metastatic sites	Other systemic therapy	Clinical course
84	F	Thigh	7.2cm	60%	XRT --> surgery	Yes	Lung, spine	No, too frail to try chemotherapy	Partial response, then mixed response at 9 months including burst fracture in L2 vertebrate; died 11 months after immunotherapy started
59	M	Thigh	28.2cm	15%	XRT --> surgery	Yes	Lung, spine, pleural fluid	No, resistant to trying chemo	Rapidly progressive after 3 cycles of Keytruda; died 3 months after immunotherapy started
68	M	Femur	4.2cm	80%	None to date	Yes	Femur, tibia, fibula	No, resistant to trying chemo	Partial response to immunotherapy after five months; continues on pembrolizumab now
53	M	Thigh	21.4cm	10%	XRT --> surgery	Yes	Lymph nodes, lung, pleural fluid	No, resistant to trying chemo	Rapidly progressive even before starting immunotherapy, died after 2nd cycle pembrolizumab

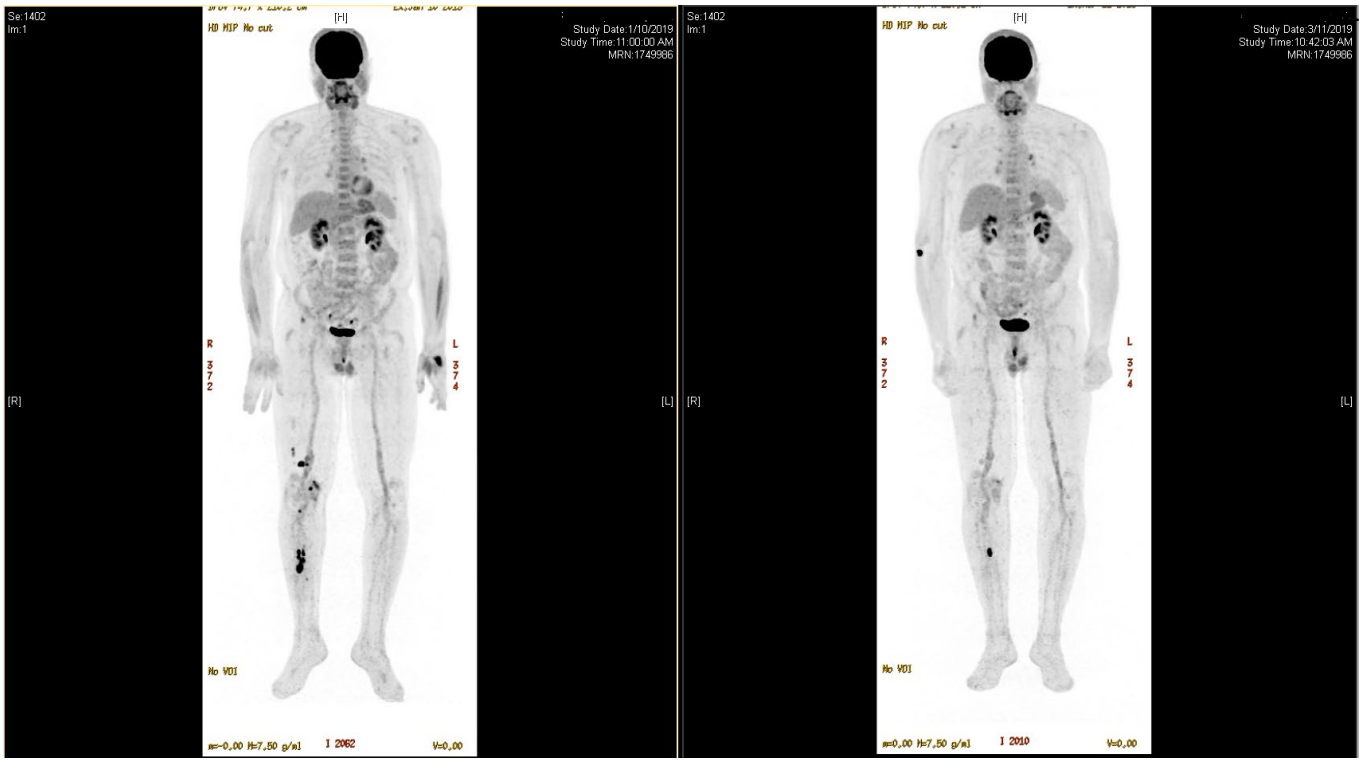
*PDL-1 expression was carried out via immunohistochemistry on primary tumor cells, not metastatic site, using DAKO PD-L1 IHC 22C3 pharmDX.



PDL-1 expression was carried out via immunohistochemistry on primary tumor cells, not metastatic site, using DAKO PD-L1 IHC 22C3 pharmDX. The patient in left lower quadrant with PDL-1 expression 80% is the one with ongoing response.



59 yo M with PDL-1 expression of 15% on primary UPS of left thigh with metastatic disease to lungs at diagnosis. He was started on pembrolizumab early Oct 2018. CT scans show rapidly progressive disease in lungs/pleura after 3 cycles (Sept 2018 - left; Nov 2018 - right). He died 3 months after starting immunotherapy.



68 yo M with PDL-1 expression of 80% on an undifferentiated sarcoma involving the right femur with metastatic deposits in right fibula, right tibia and further up the same femur. When faced with definitive amputation as his surgical option, he decided to start upfront pembrolizumab in January 2019. PET scan images from Jan 2019 (left) compared to March 2019 (right) show partial response already.

Poster #158 3253907

MOLECULAR THERAPY FOR SOFT TISSUE SARCOMA

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Objective: Soft tissue sarcoma is a rare tumor, and its therapeutic development is not always satisfactory. Soft tissue sarcoma is a miscellaneous group of various histological types, and its biological properties are also diverse. In many solid tumors including lung cancer, detection of various genetic abnormalities and development of accompanying molecular targeted drugs have advanced. The NTRK fusion gene is a therapeutic target that holds expectation in such a situation, and the effectiveness of positive cases in soft tissue sarcoma and entrectinib, larotrectinib, etc. as therapeutic drugs are reported.

Methods: Genetic panel test results in a large-scale cohort have been reported, but its effectiveness is still limited at present. The NTRK fusion gene is a therapeutic target that holds expectation in such a situation, and the effectiveness of positive cases in soft tissue sarcoma and entrectinib, larotrectinib, etc. as therapeutic drugs are reported. At the National Cancer Center East Hospital, we have conducted genetic panel testing for screening NTRK fusion genes using RNA-based next generation sequencing. Histologically confirmed advanced solid tumor including soft tissue sarcomas were eligible. Written informed consent was obtained from all patients. From FFPE samples RNA was extracted. Archer FusionPlex was used to explore NTRK fusions.

Results: A total of 106 patients were enrolled to our screening study. Samples were available in 88 patients, including 38 breast cancer, 13 soft tissue sarcoma, 11 genuitary cancer, 6 cancer of unknown primary, and 19 others. However none of the patients had NTRK fusions. One BRAF fusion and one PPARG fusion was detected. Most frequently detected potentially druggable mutaitons were PIK3CA mutation and AKT1 mutations. One patient with BRAF mutation participated in investigational drug study.

Conclusion: Although no NTRK fusion was detected in our study, the continuous effort is required as the reported incidence of NTRK fusion across tumor types is below 0.5%. Outline of molecular medicine in soft tissue sarcoma, focusing on the effectiveness of entrectinib on the NTRK fusion gene will be discussed.

Poster #159 3256526

CELL CYCLE CHECKPOINT INHIBITION SYNERGIZES WITH MITOTIC SPINDLE INHIBITION IN LEIOMYOSARCOMA

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Objective: Leiomyosarcoma (LMS) is a soft tissue sarcoma with limited treatment options available to patients. Mitotic spindle inhibitors (MI) are a standard of care therapy for LMS; however, only a minority of patients respond to treatment. Data from other tumors suggest the efficacy of MIs depends upon G2/M checkpoint status to effectively exert their effect. Cell cycle alterations in the G1/S checkpoint are a common feature of LMS. We therefore set out to determine whether additional modulation of cell cycle checkpoints would alter the efficacy of the MIs in LMS.

Methods: Genomic data of G1/S genes were obtained from The Cancer Genome Atlas with corresponding survival data. Four cell lines (3 brought into culture from patients: Leio-012, LMS-117, LMS1, Leio-196A and commercial cell line SK-LMS1) were treated with eribulin and paclitaxel using XTT proliferation assays to determine IC50 dosages. Pharmacologic perturbation of the cell cycle G1/S checkpoint was conducted using the CDK4/6 inhibitor palbociclib and G2/M using the WEE1 inhibitor adavosertib. Cell cycle status was quantified with Propidium Iodide (PI) staining and flow cytometry. Protein expression was measured by western blot and processed in Image Studio Lite. Synergy determination as defined by cooperativity index (CI) was performed using CalcuSyn and descriptive statistics were calculated using GraphPad Prism 6.0.

Results: A G1/S and G2/M cell cycle signature were computed based on RNA-sequencing data. The G1/S signature demonstrated a survival difference in the LMS population. SKLMS1 and Leio-196A were sensitive to MIs (IC50<5nM) while Leio-012 and LMS-117 were resistant (IC50>25nM). RNA-seq shows *CDKN2A* alterations in both MI sensitive cell lines. Treatment in vitro with CDK4/6 inhibitor palbociclib effectively abrogated the G1/S transition and was antagonistic with eribulin across all cell lines (CI > 1). Conversely, the WEE1 inhibitor adavosertib abrogated the G2/M transition and was highly synergistic in combination with eribulin (CI<1).

Conclusion: Inhibition of the G2/M checkpoint with adavosertib synergizes with MI in leiomyosarcoma, independent of mutations in the G1/S which are variable. More complete understanding of phenotypic markers for MI sensitivity may help improve therapy selection for patients. Further study is necessary to confirm these findings.

Poster #160 3258092

HIGH-THROUGHPUT DRUG SCREENING OF PATIENT-DERIVED TUMOR ORGANOIDS FROM OSTEOSARCOMA PULMONARY METASTASES

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Objective: Tumor organoids recapitulate many features of the cancer they are derived from and are considered accurate preclinical models to rapidly predict drug response in patients. We have developed a fully optimized high-throughput screening approach to test the response of tumor organoids to hundreds of therapeutic agents (Phan et al, Communications Biology, 2019). Our well-established system is particularly relevant for patients with osteosarcoma pulmonary metastases. Prognosis is poor for the population of patients with recurrent pulmonary metastases, and existing therapeutic options – including repeated thoracotomies and second-line/salvage chemotherapies – are both morbid and controversial in terms of efficacy. Our functional profiling method aims to select effective and personalized therapies, as well as shed light on the tumor biology of synchronous and metachronous osteosarcoma pulmonary metastases.

Methods: Patient tumors were obtained fresh from pediatric osteosarcoma pulmonary metastasectomy cases, processed to single cell suspension and seeded in Matrigel or BME in 96 well plates following our established mini-ring methodology. Organoids were grown for 3-5 days then treated twice using a library of up to 430 investigational and FDA approved compounds. After the samples were exposed to drugs for 48 hours, we assessed response by measuring cell viability (ATP release assay). We also validated the models by comparing organoid histology to that of the original tumor.

Results: We collected fresh tumor tissue from four osteosarcoma patients undergoing lung metastasectomies. Specimens collected include multiple metachronous and synchronous pulmonary metastases from individual patients. In one patient who underwent resection of pulmonary metastases (Lung met #1) followed by additional systemic therapy and a second operation seven months later for recurrent pulmonary metastases (Lung met #2), drug sensitivity and resistance patterns differed significantly for metachronous pulmonary metastases. Organoids created from Lung met #1 and Lung met #2 were screened for response to 223 and 430 drugs, respectively. We observed a fairly divergent drug sensitivity profile across lesions. (Table 1) Lung met #1 showed a response to 3% of drugs tested (8/223 inducing ≥ 50% cell death), with 3/8 (37.5%) of these drugs inducing over 75% cell death. These were mostly EGFR or VEGFR inhibitors. Lung met #2 showed a similar overall response rate (3% or 13/430 inducing ≥ 50% cell death), with only 1/13 (7.7%) of these drugs causing ≥ 75% cell death. Effective drugs included inhibitors of FAK, PKC, IGF-1 and EGFR. Considering the subgroup of 223 overlapping drugs, Lung met #2 had an increase in drug resistance, with 1.8% of drugs tested causing ≥ 50% cell death vs 3% for Lung met #1.

Drug	Target	Cell death (%)
Lung Met #1		
Staurosporine	PKC, PKA, PKG, S6K, CaMKII	85
WZ8040	EGFR	85
Pelitinib	EGFR, HER2, Src, MEK/ERK, Raf	82
OSI-930	c-Kit, VEGFR	72
KU-0063794	mTOR	68
Cediranib	VEGFR, Flt	63
BX-912	PDK-1	52
CUDC-101	HDAC, EGFR, HER2	49
Sorafenib Tosylate	VEGFR, PDGFR, Raf	49
Lung Met #2		
Staurosporine	PKC, PKA, PKG, S6K, CaMKII	91
Bosutinib	Src, Bcr-Abl	69
Pluripotin (SC1)	ERK, MAPK3, RasGAP	69
Midostaurin	PKC, FLT3	67
BMS-536924	IGF-1R, FAK, MEK, LCK	59
Afatinib	EGFR (wt & mut), HER2, HER4	58
PF-431396	FAK, PYK2	57
Go 6983	PKC	56
Omipalisib	mTOR, p100	55
Pelitinib	EGFR, HER2, Src, MEK/ERK, Raf	53
P276-00	CDK (1,4,9), GSK-3β	50

Conclusion: We have successfully established organoids from osteosarcoma pulmonary metastases to yield biologically and therapeutically relevant models. Results of our high throughput functional screening may enable more personalized, effective systemic therapies as well as elucidate mechanisms of drug resistance and tumor biology in the understanding of synchronous and metachronous pulmonary metastases.

Poster #161 3256197

DEVELOPMENT OF AN *IN VITRO* DRUG PROFILING PLATFORM TO TAILOR PATIENT-SPECIFIC SARCOMA TREATMENTS

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Objective: Cancer therapy currently shifts from broadly used cytotoxic drug cocktails to patient-specific precision therapies. These typically are directed towards druggable driver oncogenes, which are available in only a subset of cancers. Drug profiling of cultured tumor cells could circumvent these limitations, but suitable platforms are largely unavailable for most cancer entities.

Methods: Here, we established an *in vitro* drug profiling platform for sarcoma, using both cells isolated from patient-derived xenografts (PDX) and patient tumor biopsies. Optimized culture conditions allow growth of cells in both 2D or 3D format.

Results: Under optimized conditions, cells preserve the phenotypic and molecular characteristics of the primary PDX, as shown by aCGH, RNAseq and methylation profiling. Beside a general incompatibility with serum, we also observed intolerance of bFGF stimulation in a subset of fusion-negative rhabdomyosarcoma (RMS), Ewing and Ewing-like sarcoma even when FGFR4 is mutated, suggesting that FGFR signaling network is more complicated than previously anticipated. Drug profiling revealed a surprisingly heterogeneous spectrum of responses of largely patient-specific vulnerabilities including a yet unrecognized sensitivity of RMS samples towards AKT inhibitors. We observed no differences in responses when cells were cultured in 2D versus 3D.

Conclusion: Overall, our study highlights the feasibility of *in vitro* drug profiling of primary sarcoma cells for patient-specific treatment selection in a co-clinical setting.

Poster #162 3254985

PATIENT-CENTERED CARE AT THE NEW KAROLINSKA UNIVERSITY HOSPITAL SARCOMA CENTER IMPROVED CONTINUITY AND THE ROLE OF THE CONTACT NURSE

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Objective: In 2016 while planning for the new hospital building of the tertiary referral hospital of the Karolinska University Hospital in Stockholm, a new thematic organization model was introduced, The new hospital was named New Karolinska Hospital (NKS) and clinics have gradually been replaced into patient-centered focus themes. In these themes, the patients journey throughout the health care system is the core of how we operate as a care-giving organization. A Sarcoma Center already existed as a virtual health care unit, but operated jointly by three different organizations and from different locations within the old hospital building. At the new locations at NKS, the now organization brought together all the relevant disciplines; tumor orthopedics, abdominal surgery and sarcoma oncology. Medical doctors, contact nurses and assistant nurses of these disciplines are now sharing the same outpatient department and are working closely together even though operation rooms for tumor orthopedics and abdominal surgery are separated.

Methods: Nurses and assistant nurses are sharing offices and the inter-discipline co-operation has increased immensely. For example after a surgeon or tumor orthopedic surgeon has informed a patient that the multidisciplinary conference has recommended oncological treatment, the patient will directly meet the oncology team and get a treatment and rehabilitation plan based on the information/diagnosis the patient received from the earlier caregiver. The patient will instantly receive an appointment with the oncologist and the name and contact information of the sarcoma oncology Contact Nurse for further information.

Results: Wound care is coordinated by nurses and assistant nurses at the outpatient department of the sarcoma center whereas surgical wounds, tumor wounds and post radiation reactions are frequent and require specialized treatment and are given at the ward.

Conclusion: The chemotherapy outpatient department is situated on the same loor, right in the middle of the outpatient department, and is presented for the patient in order to give the patient a view into where their treatment will be given. A floor below there an impatient department hosting patients under the care of both abdominal surgeons and oncologists.

In our experience the patients are overall satisfied with the new organization and they particularly like the active handover between the different teams. Having all the disciplines gathered and collaborating creates a sense of security to them and we feel its helping us to give a more individualized and person-centered care.

Poster #163 3256277

A CROSS-SPECIES PERSONALIZED MEDICINE APPROACH TO TREAT LEIOMYOSARCOMA

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Objective: Cancer drug discovery is an inefficient process, with more than 90% of newly discovered therapies failing to gain regulatory approval. Patient-derived models of cancer offer a promising new approach to identify new treatments; however, for rare cancers, such as sarcomas, access to patient samples is limited, which precludes development of patient-derived models. To address the limited access to patient samples, we have turned to pet dogs with naturally-occurring sarcomas. Although sarcomas make up less than 1% of all human cancers, sarcomas represent 15% of cancers in dogs. Dogs have intact immune systems, an accelerated pace of cancer progression, and a shared environment with humans, making them ideal models that bridge gaps between mouse models and human cancers.

Methods: Here, we developed a cross-species personalized medicine pipeline to identify new therapies for sarcomas. We tested this paradigm through the study of a pet dog, Teddy, who presented with six synchronous leiomyosarcomas. Using our pipeline, we identified proteasome inhibitors as a potential therapy for Teddy.

Results: Teddy was treated with bortezomib and showed a varied response across tumors. Whole exome sequencing revealed substantial genetic heterogeneity across Teddy's recurrent tumors and metastases, suggesting that intra-patient heterogeneity was responsible for the heterogeneous clinical response. Ubiquitin proteomics coupled with exome sequencing revealed multiple candidate driver mutations in proteins related to the proteasome pathway.

Conclusion: Together, our results demonstrate how the comparative study of canine sarcomas offers important insights into the development of personalized medicine approaches that can lead to new treatments for sarcomas in both humans and canines.

Poster #164 3256378

QUANTIFICATION OF SERUM LEVEL OF CIRCULATING DNA AND DNASE I IN LOCALLY ADVANCED AND METASTATIC SYNOVIAL SARCOMA, PILOT STUDY. CORRELATION WITH RESPONSE TO TREATMENT

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Objective: To determine that changes in the serum concentration of circulating DNA and DNAse I as well as the activity of the latter in patients with locally advanced synovial sarcoma predict recurrence; and in metastatic are predictors of response to treatment.

Methods: It is a pilot study: (prospective, observational, comparative).
First-time patients with the diagnosis confirmed by histopathological report plus cytogenetics of synovial sarcoma of the external consultation of the medical oncology service sarcomas of the National Institute of Cancerology for the period from September 1, 2016 to September 1, 2018. The double of healthy volunteers will be analyzed.

Older than 18 years
Patient with confirmed histopathological diagnosis of synovial sarcoma with positive cytogenetic study for t (X; 18).

Patients in clinical stages III and IV.
Patients who agree to be part of the study prior signed informed consent. All the subjects of the study will be extracted 15 ml of peripheral blood and serum and plasma will be isolated in which the corresponding determinations will be made of the concentration and the analysis of some molecular markers related to the synovial sarcoma in the circulating DNA.

The following patients were taken blood samples: Patients candidates for adjuvance, prior to the start of the tx, at the end of the systemic treatment and the first recurrence. Metastatic or unresectable patients: before the first line of systemic treatment or QT of induction and after every three treatment cycles. In case of being subjected to surgical control, it will be taken 4 to 8 weeks after surgery. Extraction of circulating DNA was isolated from the serum samples. (Washes phenol-chloroform) Its concentration was determined by fluorometry. The concentration of DNAse I was quantified by the quantitative ELISA method. The activity of DNAse I in the plasma will be determined by the flourescence method. The tissue available in the pathology department (paraffin blocks) of the patient will be analyzed to determine molecular markers (SYT-SSX1, SYT-SSX2, SYT-SSX4) of genomic DNA and compare them with those of circulating DNA.) The analysis of the molecular markers of the postreatment patients will also be done, from the circulating DNA of the serum samples. By standard PCR / FISH method determining the presence or absence of the aforementioned genes.

Statistics: Central tendency measurements (mean +/- SD) of the cDNA / DNAse I concentration determinations were made and compared with the central tendencies of the control group by parametric (Chi square) and nonparametric tests.

Results: Differences in cDNA concentration in patients with synovial sarcoma vs healthy volunteers. Differences in the concentration of DNase I in patients with synovial sarcoma vs healthy volunteers. Differences in cDNA concentration between patients with synovial sarcoma with locally advanced and metastatic disease vs healthy volunteers. Differences in the concentration of DNase I between patients with synovial sarcoma with locally advanced and metastatic disease vs healthy volunteers. Significant decrease in DNA and DNAse I levels in patients who responded to doxorubicin chemotherapy.

Conclusion: This is the first prospective study (Mexico) that currently includes 16 patients, which compares the determination of serum levels of cDNA and DNase I in patients with the diagnosis of synovial sarcoma with healthy individuals. There is a significant difference when comparing basal cDNA serum levels between patients and the control group p: 0.0015. As far as we know this is the only report in the Latino population. In addition, these results show that serum cDNA levels determine the biological behavior of the tumor.

Poster #165 3241353

PATIENT BURDEN AND MEDICAL CARE OF SARCOMA IN GERMANY: NATIONWIDE COHORT STUDY FOCUSING ON MODIFIABLE DETERMINANTS OF PATIENT-REPORTED OUTCOME MEASURES IN SARCOMA PATIENTS (PROSA) - BASELINE DESCRIPTION

Bernd Kasper, MD, PhD[1]*; Peter Hohenberger*[1]*; Martin Eichler*[2]*; Stephan Richter*[2]*; Andreou Dimosthenis*[3]*; Daniel Pink*[4]*; Henriette Golcher*[5]*; Stephen Fung*[6]*; Eva Wardelmann*[7]*; Karin Arndt*[8]*; Leopold Hentschel*[9]*; Maria Eberlein-Gonska*[10]*; Martin Bornhäuser*[9]*; Jochen Schmitt*[12]*; Markus Schuler*[11]

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Objective: Sarcoma treatment challenges clinical care and research because of a complex diagnostic and treatment algorithm and a high disease burden. There is scarce knowledge about the real-world situation of sarcoma care in Germany such as compliance to treatment guidelines and the quality of care. Moreover, little is known about quality of life (QoL) and other patient-reported outcomes (PRO).

Methods: We established a German nationwide study-network in 2017 and conducted a prospective cohort study between 09/2017 and 01/2019. We included adult bone and soft tissue sarcoma patients based on the WHO Classification of Tumours of Soft Tissue and Bone (4th Edition). Clinical data on patient- and institutional-level and PRO via standardized and self-developed questionnaires were collected online or via mail at 0, 6 and 12 months after recruitment. Study data were managed using REDCap electronic data capture tools. Standards of care were determined based on established guidelines and with the help of expert consultations. For the measurement of patient reported outcomes, we used established validated instruments. At baseline we assessed quality of life (EORTC QLQ-C30), psychological distress (PHQ 4), pain (BPI), physical activity (BSA) and treatment decision making (CPS). Baseline clinical data collection closes in 06/2019. Final descriptive baseline results will be presented at the conference.

Results: 1309 patients were recruited in 60 German study centers (office-based practices and hospitals of all kind). 1111 patients returned questionnaires. Recruitment rate ranged from 55 % to 80 % in the various centers. Mean age was 53.2 years (SD: 17 years). 48 % of patients were female, 30 % were diagnosed until 2013, 30 % between 2014 and 2016 and 40 % in 2017 or after. 70 % of the patients had soft tissue sarcoma, 18 % bone sarcoma and 12 % GIST. The largest histological subgroups were liposarcomas with 18 %, undifferentiated/unclassified sarcomas with 15 %, fibro-/myofibroblastic tumors with 11 % und leiomyosarcomas with 11 %. 74 % were in a curative treatment situation. Excluding GIST, 59 % were diagnosed with a high-grade sarcoma (17 % low-grade, 24 % unknown/not applicable). 33 % of the patients were under treatment at the time of recruitment. 86 % had at least one surgery, 44 % at least one chemo- and 37 % at least one radiotherapy treatment.

Conclusion: PROSa will provide detailed information on the quality of care and guideline adherence in Germany as well as PRO. The study supports the identification of potentially insufficient healthcare structures as well as potentially vulnerable groups. Ultimately, it might contribute to an optimization of healthcare service for adult sarcoma patients in Germany.

Poster #166 3253141

DEVELOPING HOLISTIC PERSONALISED MODELS OF REHABILITATION TO OPTIMISE SURVIVORSHIP OUTCOMES AFTER TREATMENT FOR LOWER EXTREMITY SARCOMA – A FEASIBILITY STUDY

Sherron Furtado, PhD[1]*; Silvia Del Din*[2]*; Jan Lecouturier*[3]*; Rana Zia Ur Rehman*[2]*; Kenneth Rankin*[4]*; Lynn Rochester*[2]*; Craig Gerrand*[1]

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Objective: The objective was to assess the feasibility of developing holistic personalised rehabilitation plans (PRPs) using structured rehabilitation problem-solving (RPS) assessments (Steiner et al., 2002) [based on the International Classification of Functioning, Disability and Health (ICF)] in patients treated for lower extremity sarcomas.

Methods: This was a prospective study of 11 patients treated for lower extremity sarcoma. Patients underwent an RPS assessment using impairment (Musculoskeletal Tumor Rating System (MSTS)), disability (Toronto Extremity Salvage Scale (TESS)), quality of life (Quality of Life-Cancer Surviors (QoL-CS)) scales, interviews, instrumented testing of balance and gait in the clinic and 7 day community monitoring using a body worn monitor (BWM)/activity monitor (Axivity AX3). Domains of the RPS map to commonly used interventions (e.g: impaired --> balance balance rehabilitation, reduced physical activity levels --> activity reminders). PRPs were developed for each patient, based on their RPS assessment.

Results: It was feasible to perform RPS assessments (Figure 1) and develop PRPs using traditional measures and data from Axivity in patients treated for lower extremity sarcoma. Patient outcomes were compared to healthy controls using visual inspection/graphical methods (Figure 2) which confirmed that multiple domains of physical function (balance, gait, disability, physical activity, QoL) are affected after sarcoma treatment. An RPS assessment was effective in capturing patient preferences and goals. The RPS also detected other less commonly captured problems such as falls, psychological issues, weight gain, diet, lymphedema, fatigue, pain, and a lack of information about community centres, disability sport and driving. Patients were directed to relevant support based on issues identified during the process. RPS assessments provide a holistic evidence-based framework of care and could provide valuable insights into information about rehabilitation strategies and goal setting. However, PRPs had to be adapted during treatment because of complications or disease progression.

Conclusion: RPS assessments to develop PRPs for patients after sarcoma are feasible and highlight issues not routinely monitored yet important to patients. Each PRP was delivered successfully, and was refined during the clinical journey. The implementation of RPS assessment in routine clinical practice may require further refinement.

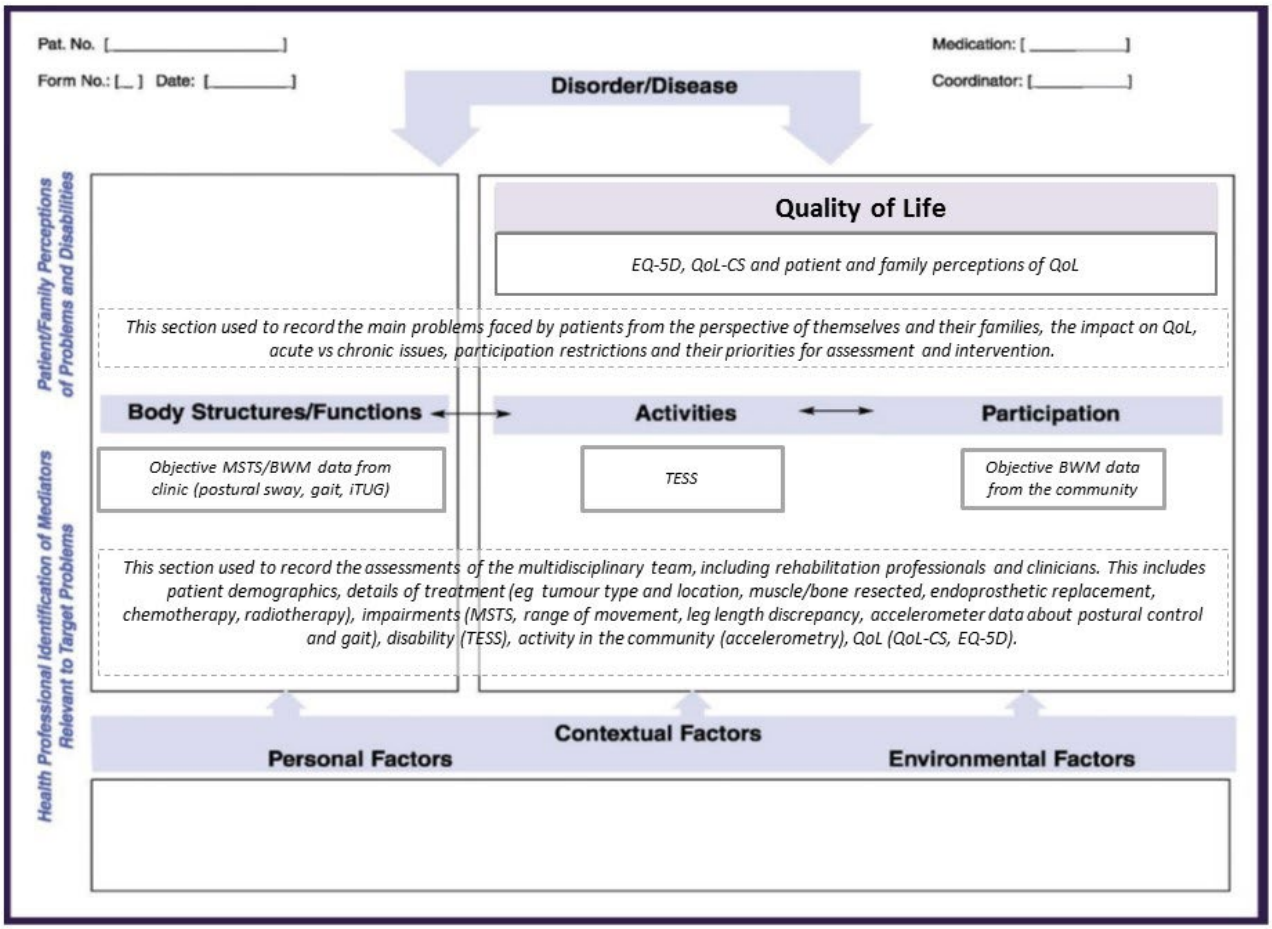

Figure 1: Example of a Rehabilitation problem-solving (RPS) assessment after treatment for lower extremity sarcoma

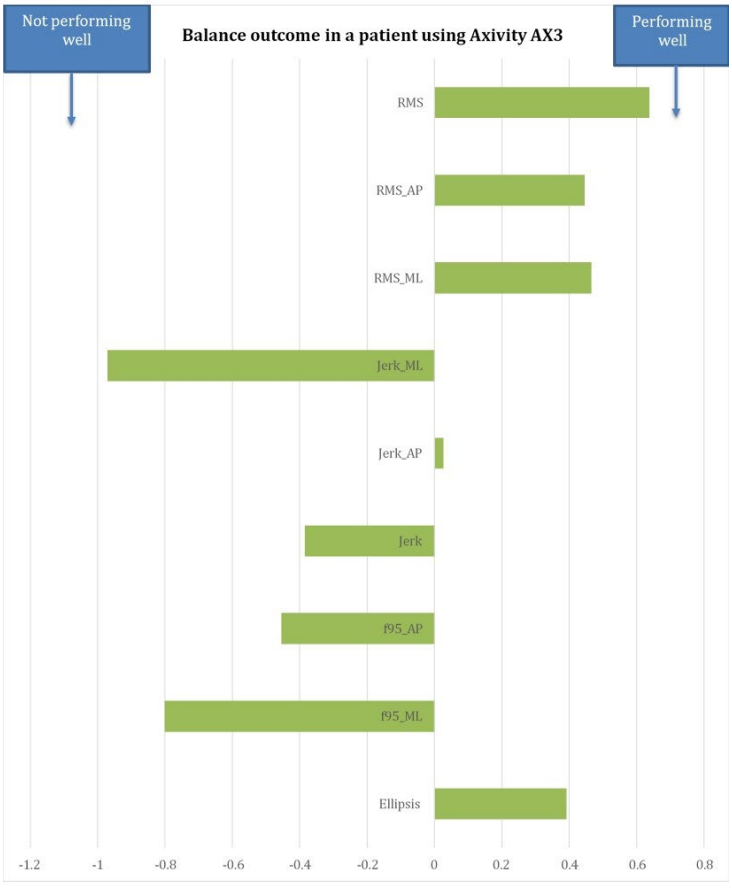

Figure 2: Graphical method - Visual representation to identify balance outcomes in which a patient is performing well (unaffected) and not performing well (affected)

Poster #167 3253147

CAN HOLISTIC PERSONALISED MODELS OF REHABILITATION IMPROVE SURVIVORSHIP OUTCOMES AFTER TREATMENT FOR LOWER EXTREMITY SARCOMAS? A PRELIMINARY EFFICACY STUDY

Sherron Furtado, PhD[1]*; Silvia Del Din*[2]*; Jan Lecouturier*[4]*; Rana Zia Ur Rehman*[2]*; Kenneth Rankin*[3]*; Lynn Rochester*[2]*; Craig Gerrand*[1]

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Objective: Treatments for sarcoma lead to a wide range of impairments, disability and participation restrictions, however rehabilitation services after sarcoma are highly variable. A personalised holistic evidence-based approach towards rehabilitation delivery might be effective in improving survivorship outcomes. The objective of this study is to investigate whether PRPs were effective in improving survivorship outcomes in patients with lower extremity sarcomas.

Methods: 11 patients treated for lower extremity sarcoma were included in a prospective study. Patients underwent RPS assessments (Steiner et al., 2002) using impairment (Musculoskeletal Tumour Society System (MSTS)), disability (Toronto Extremity Salvage Score (TESS)), quality of life (Quality of life-Cancer survivors (QoL-CS)), modified re-integration into normal living (mRNL) scales, balance, gait and walking physical activity assessments using Axivity AX3. Based on the domains of the RPS form affected; PRPs were developed for each patient in a structured manner. Pre-intervention and post-intervention scores were compared to assess the preliminary efficacy of PRPs on survivorship outcomes.

Results: Patients' mean age and BMI were 50.3±18.7 years and 31.6±6.7 respectively. Out of 11 patients, 5 with bone sarcomas and 6 with soft tissue sarcomas located in the above knee region (8) and below knee region (3) were treated with limb sparing surgery (8) and amputation (3). 5 patients were in the acute post-operative phase and 6 were>6 months post-treatment. PRPs significantly improved re-integration into normal living, swing time, step velocity, mean walking bout length and variability in the community ($p<0.05$). mRNL scores increased from 64.8±17.5 to 73.9±21.1, p=0.019* (scores difference=9.10) (Figure 1); swing time reduced from 0.5±0.1 to 0.4±0.8, p=0.032* (scores difference=0.09); step velocity increased from 1.0±0.1 to 1.1±0.7, p=0.018* (scores difference=0.12); mean walking bout length time increased from 17.8±4.0 to 19.9±3.4, p=0.029* (scores difference=2.13) (Figure 2); variability increased from 0.87±0.10 to 0.92±0.07, p=0.032* (scores difference=-0.04). The PRPs did not change balance outcomes, MSTS, TESS and QoL.

Conclusion: These preliminary results support the efficacy of PRPs in improving survivorship outcomes for patients treated for sarcomas. Patients experienced better re-integration into their normal living environment, reduced time in the gait cycle, increased walking pace, and increased average walking time in each bout of ambulatory activity, and an increased variation in longer and shorter bouts. There is a need for intervening at multiple time points during the clinical pathway to optimise patient outcomes.

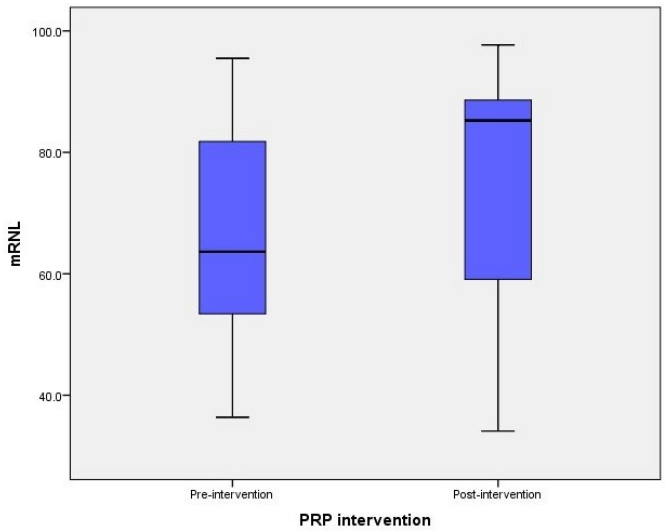

Figure 1: Boxplots to represent differences in mRNL outcome pre and post PRP intervention

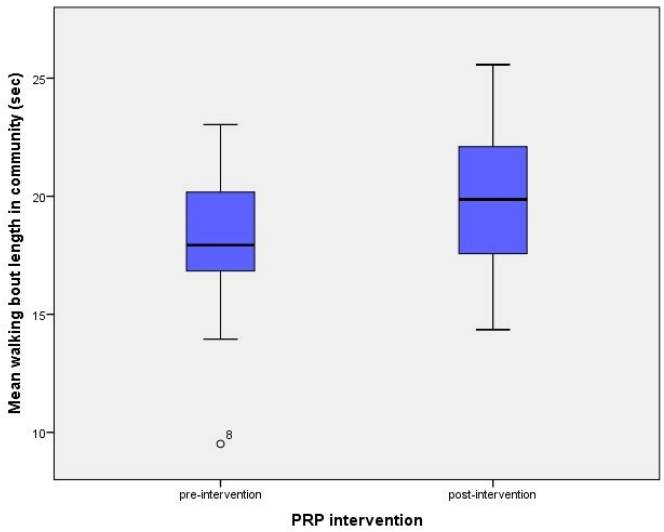

Figure 2 - Boxplots to represent differences in mean walking bout length in community outcome pre and post PRP intervention

Poster #168 3253216

INCORPORATING THE PATIENT VOICE IN SARCOMA RESEARCH: HOW CAN WE ASSESS HEALTH-RELATED QUALITY OF LIFE IN THIS HETEROGENEOUS GROUP OF PATIENTS?

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Objective: Although the clinical effectiveness of sarcoma treatment in general has improved, long-lasting and cumulative treatment side-effects may often detract from the overall marginal advantage. Information only on survival is insufficient to determine the net clinical benefit of a treatment. It is important to assess treatment effectiveness both in terms of objective outcomes (e.g., response, recurrence and survival) and in terms of subjective patient reported outcomes (PROs), including health-related quality of life (HRQoL).

There is limited high-quality HRQoL data in sarcoma. Previous studies have predominantly used generic HRQoL instruments, which cover some relevant issues but do not capture all the unique experiences of patients with sarcoma, and thus lack content validity. A sarcoma-specific questionnaire should be able to detect, with more sensitivity, side-effects, symptoms and problems with function that are particularly relevant to patients with sarcoma. To date, there is no specific sarcoma HRQoL instrument available; and, given the heterogeneity of the disease in terms of subtype, location, age and treatment, the development of such an instrument may be challenging.

The aim of this collaborative project between the EORTC Quality of Life Group (QLG) and the EORTC Soft Tissue and Bone Sarcoma Group (STBSG) is to raise the standard of HRQoL measurement in patients with sarcoma. An important question remains to be answered: Is it possible to develop one PRO questionnaire covering HRQoL issues that are relevant to all adult patients with sarcoma, or are the HRQoL issues related to the different localization / treatment sufficiently different to warrant the creation of separate item lists selected from the EORTC QLG Item Library?

Methods: We will follow the EORTC QLG questionnaire development guidelines. First, a search of the academic literature will be performed to identify all relevant HRQoL issues for and existing HRQoL questionnaires currently used among patients with sarcoma. In parallel, semi-structured interviews will be conducted worldwide with patients with sarcoma (N=154) and health care professionals (HCPs; N=30; phase 1a). The patient sample will be stratified to capture diversity across the sarcoma population with regard to tumour location (extremities, axial, head and neck, thorax, retroperitoneal/ intra-abdominal and gynecological), stage (localized vs. metastatic disease), type or lines of treatment, age and gender. This list of HRQoL issues generated by the a) literature search, b) relevant items from the Item Library, and c) semi-structured patient and HCP interviews, and will be consolidated into a comprehensive list of issues for all languages of collaborating countries.

In phase 1b, the new list of HRQoL issues will be presented to another group of patients with sarcoma (N=475) and HCPs (N=30). Patients and HCPs will be asked to rate the HRQoL issues on relevance (4point Likert scale) and to prioritize the 25 most important issues.

Results: The literature search resulted in 3951 hits, of which approximately 200 were relevant articles. Twenty-nine different generic HRQoL and 14 functional instruments were used in previous studies. Twenty-one study centres in eleven countries participate in this study and are at various stages of analysis (Australia, Cyprus, Germany, the Netherlands), some are still in the process of obtaining ethical approval (Canada, Greece, France, Italy, Poland, Spain, United Kingdom). Currently we have interviewed 35 patients and 13 HCPs. Results of the phase 1a study will be presented during CTOS 2019.

Conclusion: PROs including HRQoL are an essential component in determining the net clinical benefits of a treatment for sarcoma. This study will provide information regarding the optimal measurement strategy of HRQoL in clinical sarcoma research and practice.

Poster #169 3255137

KNOWLEDGE OF PATIENTS WITH SARCOMA FOR THEIR ILLNESS IN AN INDIAN SETTING (KNOWSARC STUDY)

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Objective: The data on patient awareness of the specific diagnosis, causative factors and their understanding of sarcoma and its course is hardly reported in literature. Objective of our study was to know the understanding of sarcoma patients in a dedicated Sarcoma Medical Oncology Clinic in a tertiary care centre in North India.

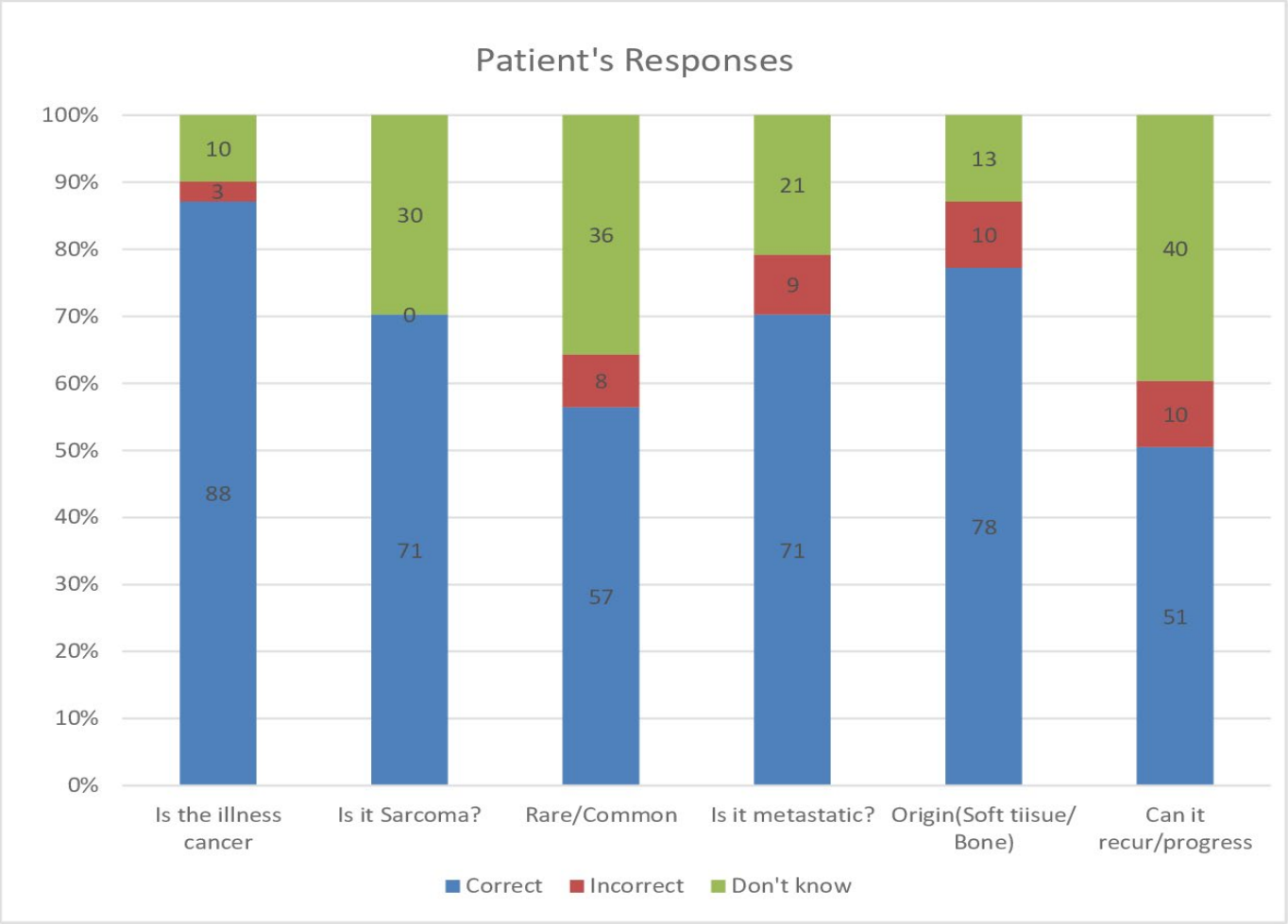
Methods: It was a prospective cross-sectional questionnaire-based study from 1st May 2019 to 15th June 2019 of all patients who came to Out Patient Department in Sarcoma Medical Oncology Clinic and gave consent to participate in study. As a routine, all patients coming to the OPD are counselled about the disease and outcomes with therapy. There are regular educational sessions with active interaction with patients. Ethical clearance was taken from IEC. A questionnaire was prepared both in English and local language (Hindi) which asked patients whether their illness is cancer, is it sarcoma, sarcoma subtype, is this disease common or rare, its origin-bone or soft tissue, metastatic-yes or no, and possibility of recurrence/progression. We analysed if patient's educational status had any role in this knowledge.

Results: There were a total of 101 patients with sarcoma who consented to participate in the study. The median time from diagnosis of patients with disease to conduct of this study was 1 year (range 1 month – 6 years). Majority of them were males (n= 63, 62.3%). The median age was 31 (range 18 -75 years). Of 101 patients, there were 63 (62.3%) soft tissue sarcomas and 38 (37.7%) bone sarcomas. Of all patients, 49 (48.5%) had metastatic disease. The most common type of sarcoma was Ewings (21%) followed by synovial sarcoma (18%), osteosarcoma (17%), leiomyosarcoma (9%), and UPS (6%) and others were 29% (including MPNST, angiosarcoma, ASPS, rhabdomyosarcoma, etc). We divided patients broadly into those who had completed 12th grade or lower (n=53) (lower education status) and those who had been to university (n=48) (higher education status).

Of 101 patients, 88 (87%) were aware that they had some form of cancer, 10 (9.9%) patients did not know and 3 patients said they don't have any cancer. Of these 88 patients who were aware, 71 (80%) patients knew that they had sarcoma. Only 57 (56%) patients knew that their illness is a rare disease, 36 (35.6%) did not know while 8 (8.4%) reported that it is a common illness. About metastasis, 71 (70.2%) patients correctly reported their metastatic or non-metastatic disease status. Twenty-one (20.8%) patients didn't know about the status of being metastatic or non-metastatic while nine (9%) patients reported it wrong. Regarding origin of sarcoma from bone or soft tissue, 13 (12.8%) patients didn't know the site of origin, 10 (9.9%) patients reported it wrongly while 78 (77.3%) patients reported it correctly. Asked if this disease can recur/progress in non-metastatic and metastatic patients, 51 (50.5%) patients knew that it could, 10 (9.9%) patients reported that it can't whereas 40 (39.6%) patients didn't know. Of 101 patients, only 54 (53.5%) patients could report the specific type of sarcoma. Those who reported (n=54) had 100 percent concordance. When asked about causative factors, 85 (84.2%) patients said they do not know, others said lifestyle (n=5) followed by trauma (n=4), pollution, genetics and smoking (n=2 each) and age(n=1).

Patients with higher education status were more aware about the rarity of disease (73% vs 39%;p value=0.001) specific sarcoma subtype (65% vs 28%: p value=0.000) than those who were lesser educated. However, there was no significant relationship between the level of education and knowledge about the recurrence of disease. (48% vs 56%;p value=0.15)

Conclusion: For a rare disease like sarcoma, in spite of active counselling, regular and frequent educational sessions, there is still a huge knowledge gap that needs to be addressed, more so in patients who have received lesser education.



Patient's responses to questionnaire

Poster #170 3255976

MOBILE APPLICATION FOR SARCOMA PATIENTS AND THEIR RELATIVES

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Objective: Patient information about sarcoma, sarcoma treatment and the time after treatment are often given as loose sheets. This information is not covering all patient needs. In a survey done with members of the patient-organization "Sarkomer" in Norway, 51, 5 % of the members answered that they did not receive enough information. 81, 6 % of the members said yes - they desire a mobile application with all information in one place.

All sarcoma patients and their relatives will receive correct information at the right time point.

Methods: Complete a mobile application where you will receive information about sarcoma and sarcoma treatment according to the phase you are in - before treatment, during treatment and after treatment. "Sarkomer" is responsible for the mobile application, and health care professionals at Oslo University Hospital are responsible for the professional contents.

Results: A mobile application will be released during 2019.

Conclusion: Correct and sufficient information will make patients and their relatives feel safer and they will master their everyday life better.

Poster #171 3256393

PREVALENCE, TEMPORALITY AND ASSOCIATION WITH MORTALITY OF SYMPTOM CLUSTERS AMONG SARCOMA PATIENTS ON SYSTEMIC TREATMENT

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Objective: Sarcoma patients frequently experience symptoms related to their disease or treatment. Two or three co-occurring uncontrolled symptoms defines a symptom cluster; presence of symptom clusters has been associated with worse morbidity and mortality. Although symptom clusters have been identified in other oncology patient populations, little research has been conducted in sarcoma. The primary objectives of this study were to determine if symptom clusters exist in sarcoma patients undergoing active treatment, to define those clusters, and determine their temporality and association with mortality.

Methods: Demographic, disease and treatment specific data were collected for adult sarcoma patients receiving oral or intravenous chemo-, targeted or immuno-therapy, including those on trials, between 09/2018-01/2019 at Seattle Cancer Care Alliance sarcoma clinic. Patients completed a 33-item, modified Patient Reported Outcomes-Common Terminology Criteria for Adverse Events (mPRO-CTCAE) based review of systems (hereafter "form") for ongoing clinical care. Presence of an individual symptom was dichotomized as present if occurring more than "occasionally". Symptom clusters (specifically triads of symptoms) were defined by the presence of at least three symptoms more than occasionally on one form. Descriptive data (%'s) and survival analyses (Cox-Proportional Hazards model) will be presented.

Results: Patients (n=165 completing 449 forms) were median 58 years old (range 20-81), 53% male, 72% Caucasian, with abdominal (45.5%) and lower extremity (29.7%) sarcoma. Leiomyosarcoma (17%), liposarcoma (14%), GIST (11%), and sarcoma NOS/other (26.1%) were the most common subtypes (see Table 1). Stage of disease included: local 24.8%, locally advanced/recurrent 22.6%, metastatic 61.3% and both locally recurrent and metastatic 16.1%. Sixty-seven percent (n=111) of patients were receiving intravenous (IV) chemotherapy, 30.9% oral (n=51), and 1.8% were receiving both (n=3). The majority of IV chemotherapy was anthracycline (41.2%, n=47) or gemcitabine (13.2%, n=15) based, while oral chemotherapy was primarily tyrosine-kinase inhibitors (61.1%, n=33), pazopanib (14.8%, n=8) or investigational/other agents (14.8%, n=8). Four symptom cluster triads were identified in >25% of pts who completed at least one form (Defined at T1, see Table 2). During the study period, 108 patients completed at least 2 forms with a median of 22 days between forms. Symptom clusters persisted for the majority of patients completing two or more forms without missing data (Defined as T2, see Table 2). The presence of either Pain/Fatigue/Appetite or Shortness of Breath/Pain/Appetite at T1 was associated with overall survival with hazard ratio (HR) 2.96 (p=0.02) and 3.69 (p=0.007) (respectively) when controlling for treatment and metastatic disease.

Conclusion: Symptom clusters are common among sarcoma patients receiving active treatment and some clusters do appear predictive of overall survival. Patients frequently continue to have symptom clusters at subsequent visits, demonstrating the potential impact that addressing these clusters could have on patient quality of life and end of life care. Future research should address optimal management of symptoms clusters.

Table 1: Patient demographics

Variables	Categories	Total (N=165)
Age	Median (Range)	57.8 (20.4-81.2)
Gender	Male	87 (52.7%)
Primary language	English or missing	158 (95.7%)
	Spanish	4 (2.5%)
	Other	3 (1.8%)
Ethnicity	Caucasian or unknown	110 (72.1%)
	Hispanic or Latino	8 (4.8%)
	Asian	17 (10.3%)
	Black or African American	8 (4.8%)
	Other	13 (7.9%)
Primary location	Extremity (arm - shoulder)	11 (6.7%)
	Extremity (leg - buttock)	49 (29.7%)
	Abdomen	75 (45.5%)
	Head and Neck (including central nervous system)	11 (6.7%)
	Lung	4 (2.4%)
	Thorax (chest wall)	15 (9.1%)
Sarcoma subtype	NOS, other	43 (26.1%)
	Leiomyosarcoma	28 (17.0%)
	Liposarcoma	23 (13.9%)
	Gastrointestinal stromal tumor	18 (10.9%)
	Pleomorphic sarcoma	11 (6.7%)
	Angiosarcoma	10 (6.1%)
	Osteosarcoma	7 (4.2%)
	Rhabdomyosarcoma	6 (3.6%)
	Desmoid fibromatosis	7 (4.2%)
	Chondrosarcoma	6 (3.6%)
	Ewing	6 (3.6%)

Table 2. Presence of symptom triad at second survey among those with triad at first survey

Symptom Triad	Patients with Triad at T1	Patients with Triad at T1 and T2
Pain, Decreased Appetite, Fatigue	37 (29.8% of 124)	9 (45% of 20)
Pain, Fatigue, Insomnia	35 (28.9% of 121)	11 (52% of 21)
Decreased Appetite, Fatigue, Insomnia	34 (25% 136)	17 (58% of 29)
Diarrhea, Pain, Fatigue	31 (25% 124)	8 (50% of 16)
*Shortness of breath, pain, appetite	21 (16.7% of 126)	

*Triad included due to relationship to mortality.

Poster #172 3256444

HEALTH-RELATED QUALITY OF LIFE IN TENOSYNOVIHEALTH-RELATED QUALITY OF LIFE IN TENOSYNOVIAL GIANT CELL TUMORS (TGCT) PATIENTS IN EUROPE AND US: AN OBSERVATIONAL DISEASE REGISTRY

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Objective: Tenosynovial giant cell tumor (TGCT) is a rare, locally aggressive neoplasm of joints and tendon sheaths. The TGCT Observational Platform Project (TOPP) assessed the health-related quality of life (HRQOL) of patients with TGCT.

Methods: TOPP is an observational prospective study conducted in EU and US on adult patients with a histologically confirmed diagnosis of TGCT, enrolled between November 2016 and March 2019. Patients were followed up for two years. Patient demographics, disease and treatment history, health care resource utilization and patient reported outcomes were collected. Patient were stratified by severity (moderate versus severe) based on magnetic resonance imaging parameters determined by investigators. EQ-5D-5L questionnaires were administered to patients at baseline, 6 months follow-up (FU), 18 months FU and 24 months FU. A baseline snapshot was taken from patients available for this analysis.

Results: 183 patients were enrolled (median age: 44 years), of which 155 completed EQ-5D-5L. 34.2% of patients experienced moderate or severe disability in mobility, 23.8% had at least slight or moderate problems in self-care, 34.2% suffered moderate or severe problems performing usual activities, 45.8% had moderate or severe pain or discomfort, and 17.4% demonstrated moderate or severe anxiety or depression. Mean (SD) EQ-5D index score was 0.75 (0.21) and mean (SD) visual analogue scale (VAS) score was 69.1 (20.57). For patients with a moderate disease extent mean index score was 0.76 and VAS score was 70, while for patients with a severe disease extent, mean index score was 0.75 and VAS score was 68.7. EQ-5D -5L index score for TGCT patients varied from 0.62 in Germany to 0.84 in France and VAS score varied from 60.38 in Germany to 75.5 in US.

Conclusion: Patients with TGCT in TOPP registry reported a relatively low HRQOL compared to the general population. No significant difference according to disease severity and country was observed.

Poster #173 3258041

HOW BENEFICIAL IS VIDEO SEMINAR FOR SARCOMA PATIENTS?

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Objective: The difficulty in obtaining the latest information on diseases is a challenge of rare cancer care. We began to hold seminar sessions entitled: "Meet the Expert on Rare Cancer (MtE)" through collaboration with CancerNet Japan and Oncolosince 2017. During these sessions, doctors with expertise as lecturers explain each type of rare cancer including sarcoma, with the latest information.

Methods: A total of 35 MtE sessions were held within the 2-year period between 2017 and 2018. and 8 of them were sessions for sarcoma, with cooperation from 6 patient support groups. Each session is video - recorded and shared through video - streaming on a website. The themes of sarcoma sessions included an extremity sarcoma, uterine sarcoma, pediatric / AYA sarcoma, trunk sarcoma, etc.

A questionnaire survey was conducted to examine the details of the 8 MtE sarcoma sessions. The study items included: the contents of lectures, number, and types of participants, purpose, and satisfaction with the seminar.

Results: The total number of participants during the study period was 287. The mean number of participants was 36 per session and this was equivalent to that of other cancer sessions. Participants were mainly patients (38%) and their families (34%). The most frequent reason for participating in the seminar was "to obtain accurate information (87%)", followed by "to collect information regarding sarcoma, which is not sufficiently available (84%)", "to learn about the newest treatment method (82%)". The information which the participants want to know were "basic information of sarcoma (93%)", "standard of care (78%), "diagnosis (66%)", and "clinical trials (55%). Among all participants, 93% were satisfied with the seminar. The total view count of the videos of 8 sarcoma sessions already published online was 22,180 as of June 2019.

Conclusion: The results confirmed that the video seminar providing information on sarcoma is markedly needed. As the number of video-streaming views was nearly 50 times larger than that of participants, there may also be a marked potential need for such seminars. As a future perspective, measures to effectively transmit more beneficial and useful information regarding sarcoma will be examined by analyzing responses to this questionnaire and video-streaming view frequencies.

Poster #174 3239614

FEMORAL FRACTURE IN PRIMARY SOFT-TISSUE SARCOMA OF THE THIGH AND GROIN TREATED WITH INTENSITY-MODULATED RADIATION THERAPY WITH AND WITHOUT DOSE CONSTRAINTS

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Objective: We previously reported on the cumulative risk of femoral fracture in patients treated with intensity-modulated radiation therapy (IMRT) from 2002-2010 for thigh and groin soft-tissue sarcoma (STS) and found it to be low. In the current study, we sought to evaluate the effect of radiation dose constraints on the rate of femoral fracture in a more contemporary cohort.

Methods: All patients treated with IMRT for STS of the thigh/groin from 2006-2015 were included (n=117). Beginning in 2011, radiation dose constraints (specifically, mean dose <37 Gy, V40 <64%) were utilized to limit dose to the femur. Sixty-one patients were treated before dose constraints were implemented (2006-2010), while 56 were treated after (2011-2015). Cumulative incidence of femoral fracture was calculated using competing risk analysis, with subgroups of patients compared via Gray's method.

Results: Median follow-up among the entire cohort was 5.1 years (range, 0.7-10.3 years). For patients treated before and after constraints were implemented, median follow-up was 4.8 years and 5.2 years, respectively. The 5-year cumulative incidence of femoral fracture among the entire cohort was 3.0% (95% CI, 1.0-9.3%). Comparing patients treated before and after constraints were implemented, the two groups were similar with regards to age, gender, tumor compartment within the thigh, tumor size, presence of periosteal stripping at the time of surgery, receipt of preoperative versus postoperative radiation, and utilization of chemotherapy. The 5-year cumulative incidence of femoral fracture among patients treated with and without dose constraints was 1.9% (95% CI, 0.3-13.4%) versus 4.1% (95% CI, 1.0-16.4%, p=0.32). Age ≥ 60 was significantly associated with increased risk of femoral fracture (5-year cumulative incidence of 10.8% for age ≥ 60 versus 0% for age <60, p=0.02).

Conclusion: The overall risk of femoral fracture after IMRT for STS of the thigh/groin is very low, and with the implementation of radiation dose constraints, the risk is <2%. Although longer follow up is needed to continue to observe for femoral fracture beyond the median follow-up time of 5.1 years, our results support the utilization of extremity sarcoma IMRT-specific dose constraints for fracture prevention.

Poster #175 3241461

GENOMIC CHARACTERIZATION OF RADIATION-INDUCED SARCOMA USING WHOLE GENOME SEQUENCING

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Objective: Radiation-induced sarcoma (RIS) is a rare but serious complication after radiotherapy. To identify predisposing variants and mutational landscape, we analyzed the genomes of RIS samples. Herein, we report the interim results of our analysis

Methods: Sarcoma specimens developed in the previously irradiated area were reviewed by experienced pathologist. DNA was extracted from freshly frozen tumor tissues or isolated tumor region through microdissection, along with isolated normal tissue or blood derived from the same individuals. In all cases, whole genome sequencing (WGS) was performed with the average coverage of tumor DNA 90 x and of normal DNA 60 x , and targeted panel sequencing of cancer-related genes was also performed in selected two cases for validation.

Results: Of total 25 samples, WGS sequencing of five patients were completed. RIS from different primary tumors included 2 undifferentiated pleomorphic sarcoma, 1 undifferentiated spindle cell sarcoma, 1 osteosarcoma and 1 angiosarcoma. The median latency of RIS was 8 years (range, 5–12). RIS harbored median 4,218 substitutions (range, 962–45,597) per genome and median 987 indels (range, 590–44,957) per genome. Excess of deletions relative to insertion was observed in all five samples. However, there was no significant somatic mutation in cancer-related genes for all cases. Each of the five cases showed different patterns in the copy number analyses, and inter-chromosomal translocation did not appear constantly through all samples.

Conclusion: We identified excessive deletions and low number of mutations without cancer driver mutation in RIS patients. The further analysis with additional patients is ongoing, and we suggest that this genetic study may reveal the underlying mechanism of the development of RIS and help patients to be treated with a novel treatment strategy.

Poster #176 3256155

MODELING GENOMIC ADJUSTED RADIATION DOSE (GARD) IN SOFT TISSUE SARCOMA

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Objective: Sarcomas are a heterogenous group of cancers with wide variation in histopathological features and response to perioperative radiation therapy (RT). We have previously developed and validated a genome-based gene expression signature to measure tumor intrinsic radiosensitivity – the radiosensitivity index (RSI), and noted a significant difference in LRC between radiosensitive (RS) histologies including angiosarcoma and leiomyosarcoma when compared to radioresistant (RR) histologies such as non-myxoid liposarcoma (3-year LRC: 95% vs. 79%, p=0.021). In this study, we modeled the genomic adjusted radiation dose (GARD) between RR and RS histologies and estimated radiation doses required to optimize LRC.

Methods: A cohort of 116 resected sarcoma samples were identified from our prospective observational protocol. To model an appropriate GARD above which locoregional control was optimized, we utilized received operator characteristic (ROC) curve analysis. The dose required to achieve a RS EQD2 equivalent in the RR histologies were calculated from the histologies estimated α/β.

Results: The median GARD for RR histologies (non-myxoid liposarcoma) were 12.4 (range 0.0 – 34.7) and for RS histologies (angiosarcoma and leiomyosarcoma) were 20.6 (range 11.2-40.2) and 16.4 (range 8.9 -60.2) respectively. The α/β ratio was calculated using RSI, with a modeled α/β ratio of 2.94 for RR histologies and 5.34 for RS histologies. The additional number of fractions (at 2 Gy per fraction) and dose per fraction were modeled to achieve the estimated threshold for optimal LRC (GARD=15), and showed that RR histologies require an additional 5.4 fractions at 2 Gy per fraction (30.4 fractions, for a total modeled dose of 60.8 Gy) or 2.3 Gy per fraction in 25 fractions to achieve the dose equivalent to preoperative radiation (50Gy) to the RS histologies.

Conclusion: There are significant differences in the intrinsic radiosensitivity between RR and RS subtypes which translated to variance in estimated α/β and genomically adjusted radiation dose. These data suggest a potential area for genomic derived dose escalation and the rationale for potentially dose escalating RR histologies similar to preliminary data in retroperitoneal sarcoma.

Poster #177 3235168

EARLY OUTCOMES OF PREOPERATIVE 5-FRACTION RADIATION THERAPY FOR SOFT TISSUE SARCOMA WITH IMMEDIATE RESECTION

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Objective: To report early clinical, pathologic, and toxicity outcomes of patients receiving hypofractionated RT followed by immediate surgical resection.

Methods: An IRB-approved database of patients treated with preoperative RT for soft tissue sarcoma was queried. Patients treated with 5-fraction RT followed by immediate (within 7 days) planned, wide surgical resection from 2016-2018 were eligible. Toxicity was graded by CTCAE version 4.

Results: Ten patients met eligibility criteria. Median follow-up was 7.1 months (range 1.6-24.2). Median patient age was 60 years (range 33-83). Histologic findings and pathologic responses are summarized in Table 1. Sarcomas were located in the extremity (7), trunk (2), and retroperitoneum (1). Four patients had metastatic disease at diagnosis. Median radiation dose was 30 Gy in 5 fractions (range 27.5-40 Gy) on consecutive days. Median time to surgical resection following completion of RT was 3 days (range 0-7). Median time from initial biopsy results to surgical resection of the primary tumor was 22 days (range 16-42). Eight patients achieved R0 resection. Of the 9 patients assessed for local control, no patients developed local failure, although one patient had persistently positive margins. Two of ten patients had progression of distant metastatic disease. One patient with a retroperitoneal sarcoma developed acute grade 4 tumor lysis syndrome. No other acute grade ≥3 toxicities were observed. Two patients developed late grade 3 toxicity consisting of fracture and delayed wound healing. The pathologic stress fracture occurred after trauma in a patient who had undergone re-irradiation for persistently positive margins. Nine patients had an uneventful postoperative course without wound healing issues.

Conclusion: This experience of hypofractionated preoperative RT for soft tissue sarcoma with immediate resection resulted in a median of 22 days from biopsy results to resection of the primary tumor. Early outcomes reveal low toxicity. Further prospective data with long-term follow-up is required to determine the oncologic outcomes and toxicity of hypofractionated preoperative RT.

Table 1. Histologic findings and pathologic responses.

	Diagnosis	Histologic Findings
Patient 1	Myxoid liposarcoma	0% necrosis
Patient 2	Myxoid liposarcoma	10% necrosis & lymphocytic response
Patient 3	Myxoid liposarcoma	0% necrosis & 10% fibrosis and lymphocytic response
Patient 4	Dedifferentiated liposarcoma	10% necrosis & organizing thrombi
Patient 5	Dedifferentiated liposarcoma	0% necrosis & focal lymphocytic response
Patient 6	Synovial sarcoma	0% necrosis & 10% cystic changes, hemosiderin
Patient 7	Synovial sarcoma	0% necrosis
Patient 8	Undifferentiated pleomorphic sarcoma	75% necrosis
Patient 9	Undifferentiated spindle cell sarcoma	20% necrosis & hemorrhage/ hemosiderin
Patient 10	Pleomorphic rhabdomyosarcoma	80% necrosis

Poster #178 3239332

EFFICACY OF AN ESOPHAGEAL SPACER FOR HIGH-DOSE SINGLE-FRACTION RADIOSURGERY FOR DE NOVO SPINE CHORDOMA- FIRST EXPERIENCE

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Objective: Implanted hydrogel spacers to facilitate the delivery of high-dose stereotactic radiosurgery (SRS) has theoretical advantages for the treatment of spine and paraspinal tumours in close proximity to the esophagus, but its use has not previously been reported. This study assessed the use of an esophageal hydrogel spacer for high-dose single-fraction SRS as definitive therapy for a case of de novo chordoma of the thoracic spine, investigating practicality, dosimetric impact, and early toxicity.

Methods: A 31-year-old woman, otherwise asymptomatic, was incidentally found to have a localized de novo conventional chordoma invading T4-T5 vertebral bodies, emanating into the paraspinal space with three-level paraspinal disease abutting the esophagus (Fig 1A). Conventionally advocated en bloc resection was deemed to be not without significant morbidity and recurrence risk. Prior institutional experience has demonstrated SRS to 24Gy single fraction to have local control and cure rates of 90% at 5 years in the de novo chordoma setting. Given that dose-escalation was limited by esophageal constraints, a hydrogel spacer (SpaceOAR, Boston Scientific, Bedford, MA) was placed via a uniportal video-assisted thoracic surgery (uVATS) approach between the tumor and esophagus (Fig 2), followed by image-guided SRS with 24Gy single-fraction. CT myelogram based simulation for SRS was performed on postoperative day (POD) 1 to clearly define the spinal cord. Post-spacer T2 MR images (Fig 1B) were fused with the planning CT to assist with spacer delineation. Omnipaque esophageal contrast prior to simulation and treatment was used to verify esophagus position. MR scans acquired pre-spacer (Fig 1A) were used to generate an SRS plan that was compared to the post-spacer insertion plan. Plans were evaluated for target coverage, conformality, and organs at risk coverage. Results were examined to determine spacer insertion tolerability, changes in dosimetry, and early toxicity effects.

Results: The patient had successful spacer insertion under general anesthetic with maximal Grade 1 toxicity, and discharge on POD 2. Both pre- and post-spacer plans were highly conformal, with no significant differences in planning target volume dose coverage (Table 1). Substantial improvements in esophageal dose metrics were observed in post-spacer plans, e.g. the dose to 2.5cc was reduced by 96% (Table 1, Fig 3). To date, she has reported only Grade 1 pain flare following SRS, with no issues with swallowing or acute esophagitis within 8 weeks post-SRS. The spacer was well-tolerated and allowed this patient to achieve both target volume objectives and normal tissue constraints, with corresponding no acute esophageal toxicity despite initial multi-spinal level tumor abutment and displacement of the esophagus.

Conclusion: This is the first case to investigate the use of an esophageal hydrogel spacer in spine SRS. The tolerability of a uVATS insertion approach and 96% dose reduction to the esophagus is predicted to result in meaningful clinical benefit, by reducing the incidence of high grade esophageal toxicities and permitting dose escalation to optimize tumor control. This promising treatment strategy merits further investigation in large prospective clinical trials.

Comparison of key dose metrics pre- and post-spacer. All constraints were achieved post-spacer.

Organ at risk	Metric	Constraint	Pre-spacer plan	Post-spacer plan
Planning target volume (PTV)	V95%	≥95% (goal)	96.2%	96.8%
Gross tumor volume (GTV)	D100%	≥1500 cGy (limit)	2311 cGy	2335 cGy
Esophagus	D2.5cc	≤1400 cGy (goal), ≤1800 cGy (limit)	2182 cGy	97.3 cGy
Spinal cord	Dmax	≤1400 cGy (limit)	1323 cGy	1315 cGy

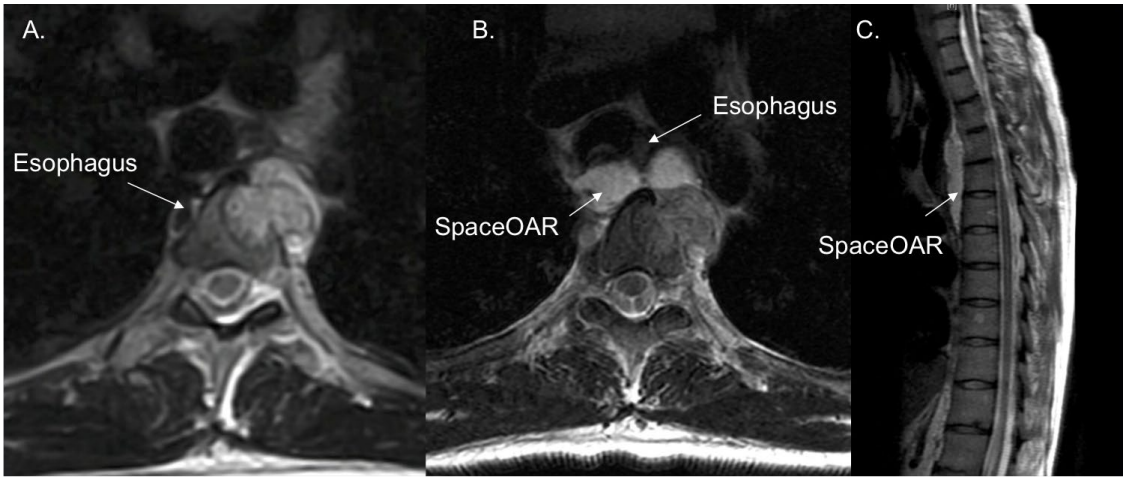

Fig 1. Representative T2-weighted MRI views, acquired at diagnosis (A), and following spacer insertion axial (B) and sagittal (C).

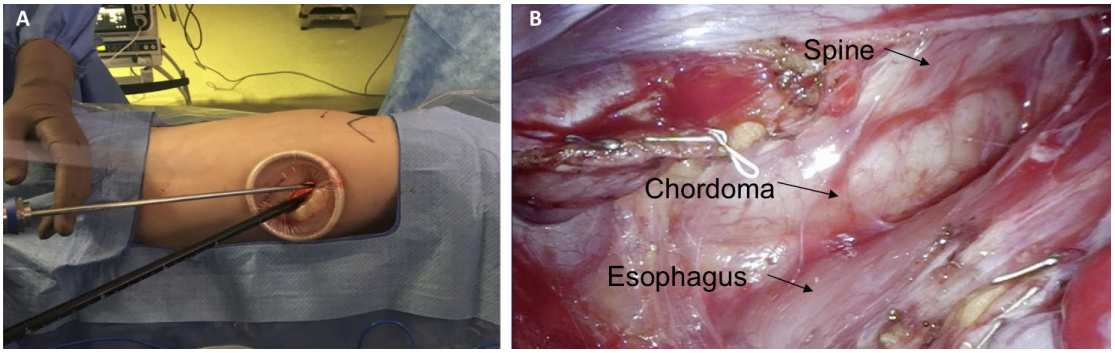

Fig 2. The hydrogel esophageal spacer was placed via a uVATS approach (A) to displace the esophagus from the tumor (B).

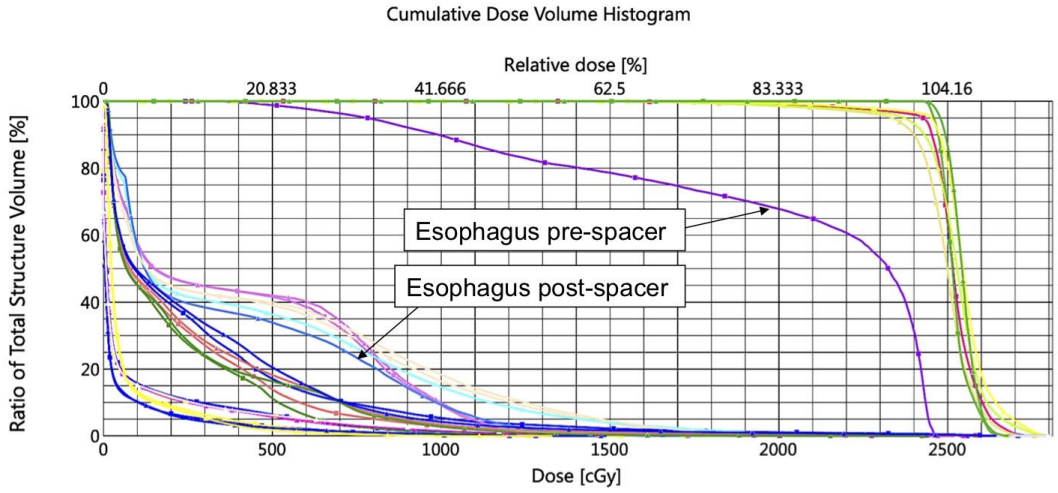

Fig 3. Dose volume histograms illustrate the esophageal dose sparing post- vs pre- spacer.

Poster #179 3256255

CLINICAL OUTCOME OF NEOADJUVANT ALTERNATING CHEMORADIOTHERAPY FOR SOFT TISSUE SARCOMAS

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Objective: Although adjuvant chemotherapy or radiotherapy for high-grade soft tissue sarcoma has been reported to be effective in the clinical outcome, there are few studies about the efficacy of chemoradiotherapy. Therefore, there is no definitive opinion of chemoradiotherapy for high-grade soft tissue sarcoma about optimal drug regimen, timing and dose of the irradiation. The purpose of the present study was to retrospective analyze the clinical outcome and adverse events of neoadjuvant alternating chemoradiotherapy (NACRT) for soft tissue sarcomas.

Methods: We have performed NACRT for large (over 5 cm diameter), deep-seated and high-grade soft tissue sarcomas. NACRT was performed as three cycles of neoadjuvant chemotherapy (doxorubicin and ifosfamide), and interdigitated preoperative radiation therapy (40Gy administered in split courses), and three cycles of postoperative chemotherapy in principle (Fig. 1). Twenty seven patients who had underwent NACRT between June 2007 and December 2016 were included in this analysis. There were twenty male and seven female patients with a median age of 48.7 years (range, 28-65) at the time of diagnosis. The mean follow-up period was 64 months (range, 7-138). The median tumor size as measured by MRI was 9.9 cm (range, 5-30). Anatomical sites of tumor were 25 in extremity and 2 in non-extremity. The stage (AJCC Cancer Staging Manual, 8th Edition) of tumors was composed of 18 in Stage 3A, 6 in Stage 3B and 3 in Stage 4. The pathological diagnosis were liposarcoma 14 (myxoid 13, dedifferentiated 1), leiomyosarcoma 3, malignant peripheral nerve sheath tumor 3, epithelioid sarcoma 2, undifferentiated pleomorphic sarcoma 2, synovial sarcoma 1, others 2 (Table 1). We retrospectively reviewed histological response, surgical margin, local recurrence, distant metastasis, oncological outcome, 5-year disease-free and overall survival rate. Hematologic toxicities, radiation dermatitis and wound complications after NACRT (Common Terminology Criteria for Adverse Events v4.0, grade ⍰3) were also investigated.

Results: Histological response were good (less than 10% viable tumor cells) in 8, poor (more than 10% viable tumor cells) in 19. Surgical margins were R0 in 24 patients including 2 amputations and R1 in 3 patients. The rates of local recurrence and distant metastasis were 7.4% and 29.2% respectively. Oncological outcomes were CDF in 17, NED in 2, AWD in 4 and DOD in 4. The 5-year disease-free and overall survival rate were 67.9% and 84.7%. There were 11 patients (40.7%) who could complete postoperative chemotherapy and 10 patients (37%) who could not receive postoperative chemotherapy. Twenty four (88.9%) patients experienced over grade 3 hematologic toxicity included 13 patients (48.1%) with grade 4 neutropenia, 2 patients (7.4%) with grade 4 anemia, one patients (3.7%) with grade 4 thrombocytopenia. There were no adverse events that changed the surgical procedure, but additional surgery was performed in 8 patients (29.6%) due to delayed wound healing (Table 2).

Conclusion: In 2013, Look Hong NJ et al. reported that the local recurrence rate, the distant metastasis rate and the 5-year overall survival rate were 8%, 30% and 86% as results of NACRT using MAID, which the result was almost the same as our study. Although NACRT seems to be effective as adjuvant therapy for high grade soft tissue sarcomas, it is necessary to pay attention for postoperative wound complications.

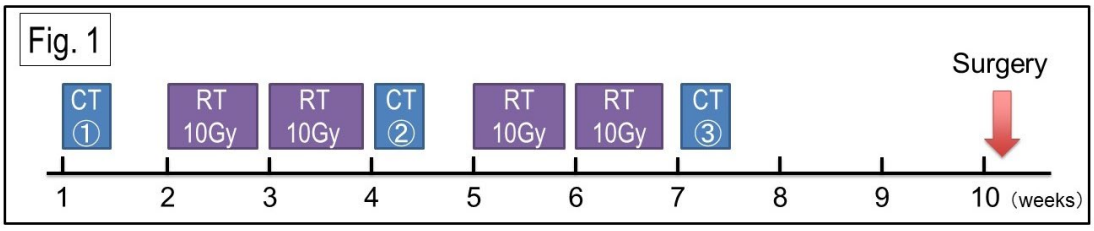

Fig. 1. Protocol of NACRT

CT, Chemotherapy (doxorubicin 60mg/m^2/2 days, ifosfamide 7.5g/m^2/3 days);

RT, Radiotherapy.

Table 1. Patients and tumor characteristics

All patients (n=27)	N	(%)
Gender		
Male	20	(74.1)
Female	7	(25.9)
Age at diagnosis (years)	Median: 48.7(range, 28-65)	
Follow up period (months)	Median: 64 (range, 7-138)	
Anatomical site		
Extremity	25	(92.6)
Non-extremity	2	(7.4)
Tumor size (cm)	Median: 9.9 (range, 5-30)	
AJCC stage 8th		
IIIA	18	(66.7)
IIIB	6	(22.2)
IV	3	(11.1)
Histological type		
Liposarcoma	14	(51.9)
Leiomyosarcoma	3	(11.1)
MPNST	3	(11.1)
Epithelioid sarcoma	2	(7.4)
UPS	2	(7.4)
Synovial sarcoma	1	(3.7)
Others	2	(7.4)

AJCC, American Joint Committee On Cancer; MPSNT, malignant peripheral nerve sheath tumor; UPS, undifferentiated pleomorphic sarcoma

Table 2. Clinical outcome, toxicities and complications

All patients (n=27)	N	(%)
Histological response		
Good	8	(29.6)
Poor	19	(70.4)
Surgical margin		
R0	25	(92.6)
R1	2	(7.4)
Oncological outcome		
CDF	17	(63)
NED	2	(7.4)
AWD	4	(14.8)
DOD	4	(14.8)
Hematologic toxicities		
Leukocytopenia		
Grade 3	11	(40.7)
Grade 4	13	(48.1)
Anemia		
Grade 3	8	(29.6)
Grade 4	2	(7.4)
Thrombocytopenia		
Grade 3	2	(7.4)
Grade 4	1	(3.7)
Nonhematologic toxicities*		
Radiation dermatitis	2	(7.4)
Infection	5	(18.5)
Delayed wound healing	8	(29.6)

CDF, continuous disease free; NED, no evidence of disease; AWD, alive with disease, DOD, dead of disease
*Common Terminology Criteria for Adverse Events v4.0, grade ≧3

Poster #180 3244842

ADJUVANT INTENSITY MODULATED RADIATION THERAPY IN PRIMARY SOFT TISSUE SARCOMA OF THE SUPERFICIAL TRUNK

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Objective: Soft tissue sarcomas (STS) involving the trunk wall are rare, and in most studies they are often lumped with extremity STS. This leads to the assumption that the outcome with adjuvant radiation is similar. The purpose of this study is to evaluate the clinical outcome of patients with STS of the trunk wall who received adjuvant intensity modulated radiation therapy (IMRT) and underwent surgery with gross total resection.

Methods: Between 1/1/01 and 12/31/16, 47 adult patients with primary STS of the trunk were treated with adjuvant IMRT and gross total resection. Of the 47 patients, 37 (79%) were male, 36 (77%) were > 50 years, and 37 (79%) had tumors > 5cm. Tumor locations were as follows: chest wall in 29 (83%), abdominal wall in 6 (17%), and paraspinal in 12 (34%) patients. The most common histology was myxofibrosarcoma (32%), with 44/47 (94%) being high grade tumors. Postoperative IMRT (median 63 Gy) was given in 42 (89%) patients. During surgery, 9 (19%) received mesh reconstruction, and 5 (11%) received flap closure. Negative margin was achieved in 29 (62%) patients. Adjuvant chemotherapy was given in 10 (21%) patients.

Results: With a median follow-up of 45 months, 5 (11%) patients developed local recurrence. Overall 5-year actuarial local control was 88% (95% CI: 73%-95%), metastasis-free survival was 71% (95% CI: 54%-83%), disease-free survival was 68% (95% CI: 51%-80%), disease-specific survival was 84% (95% CI: 68%-93%), and overall survival was 84% (95% CI: 68%-93%). Age, gender, tumor size, tumor location, tumor histology, margin status, or use of chemotherapy were not prognostic of local control or other survival parameters. Acute grade ≥2 radiation dermatitis was seen in 16 (34%) patients. Grade ≥2 wound complications were observed in 2 (4.2%) patients, resulting in wound dehiscence, requiring prolonged wound care and packing. One was treated with preoperative IMRT and one with postoperative IMRT. No grade ≥2 pulmonary or GI late toxicity were observed.

Conclusion: The local control results for truncal STS treated with adjuvant IMRT are good with a favorable morbidity profile. Whether the local control is equivalent to that for IMRT in extremity STS needs further investigation in a head to head comparison.

Poster #181 3246554

KAPOSI'S SARCOMA: EXPERIENCE OF A RADIOTHERAPY DEPARTMENT

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Objective: Kaposi's sarcoma (KS) is a low-grade malignant tumor arising from lymphatic endothelial cells, usually with mucocutaneous presentation (localized disease), although multiple organs can be involved (disseminated disease). Clinical course of KS is variable. The classic form has usually a benign course, different from epidemic and iatrogenic forms that can be progressive and life threatening. There are multiple therapeutic options namely cryosurgery, laser removal, local chemical and immune-modifying agents and surgery excision. External beam radiotherapy (EBRT) or contact brachytherapy (BT) are some of the most used treatments with recognized results.

It is our objective to describe and analyze our ten-year experience in the management of KS patients (pts).

Methods: Between 2008 and 2018, 31 pts (25 males and 6 females) with histologically confirmed KS diagnosis were treated in our department. The median age was 64 (range: 33-87) years old. The Eastern Cooperative Oncology Group performance status (PS) was evaluated as 0 or 1 in 54.9% pts. Out of 31 pts, 7 had a HIV-related KS, 1 of them without antiretroviral therapy. Two patients had an iatrogenic KS associated with the use of the immunomodulatory drugs. One patient had an endemic KS. The remaining 21 pts had classic KS. The KS lesions were confined to the skin in majority of pts. Nodal involvement was present in 5 pts and visceral involvement in 3 pts. The lower limbs were the most frequently involved anatomical site (27 pts).

Some pts had been treated previously with chemotherapy (11 pts), surgery (3 pts) and laser removal (1 patient). Pts were treated with EBRT (30 pts) and high dose rate (HDR) contact BT (1 patient). The median equivalent total dose in 2 Gy/fraction (EQD_2), assuming an α/β of 10 Gy for tumors, was 30 (range: 12-50) Gy. A standard fractionation (2 Gy/fraction) was used in 54.8 % of pts. Different hypofractionation schemes were used in the others, between 3 and 8 Gy per fraction. The total BT dose was 20 Gy in 5 fractions.

Results: The median follow-up was 32 months. The median time to progression (defined as an increase in size of the irradiated lesion or appearance of new lesions) was 13 months. The majority of the progressions were out of irradiation field (75.1%). The progression-free survival (PFS) was 53% and 35% at 12 and 24 months, respectively. The overall survival (OS) was 89% and 71% at 12 and 24 months, respectively. No influence of age, sex, PS, HIV status, dose fractionation and EQD_2 was found by univariate analysis. Only one patient had grade 3 toxicity (radiodermatitis).

Conclusion: Our results are in line with the reported outcomes (PFS and OS) of other studies. There is no clinical trial comparing the available local treatmentsfor KS lesions. Radiotherapy isa good option given the low toxicity and high local control of the treated lesions. The ideal dose and fractionation have to be determined and, given the low number of pts of our series, no conclusions can be drawn. Treatment with HDR BT is also an attractive option given the shorter total treatment time.

Poster #182 3255340

RETROPERITONEAL SARCOMA PATIENTS TREATED WITH RADIOTHERAPY AFTER R1 SURGERY – A SINGLE CENTER RETROSPECTIVE STUDY

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Objective: Retroperitoneal sarcomas (RPS) are rare malignant tumors and their specific location represents 12 to 15% of soft tissue sarcomas. Currently, surgery with complete gross resection is the gold standard management and the evidence regarding radiotherapy in the neoadjuvant or adjuvant setting is scarce. With this study we aim to evaluate the response of the patients treated with radiotherapy after primary gross tumor excision with positive (R1) or close margins.

Methods: Patients diagnosed with non-metastatic RPS between 2008 and 2017 who underwent R1 surgery and were treated postoperatively with radiotherapy due to R1/close margins were retrospectively reviewed. Disease free survival (DFS) was clinically assessed through stringent regimens, including frequent computer tomography scans of the chest, abdomen and pelvis. Kaplan-Meier method was used to compute DFS and overall survival (OS). Chi-square test and Cox regression were used respectively for the univariate and multivariate analysis.

Results: Twenty-three patients were included, 52% males, 48% females with a median age of 63 years (range 22- 85 years). Liposarcoma was the most common histological type (61 %), 65% were pathologically staged IIIA or IIIB and 35% IB (AJCC 8th Edition). Chemotherapy was used in 65% of patients and the median radiotherapy dosage delivered was 50 Gy (range 30 – 66 Gy). Postoperative radiotherapy was delivered in the primary setting in 61% of patients and as a recurrent disease treatment in 39%. Median follow-up was 37.6 months (range 5 - 160 months), the 2- and 5- years DFS rates were 42.1% and 36.1%, respectively (median: 22.13 months). On univariate analysis, favorable DFS was significantly associated with primary versus recurrent status (p=0.012) and age inferior to 63 years (p=0.046). The 2- and 5- years OS rates were 72.9% and 40.5%, respectively (median: 43.13 months). On univariate analysis, OS was significantly associated with chemotherapy usage (p=0.01). On multivariate analysis for both DFS and OS, no independent prognostic factors were identified. Grade ≤ 2 acute gastrointestinal (GI) toxicity was observed in 52% of patients, no grade 3 acute GI toxicity was reported.

Conclusion: Despite the absence of clinical trials about the efficacy of postoperative radiotherapy in surgically treated patients with retroperitoneal sarcoma, there is mounting evidence that in adjuvant setting radiotherapy improves DFS and with tenuous evidence OS. The presented data are in accordance with those previous reports and the treatment shows acceptable toxicity. The recent concluded STRASS trial brought new data about the lack of usefulness of radiotherapy in neoadjuvant sequencing. Further studies are required in order to assess the appropriate sequence, the dose required and the target volume for postoperative radiotherapy.

Poster #183 3223161

THERAPEUTIC VALUES OF RADIOTHERAPY IN THE TREATMENT OF DESMOID TUMORS

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Objective: Desmoid tumors are rare non-malignant tumors and account for less than 3 percent of all soft tissue tumors. The disease, also known as aggressive fibromatosis, do not metastasize or dedifferentiate, but are locally aggressive tumors that can recur. The optimal treatment of the disease is not yet established. The aim of this study was to examine the outcome of radiotherapy in desmoid tumors and identify the therapeutic value of radiotherapy in the treatment of desmoid tumors.

Methods: Patients diagnosed with desmoid tumors and treated with radiotherapy between January, 2000 and December, 2018 were included. Twenty-two patients' data were retrospectively analyzed. Two patients had Gardner's syndrome. Fourteen patients (63.6%) were treated with radiotherapy after recurrence and eight (36.4%) patients were treated at first diagnosis. Seventeen patients (77.3%) were treated postoperatively, while five patients (22.7%) were treated radically. Radiotherapy target was created with 1.5 – 3 cm added to gross tumor or operative tumor bed. Median radiotherapy dose was 55.8 Gy, delivered with 1.8 – 2.3 Gy per fraction.

Results: Median follow up time was 35.1 months (range, 1.5 – 234.8 months). Twenty-one patients were assessed for recurrence since one patient was loss to follow up. Among them, four patients (18.2%) recurred after radiotherapy. Three local failures were classified as in-field failure while one was marginal failure. None of the failures occurred totally out-of-field. Time to local recurrence after radiotherapy ranged from 2.5 – 180.4 months. Except for the patient with 2.5 months follow up, others were treated with additional excision. One patient who recurred again after re-excision had underlying Gardner's syndrome. In postoperative cases, patients treated with more than 55.8 Gy and with clear resection margin had better recurrence free survival, although the difference did not reach statistical significance.

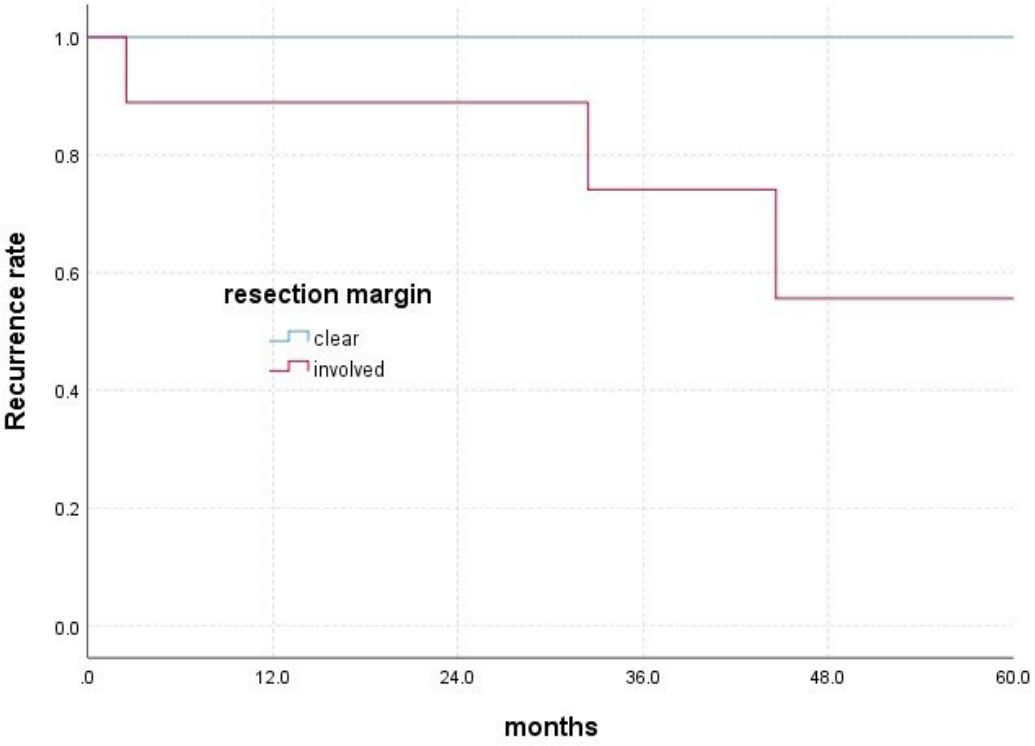
Conclusion: Role of radiation therapy in desmoid tumors is of value since local control rate was satisfactory. Resection margin status and postoperative radiotherapy dose might be crucial when considering radiotherapy in the treatment of desmoid tumors.

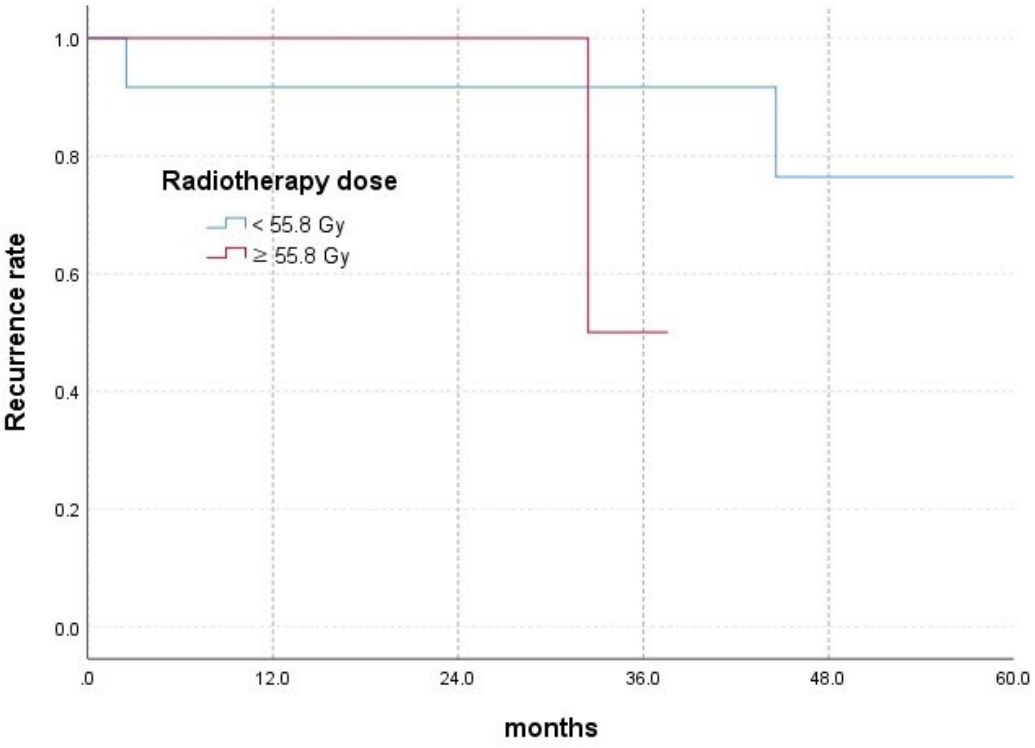
Patient characteristics

	Number of patients (%)
Age	Median 43 years old (range, 11 - 66)
< 43	12 (54.5)
≥ 43	10 (45.5)
Gender	
Male	7 (31.8)
Female	15 (68.2)
Tumor location	
Upper extremity	4 (18.2)
Lower extremity	6 (27.3)
Abdominal or chest wall	6 (27.3)
Back	4 (28.2)
Others	2 (9.0)
Tumor size	Median 9.5 cm (range, 2.1 - 22)
Tumor character	
First diagnosed	8 (36.4)
Recurrent	14 (63.6)
Radiotherapy aim	
Radical	5 (22.7)
Adjuvant	17 (77.3)
Radiotherapy dose	Median 55.8 Gy (range, 20 - 72)

Resection margin status of adjuvant radiotherapy cases

Postoperative cases	17 cases (%)
Clear resection margin	7 (41.2)
Involved resection margin	10 (59.8)





Poster #184 3239881

TARGETING PAX3-FOXO1 ONCOPROTEIN: AN INVESTIGATION OF SMALL MOLECULE INHIBITORS FOR RHABDOMYOSARCOMA

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Objective: Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma that mainly affects children and young adults. Of the 2 histological subtypes, patients with embryonal RMS (eRMS) have a more favorable outcome and better treatment options. However, alveolar RMS (ARMS) is a more aggressive disease and patients have a worse prognosis. The PAX3-FOXO1 fusion protein is specific to around 60% of ARMS tumors and results from the reciprocal translocation of chromosomes 2 and 13. The fusion protein contributes to the malignant phenotype and expression of PAX3-FOXO1 correlates with worse patient outcomes. Since PAX3-FOXO1 is expressed only in tumor cells, it presents an ideal target for treatment. We hypothesized that small molecules that can directly bind to PAX3-FOXO1 may inhibit its oncogenic function by preventing its specific protein-protein interactions.

Methods: Column chromatography for protein purification, surface plasmon resonance for small molecule binding screen, luciferase reporter assays for compound specificity selection.

Results: We purified PAX3-FOXO1 by affinity column chromatography and used surface plasmon resonance (SPR) to screen small molecule libraries. We identified 119 primary hits that bound specifically to PAX3-FOXO1 protein on the microchip. We then tested these primary hits in a luciferase assay with an ARMS cell line and found that 10 of them selectively inhibited the PAX3-FOXO1 responsive promoter activity compared to a negative control luciferase reporter. Further validation of 10 hits with multiple assays that focus on transcriptional activity are underway.

Conclusion: In summary, we successfully expressed and purified recombinant PAX3-FOXO1 protein and used it in a screening experiment. A number of compounds were discovered to directly bind the fusion protein and specifically inhibit its function in an ARMS cell line.

Poster #185 3256164

EPIGENETIC CHEMICAL SCREENS TO IDENTIFY NOVEL THERAPEUTIC STRATEGIES FOR RHABDOMYOSARCOMA (RMS)

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Objective: RMS is the most common type of sarcoma in children and adolescents. Despite treatment with chemotherapy, radiation and/or surgery, >70% of high-risk patients have poor outcome, with little improvement over the past decade. The two most common RMS histological subtypes are embryonal (ERMS) and alveolar (ARMS), the latter of which is defined by *PAX3-FOXO1* or *PAX7-FOXO1* gene fusions. Although the genomic landscape of RMS is well characterized, epigenetic vulnerability is emerging as a novel potential therapeutic target. Thus, the aim of our study was 1) to discover epigenetic compounds that are effective in the treatment of RMS; 2) to report the development of a novel immunocompetent murine model of RMS to validate epigenetic drugs.

Methods: We functionally assayed epigenetic inhibitors in a panel of patient-derived human ARMS and ERMS cell lines (n=4) and murine RMS tumor derived cell lines (n=2) and one non-transformed fibroblast cell line. We used 2 complementary sources of compounds: SGC (Structural Genomics Consortium) epigenetic chemical probes and OICR (Ontario Institute for Cancer Research) epigenetic collection (240 total). Epigenetic inhibitors currently in preclinical and clinical trials are represented in these libraries. Compound addition was performed digitally using 12-point serial dilutions and viability was assayed with ATPlite after approximately 7 days to assess metabolic activity. Our primary screen included 12-point dose response curves (2.6nM-10 mM) to determine IC_{50} values.

Mouse models were created using genetically-manipulated maturing myoblasts (MB), a likely RMS cell-of-origin. Lentiviral particles encoding distinct PAX3-FOXO1 fusion transduced primary MB isolated from p53-deficient (*p53*$^{-/-}$) mice. Transgene-expressing MB were expanded following selection and PAX3-FOXO1 mutant and control MB were injected into syngeneic, neonatal skeletal muscle and observed for tumor formation. Previous ERMS models using this approach have been published by our group and are ideal tools for in vivo target validation.

Results: The most promising candidates from the screen were reviewed to triage hits for genetic validation, specifically hits possessing: a) IC_{50} <1 μM, b) mechanism(s) promising in RMS, and c) data on pathway/compound toxicity. The candidates identified for further validation included HDAC and EZH2 inhibitors. Validation data including on target effects is ongoing.

The novel ARMS model resulted in tumor formation (median latency = 25.7 weeks). Mice injected with empty vector controls did not form tumors when aged for one year. Metastases were not identified. Histopathology demonstrated that PAX3-FOXO1 tumors recapitulated human ARMS based on expression of desmin and myogenin, and PAX3-FOXO1 expression by RT-PCR and Western blots. In addition, intramuscular injection of PAX3-FOXO1- tumor-derived cells resulted in rapid and reproducible tumor formation with a mean latency of 3.5 weeks. Molecular analysis and histopathology of the secondary model tumors confirmed human RMS based on RMS markers.

Conclusion: We performed a comprehensive epigenetic screen on ARMS and ERMS human and murine cell lines and identified promising epigenetic targets. Ongoing experiments include identifying other potential target genes in the top hits, studying their biological effects, and defining their mechanisms of action. Furthermore, we have developed a novel RMS mouse model overexpressing PAX3-FOXO1 that recapitulates human ARMS. Finally, our immunocompetent mouse models will provide preclinical tumour models to test promising epigenetic agents alone and in combination.

Poster #186 3256678

CLONAL EVOLUTION OF CHEMOTHERAPY RESISTANT RHABDOMYOSARCOMA VIA MULTIFOCAL GENOMIC ANALYSIS OF PRE-TREATMENT AND TREATMENT-RESISTANT AUTOPSY SPECIMENS

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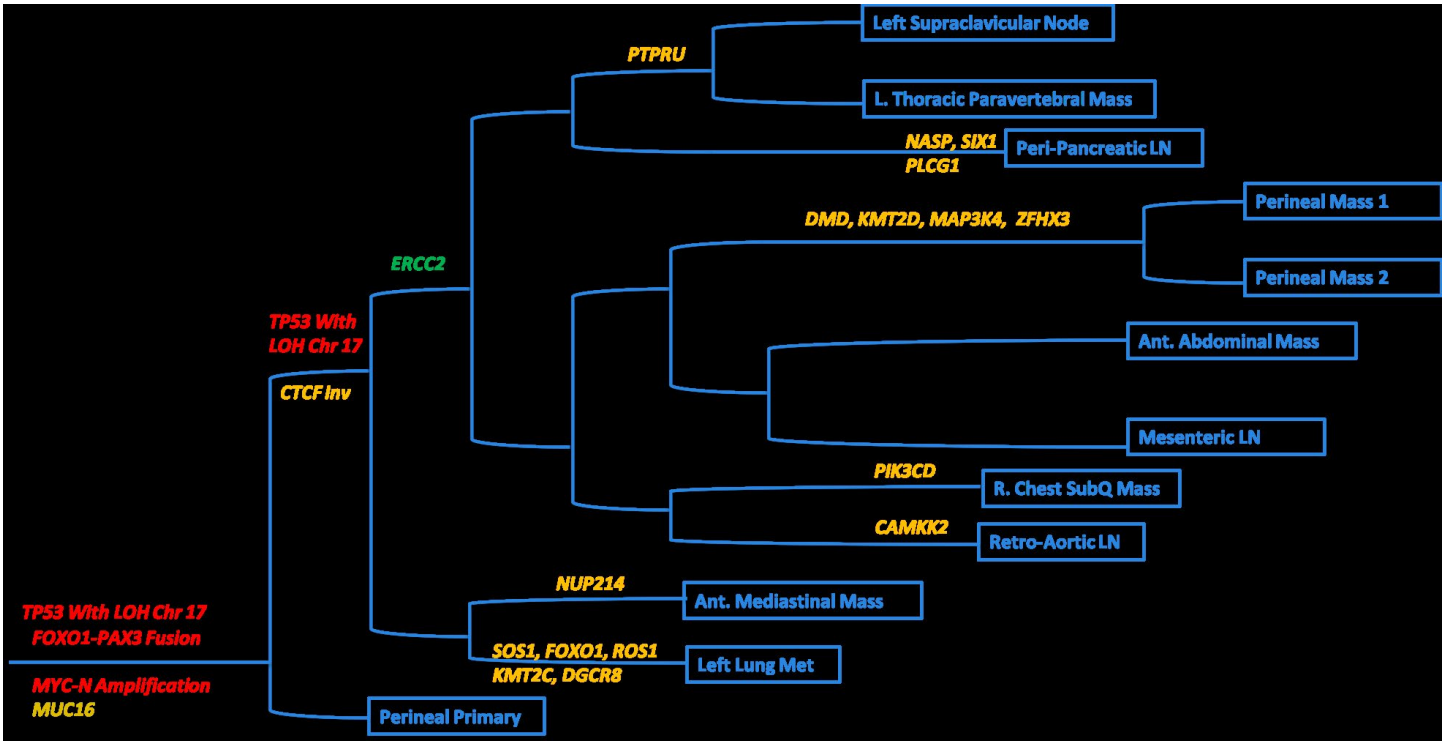
Objective: Outcomes for patients with rhabdomyosarcoma (RMS) who have relapsed or refractory disease remain poor. Multiple large-scale tumor genomic profiling efforts have been undertaken, however little is known about its spatial intratumoral heterogeneity (ITH) and temporal clonal evolutionary processes.

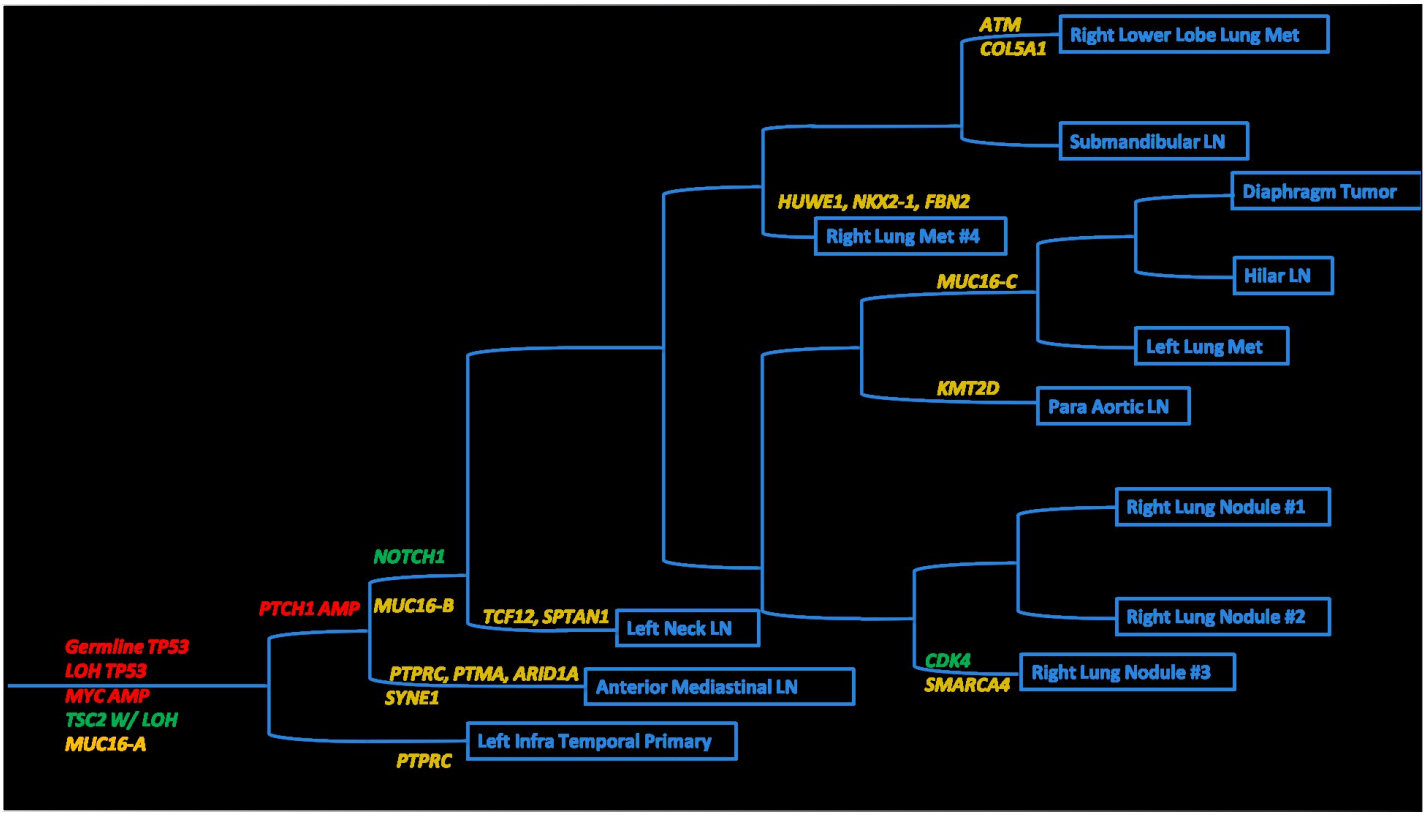
Methods: To address this issue, we performed 80x whole genome sequencing of 23 metastases and 2 pre-treatment samples from two patients with lethal rhabdomyosarcoma. Multiregion and spatially separated metastases were available through our research autopsy donation program. RA 17-1 had fusion-positive alveolar RMS, while RA 17-10 had Li-Fraumeni Syndrome and anaplastic embryonal RMS.

Results: We observed on average 65 and 98 coding single nucleotide variants (SNV) per sample in RA 17-1 and RA 17-10 respectively. RA 17-1 was found to have the canonical PAX03-FOX01 fusion along with MYC-N amplification, which was truncal to all samples. A somatic TP53 mutation in combination with TP53 loss of heterozygosity (LOH) was present in all metastases sequenced at autopsy. A TP53 mutation was not identified in the pretreatment biopsy sample selected for sequencing, however, TP53 immunohistochemistry demonstrated the presence of a TP53 mutation in at least 2 out of 6 pretreatment biopsy cores. In RA 17-10 each sample exhibited numerous copy number alterations and complex structural variants, including LOH of TP53, a TSC2 mutation with LOH, and MYC amplification, which were truncal to all samples. PTCH1 amplification was private to all relapse specimens in RA 17-10. RA 17-10 had more structural and copy number variations per sample than RA 17-1. Phylogenies were derived based on SNV's and demonstrated a branched evolutionary pattern for each patient. When comparing related samples mutational signatures, several dynamics were apparent, including the predominance of signatures 3 and 8 (DNA double-strand break repair pathways) in metastatic samples, consistent with the fact that both patients harbored TP53 mutations.

Conclusion: Defining important elements of ITH within metastases remains a goal for genomic study in pediatrics, especially in patients with germline predisposition syndromes. Our findings demonstrate the dynamic nature of genomic instability processes, highlighting the importance of longitudinal sampling at the time of recurrence to define treatment effect and the changing mutational landscape in these tumors. The case of RA 17-1 demonstrates the limitations of targeted sequencing on a single sample at diagnoses, as the subclonal TP53 mutation was not originally identified on the clinical assay. TP53 mutations in fusion-positive RMS has rarely been described and likely contributed to this patient's refractory disease course. Both RA 17-1 and RA 17-10 had more structural variants per sample then what has previously been reported for fusion positive and fusion negative RMS respectively, likely highlighting the contribution of the TP53 mutation to genomic instability in each patient. A number of "actionable" mutations were found to be subclonal and private to a single relapse site including ATM, CDK4, and ROS1, highlighting the importance of taking a cautious approach to interpreting targeted sequencing data from a single site of multifocal relapse.



RA 17-1 Phylogenetic Evolutionary Tree



RA 17-10 Phylogenetic Evolutionary Tree

Poster #187 3256484

INTERIM RESULTS FROM A PHASE I/II TRIAL OF GANITUMAB PLUS DASATINIB IN PATIENTS WITH RELAPSED RHABDOMYOSARCOMA (RMS)

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Objective: Preclinical data suggests that co-targeting the IGF-1 receptor and the SFK YES results in improved durability of growth inhibition in *in vivo* models of RMS, compared to IGF-1R targeting alone. The objectives of this study are to determine the safe dose of the IGF-1R antibody ganitumab given in combination with the multi-kinase inhibitor dasatinib in patients with relapsed and/or refractory RMS, and to describe the activity of this combination with regard to objective response rate and PFS at 4 months.

Methods: We are conducting a phase I/II trial (NCT03041701) to determine the maximum tolerated dose (MTD) of the combination of ganitumab plus dasatinib in patients with relapsed or refractory alveolar RMS (ARMS) or embryonal RMS (ERMS), the objective response rate (PR and CR) as defined by RECIST, and the fraction of patients that are without progression at 4 months. The MTD is determined based on cycle 1 toxicities. Ganitumab is administered once every 2 weeks at a dose of 18 mg/kg throughout the phase 1 portion. Dasatinib is administered continuously at DL 1: 60 mg/m^2once daily, 2: 60 mg/m^2 twice daily. Response is assessed after cycle 2 and then every other cycle. Correlative analyses of expression of relevant targets will be performed retrospectively.

Results: Ten patients (4 M: 6 F), median age 12.5 years, (range 8-19) with ERMS (n=6) and ARMS (n=4) have enrolled at DL1 (n=7), and DL2 (n=3). One dose-limiting toxicity (grade 3 diarrhea) has been observed at DL1 and no dose-limiting toxicities have been observed at DL2 thus far. 8 patients are evaluable for MTD determination (received at least 2 ganitumab doses and >85% of dasatinib doses in cycle 1). Common non-DLT toxicities are fatigue, nausea, thrombocytopenia, anemia, lymphopenia, elevated transaminases, diarrhea, hypophosphatemia, and hypocalcemia. Patients received a median of 1.5 cycles (range 0-6). Two patients had stable disease at DL1 (2 and 6 cycles); one patient achieved a confirmed PR at DL2, which was durable for 5 cycles.

Conclusion: In pediatric patients with relapsed or refractory RMS, the combination of ganitumab plus dasatinib is tolerable at DL1. MTD has not yet been reached. In a subset of patients, the combination results in disease control (SD or PR) for longer than 4 months. Enrollment is ongoing and updates will be reported.

Poster #188 3255404

CELL-CELL INTERACTION IN UNDIFFERENTIATED PLEOMORPHIC SARCOMA

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Objective: To determine if 1) tumor cells interact with each other and affect their growth potential, 2) The molecular mechanisms involved in these interactions.

Methods: UPS cells from the KPCC mouse model. In this model, the undifferentiated pleomorphic sarcoma (UPS) is induced by intramuscular injection of an adenovirus expressing Cre recombinase to produce conditional mutation of Kras and Trp53. This model also contains a cassette with fluorescence proteins flanked by loxP sites. Cre recombinase injection results in the expression of a particular fluorescence protein in each tumor cell. Tumor cells were dissociated and separated by individual colors using flow cytometry. Four different color cell subclones from the tumor: YFP, RFP, DP and CFP were used for the studies. For the proliferation assay, each cell type was plated and treated with its own conditioned media or with media from each of the other three cell types. Cell confluency was evaluated using IncuCyte and cell proliferation was assessed using Click-iT™ Plus EdU Flow Cytometry Assay Kit. For wound healing RFP cells were cultured until completely confluent. Then, artificial scratches were made using a pipette tip and cell migration into the wounded area was evaluated using IncuCyte. Migration and invasion was evaluated using 8um of pore size insert. Cells were plated in the transwell insert coated with Matrigel (invasion assay) or without Matrigel (migration assay). The conditioned media was added to the lower chamber. After incubation, migrating and invading cells were counted. For proteomic analysis the cells were incubated with AHA and the media was collected and enriched for mass spectrometry.

Results: To determine if the conditioned media from one cell type influences the growth of another cell type, we treated each cell type, RFP, YFP, DP, and CFP, with its own media or conditioned media from each of the other cells. Conditioned media from CFP cells increased the confluency of RFP cells, compared to RFP cells treated with conditioned media from RFP cells. Conditioned media from CFP cells did not have an effect in the confluency of YFP or DP cells. Furthermore, conditioned media from RFP, YPF or DP cells did not affect the confluency of CFP cells. Since conditioned media from CFP cells had a significant effect on RFP cells, the next experiments were perfomed using CFP and RFP cells. Next, we performed proliferation assay and found that RFP cells treated with conditioned media from CFP cells have a higher proliferation rate. To determine if conditioned media from CFP cells would affect the migration capacity of the RFP cells, we performed a wound healing assay. For this, the cells were grown to confluency and then a portion of the cells were scraped with a tip. 24 hours later, the empty area in the RFP cells treated with CFP cells conditioned media was almost full, while the RFP cells treated with RFP cells conditioned media still had a significant gap. Next, we performed cell migration and invasion assays and found that RFP cells in CFP cells conditioned media have a higher migration and invasion ability than RFP cells in RFP cells conditioned media. To identify potential secreted factors released by the CFP cells, we performed proteomic analysis and identified 233 secreted proteins, of these, 37 proteins were expressed at a fold change higher than 2 in the media from CFP cells compared to the media from RFP cells media. Go analysis showed that these proteins are involved in biological processes important for cancer development including chemotaxis, cell migration, and cell adhesion.

Conclusion: CFP cells conditioned media affects the proliferation, migration and invasion ability of RFP cells, potentially by releasing proteins involved in chemotaxis, cells migration or cell adhesion. This shows that within human UPS tumors, cells interact with each other to alter sarcoma cell behavior. Targeting these interactions could be used as an approach to treat sarcomas.

FIGURE1

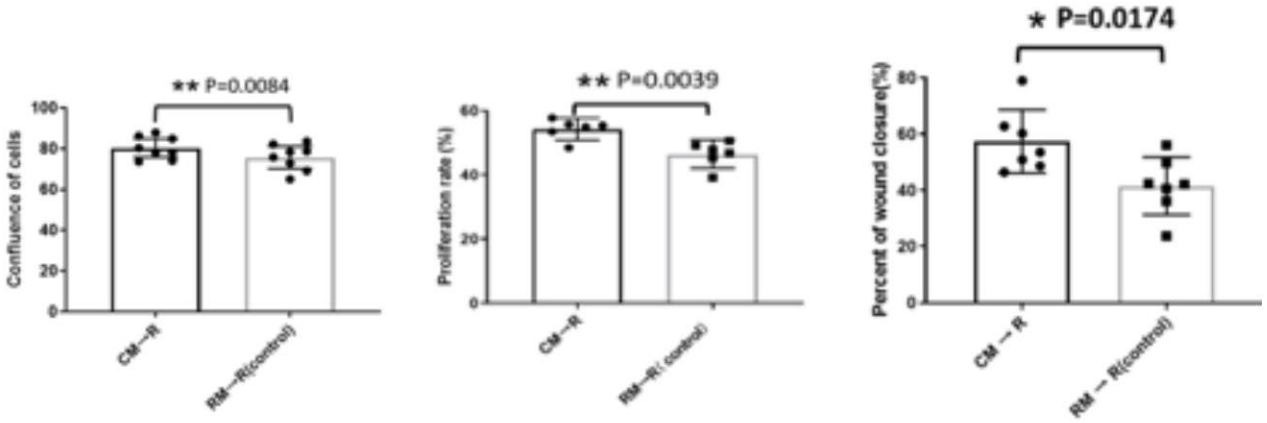
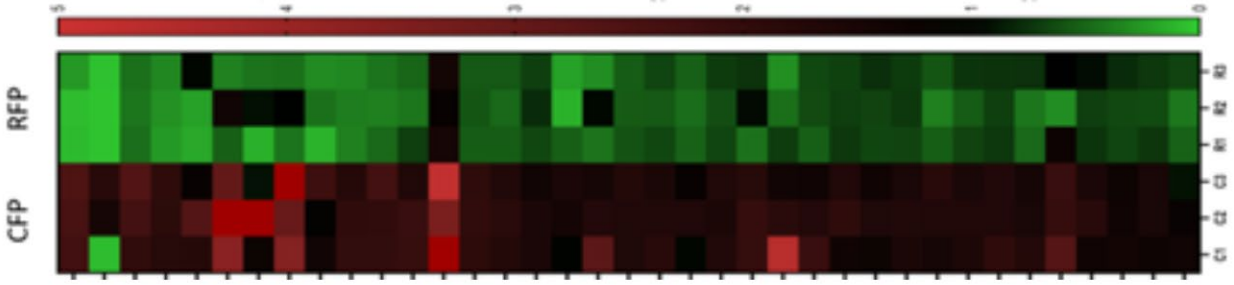


FIGURE2



Biological Process (GO)			
GO-term	*description*	*count in gene set*	*false discovery rate*
GO:0050921	positive regulation of chemotaxis	8 of 142	1.99e-07
GO:0030335	positive regulation of cell migration	11 of 500	2.36e-07
GO:0030334	regulation of cell migration	13 of 805	2.36e-07
GO:0002690	positive regulation of leukocyte chemotaxis	7 of 93	2.36e-07
GO:0009653	anatomical structure morphogenesis	18 of 2089	2.42e-07
GO:0001568	blood vessel development	10 of 504	9.16e-07
GO:0032101	regulation of response to external stimulus	11 of 681	1.09e-06
GO:0007155	cell adhesion	11 of 705	1.38e-06
GO:0048514	blood vessel morphogenesis	9 of 406	1.62e-06
GO:0051239	regulation of multicellular organismal process	19 of 2858	1.78e-06

Poster #189 3256145

E-CADHERIN REPRESSES ANCHORAGE-INDEPENDENT GROWTH IN SARCOMAS THROUGH BOTH SIGNALING AND MECHANICAL MECHANISMS

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Objective: To identify the core regulatory networks mediated by E-cadherin in sarcomas and to decipher their functional consequences.

Methods: Mathematical modeling techniques were used to analyze the prognostic significance of E-cadherin in osteosarcoma using datasets from The Cancer Genome Atlas. Additionally, *in vitro* experiments were performed with several sarcoma cell lines to investigate the functional consequences of E-cadherin expression levels.

Results: Unlike in carcinomas, E-cadherin overexpression in sarcomas does not induce a mesenchymal-epithelial transition (MET). Rather, E-cadherin acts to reduce both anchorage-independent growth and spheroid formation of sarcoma cells. Ectopic E-cadherin expression acts to downregulate phosphorylated CREB (p-CREB) and the transcription factor, TBX2, to inhibit anchorage-independent growth. RNAi-mediated knockdown of TBX2 phenocopies the effect of E-cadherin on p-CREB levels and restores anoikis sensitivity to sarcoma cells. Beyond its signaling role, E-cadherin expression in sarcoma cells also strengthens cell-cell adhesion and restricts spheroid growth through mechanical action.

Conclusion: Together, our results demonstrate that E-cadherin inhibits sarcoma aggressiveness by preventing anchorage-independent growth. E-cadherin can restrict aggressive behavior in sarcomas through both biochemical signaling and biomechanical effects.

Poster #190 3258044

REVIEW OF GENETIC ALTERATIONS IN SARCOMA PATIENTS OF HISPANIC ETHNICITY: ANALYSIS OF 167 PATIENTS, A SINGLE INSTITUTION EXPERIENCE

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Objective: Sarcomas are a rare and heterogeneous group of mesenchymal tumors arising from soft tissues and bones. Sarcomas have historically been classified based on histologic subtype. Over the last several decades, management has included combinations of surgery, radiation, and standard cytotoxic chemotherapy. Despite this approach, metastatic sarcoma continues to be associated with poor prognostic outcomes. Advances in genetic sequencing techniques have allowed identification of genetic variability among this heterogeneous population of patients and prompted the development of novel targeted therapies. There is limited data regarding genetic variability among ethnicities with sarcoma. According the United States Census Bureau 2017 data, Hispanics make up 18.1% of the nation's population and continues to increase, while; genomic data for hispanics remains grossly underrepresented. Our institution has a significant Hispanic population. The purpose of our retrospective analysis is to review the mutational variability among Hispanic and non-Hispanic subgroups.

Methods: Data for 167 patients was retrieved by chart review of electronic health records. Genomic sequencing data for all patients with a diagnosis of sarcoma from our institution was reviewed and kept in a HIPAA compliant database. The ESMO Scale of Clinical Actionability for molecular targets (ESCAT) and OncoKB precision oncology knowledge base were used to evaluate clinical relevance of various targets as defined by; Tier I: Targets used in clinical decisions, Tier II: Targets beneficial in patient population with additional data required, Tier III: Prior clinical benefit in other tumor types for similar targets, Tier IV: Pre-clinical evidence of actionability, Tier V: Evidence supporting co-targeting approaches, Tier X: Lack of evidence. We then compared the genetic alterations in hispanic and non hispanic groups.

Results: Out of 167 patients**,** 96 patients (57%) were females, 71 (43%) were males. The median age was 59 years (16-90). The majority of patients, 107 (64%) were non-Hispanics, while 60 (36%) were of Hispanic ethnicity. All patients had biopsy proven sarcoma encompassing a wide range of histologies. The most frequently observed mutation in both Hispanic and non- Hispanic patients was TP53 mutations noted in 40% and 60.75% of patients respectively. The most frequent alterations actionable or not in Hispanic and non- Hispanic patients are reported in table 1 and table 2. Among the Hispanic population, 31 patients (48%) had an actionable mutation. The most frequently observed actionable alteration was PTEN (Tier IV) seen in 10 of the 31 Hispanic patients (35%). Interestingly, 7 of the 10 patients were males. Other actionable mutations observed included; PDGFRB (Tier I), CDK4 (Tier II), KRAS (Tier IV), NRAS (tier III), BRCA1 (Tier III), EGFR (Tier III), PTCH1 (Tier III), KIT (Tier I), BRAF (Tier III) and PIK3CA (Tier III). All of these alterations had targeted agents available in clinical development; however there is paucity of FDA approved targeted agents in all sarcoma patients.

Conclusion: Advances in genetic sequencing have revealed the genetic variability amongst sarcomas of different histologies. It remains unclear if this heterogeneity exists across different ethnic groups. Our study reveals a brief comparison of genetic landscape of Hispanic and non-Hispanic patients. Further analysis including the survival data are ongoing and will be reported.

Table 1: Ten Most Frequent Genetic Alterations Observed By Incidence in Hispanic Population N=60

Gene Alteration	Incidence
TP53	24 (40%)
PTEN	11 (18.33%)
RB1	10 (16.67%)
CDKN2A/B	9 (15%)
MDM2	7 (11.67%)
CDK4	6 (10%)
ATX4	6 (10%)
FRS2	5 (8.33%)
EWSR1	5 (8.33%)
PIK3CA	5 (8.33%)
CUX1	5 (8.33%)
KRAS	5 (8.33%)
CREBBP	4 (6.67%)
PTCH1	4 (6.67%)
CRKL	3 (5%)
CDKN2A	3 (5.00%)
NF!	3 (5%)
CIC	3 (5%)
CDC73	3 (5%)
BRCA1	2 (3.33%)

Table 2: Ten Most Frequent Genetic Alterations Observed by Incidence in Non-Hispanic Population N-107

Gene Alteration	Incidence
TP53	65 (60.75%)
RB1	21 (19.63%)
ATRX	16 (14.95%)
CDKN2A/B	13 (12.15%)
NF1	10 (9.35%)
PTEN	9 (8.41%)
ATM	8 (7.48%)
KRAS	8 (7.48%)
MDM2	7 (6.54%)
CDK4	7 (6.54%)
EWSR1	6 (5.61%)
PIK3CA	6 (5.61%)
FANCA	5 (4.67%)
PDGFRA	4 (3.74%)
NF2	4 (3.74%)
MYC	4 (3.74%)
TFE3	4 (3.74%)

Poster #191 3258096

MUTATIONAL AND BIOMARKER CORRELATIVE ANALYSIS OF MTOR PATHWAY ABERRATIONS IN PATIENTS WITH ADVANCED MALIGNANT PERIVASCULAR EPITHELIOID CELL TUMORS (PECOMA) TREATED WITH *NAB*-SIROLIMUS: RESULTS FROM AMPECT, AN OPEN-LABEL PHASE 2 REGISTRATION TRIAL

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Objective: Advanced malignant PEComa is a rare, aggressive sarcoma, with no approved treatment. Loss-of-function mutation of *TSC1* or *TSC2* and mTOR pathway overactivation has been described in this disease. Case reports have suggested the benefit of mTOR inhibition in patients with PEComa. *nab*-Sirolimus is a novel albumin-bound intravenous mTOR inhibitor with increased tumor uptake and mTOR target suppression, and a distinct pharmacokinetic profile versus oral mTOR inhibitors. The AMPECT trial is the first trial to prospectively evaluate mutational status and biomarkers in this patient population.

Methods: Patients with measurable disease and ECOG 0 or 1 received intravenous *nab*-sirolimus (100 mg/m^2 IV, weekly, 2/3 weeks) until progression or unacceptable toxicity. Primary endpoint: overall response rate (ORR) by independent radiology review (IRR), assessed every 6 weeks (RECIST v1.1). Secondary endpoints: duration of response (DOR), progression-free-survival rate at 6 month (PFS6), median PFS and overall survival, and safety. Exploratory endpoints included multiple biomarkers: mutational analysis (oncopanel) was by next-generation sequencing of a 500-gene panel, including *TSC1, TSC2, TP53, PTEN*, and *FAT1*. *TFE3* translocation analysis was done via FISH. Immunohistochemistry included phosphorylated S6, 4EBP1, and AKT and % Ki67.

Results: A total of 34 patients were treated, 31 were evaluable for efficacy (had centrally confirmed PEComa), and 28 patients had evaluable tissue for oncopanel, IHC, and/or FISH. IRR of response identified 39% ORR (all partial responses [PR], 12/31, 95% CI: 21.8, 57.8), 52% stable disease (16/31, with 10/16 SD ≥12 weeks), and 10% progressive disease (3/31). One patient had an unconfirmed PR without subsequent scans and was assessed as SD ≥12 weeks. Adequate tumor tissue was available for Oncopanel and IHC analysis for 25 patients, and for 22 patients for FISH. *TSC1* or *TSC2* mutations were identified in tumors from 5 and 9 (no overlap) of 25 pts with mutational analysis, respectively. Confirmed PR was seen in 8 of 9 (89%) patients with *TSC2* mutation (1 patient with *TSC2* mutant tumor had an unconfirmed PR), 1 of 5 (20%) with *TSC1* mutation, and 1 of 11 (9%) without mutation in *TSC1* or *TSC2*. Response was significantly higher in patients with *TSC2* mutations vs TSC1 and vs pts without mutation in *TSC1* or *TSC2, P* = 0.0008 (Chi-square). SD ≥12 weeks occurred in patients in each of the above subgroups. Responses also occurred in patients with unknown mutational status (2/6, 33%).

Ongoing median duration of response (DOR) is not yet reached for patients with TSC2 mutations (8 patients, all ongoing, range: 4.2+ to 27.7+ months). One patient with a *TSC1* mutation and one patient with no *TSC1* or *TSC2* mutations had a DOR of 5.6 months and 14.1+ months respectively. The primary site of tumors for the 9 patients with *TSC2* mutations were retroperitoneum (3), kidney (2), uterus (2), liver (1) and small bowel (1).

In 25 patients whose pS6 status was available, 17 tumors were pS6+ and 8 tumors were pS6-. Responses occurred in 10/17 (59%) of pS6+ patients versus none of 8 pS6- patients, *P* = 0.0077 (Fisher exact test).

TFE3 translocation was identified by FISH in 2 of 25 patients; both patients had stable disease, pS6-, and no mutations in *TSC1* or *TSC2*.

Conclusion: In a prospective exploratory analysis of the AMPECT registrational trial, *TSC2* mutation was significantly associated with response to *nab*-sirolimus in patients with advanced malignant PEComa. The absence of phosphorylated S6 IHC staining was significantly associated with non-response to *nab*-sirolimus treatment. Durable responses and stable disease were also observed in patients with *TSC1* mutations and in patients without *TSC1* or *TSC2* mutations. NCT02494570

Poster #192 3255343

THE SAINT: RESULTS OF A PHASE 1/2 STUDY OF SAFETY/EFFICACY USING SAFE AMOUNTS OF IPILIMUMAB, NIVOLUMAB AND TRABECTEDIN AS FIRST LINE TREATMENT OF ADVANCED SOFT TISSUE SARCOMA *(NCT 03138161)*

Erlinda M. Gordon, MD*; Victoria Chua-Alcala; Katherine M. Kim; Nicole Angel; Rekha Baby; Ania Moradkhani; Doris M. Quon; Steven Wong; Sant P Chawla M. Inc*
Sarcoma Oncology Center, Santa Monica, CA, USA

Objective: Sarcoma cells are most immunogenic earlier in the disease course and prior to treatment when the immune system can recognize and destroy them. Hypothesis: Immune checkpoint inhibitors would be most effective when given as first line therapy.

Objectives:
(1) To evaluate the safety of ipilimumab (I), a CTLA4 inhibitor, nivolumab (N), a PD-1 inhibitor, and escalating doses of trabectedin (T), a marine- derived natural alkaloid with pro-apoptosis and immune modulator properties, in advanced soft tissue sarcoma (STS),
(2) To investigate the disease control response rate (DCR), objective response rate (ORR), progression free survival (PFS) and overall survival (OS), and
(3) to correlate response with immune cell trafficking in the tumor microenvironment.

Methods: This is an IRB-approved dose-seeking Phase 1/2 protocol using defined doses of I (1 mg/kg i.v. q 12 weeks), N (3 mg/kg i.v. q 2 weeks) and escalating doses of T (1.0, 1.2, 1.5 mg/m2 i.v. q 3 weeks), employing the "Cohort of Three" design in previously treated patients. This is followed by an expanded Phase 2 using defined doses of I and N at the above schedules, and the MTD of T q 3 weeks in previously untreated patients. Treatment is continued in spite of radiologic progression provided patient has grade 1 or less toxicity. Efficacy analysis reports best overall responsein evaluable patients (Modified Recist v1.1).

Results: Nine subjects were treated in the Phase 1 part of the study, and 32 subjects in the expanded Phase 2 part. Safety Analysis (n=9 (PTPs)): Phase 1 Dose 1: Grade 3 treatment-related adverse events (TRAEs) included fatigue (n=1), increased TSH (n=1). Phase 1 Dose 2, Grade 4 TRAEs included thrombocytopenia with bleeding, DLT (n=1), increased CK (n=1); Grade 3 TRAEs included anemia (n=1), increased TSH (n=1), decreased TSH (n=1), increased AST (n=1). Efficacy analysis (evaluable patients, n =5): At Dose 1: Disease Control Rate (DCR = CR, PR, SD) was 67%, median PFS, 25 weeks; median OS, 50 weeks; At Dose 2: DCR 60%, median PFS, 24 weeks; median OS, 53 weeks. At Phase 2, Dose 2 (PUPs): Safety analysis (n=32): Grade 3 TRAEs included increased ALT (n=4), hyperglycemia (n=3), port cellulitis (n=1), neutropenia (n=1), lymphocytopenia (n=2). Efficacy analysis (n=26 evaluable): PR (n-5; 2 UPS, 1 synovial sarcoma, 1 liposarcoma, 1 clear cell sarcoma, 1 synovial sarcoma), Best ORR 18.5%, DCR 96%. PRs occurred in PUPs. Median PFS is >24 weeks and median OS is >59.5 weeks. After 4 treatment cycles, one resected tumor showed 80% necrosis and a greater number (30%) of CD8+ killer T cells, in the TME compared to archived pre-treatment tumor.

Conclusion: Taken together, these data suggest that the SAINT protocol (1) is safe with manageable adverse events with no additive toxicity, (2) the required pulses of dexamethasone with trabectedin infusion may reduce the severity of immune related adverse events without decreasing combinatorial efficacy, and (3) partial responses and disease control may be achieved with continued treatment with or without initial radiologic signs of disease progression. The Phase 2 study is on-going.

Poster #193 3255504

INITIAL RESULTS OF A PHASE 1/2 INVESTIGATION OF SAFETY/EFFICACY OF NIVOLUMAB AND ABI-009 (NAB-RAPAMYCIN) IN ADVANCED UNDIFFERENTIATED PLEOMORPHIC SARCOMA (UPS), LIPOSARCOMA (LPS), CHONDROSARCOMA (CS), OSTEOSARCOMA (OS), AND EWING'S SARCOMA (NCT 03190174)

Erlinda M. Gordon, MD; *Victoria Chua-Alcala; Katherine M. Kim; Nicole Angel; Rekha Baby; Doris Quon; Steven Wong; Ania Moradkhani; Sant P Chawla M. Inc*
Sarcoma Oncology Center, Santa Monica, CA, USA

Objective: Objectives: (1) To investigate the MTD of ABI-009 when given with nivolumab, a PD-1 inhibitor, in previously treated advanced undifferentiated pleomorphic sarcoma, liposarcoma, chondrosarcoma, osteosarcoma and Ewing sarcoma; (2) To investigate the disease control rate (DCR), progression-free survival (PFS), and overall survival (OS) of this combination therapy in the above mentioned patient group, and (3) To correlate PFS with PD-L1 and other biomarker expression in patients' tumors.

Methods: This is an IRB approved protocol with 2 parts. The Phase 1 part is a dose-finding study using the "cohort of three design", wherein standard doses of nivolumab 240 mg is given iv every 3 weeks (Day 1 of every 21-day Cycle). ABI-009 will be given IV on Days 8 and 15 of each cycle starting on Cycle 2 following the 2nd nivolumab dose. The starting dose of ABI-009 is 56 mg/m2, and sequentially escalating doses are 75, and 100 mg/m2. The Phase 2 part of study will enroll 31 additional patients to further assess efficacy and safety at the MTD.

Results: The Phase 1 part of study is closed after 9 patients were treated successfully at 3 dose levels. No dose-limiting toxicities (DLTs) were observed, the MTD was not reached, and 100 mg/m2 ABI-009 was designated as the recommended phase 2 dose. Safety analysis: At Dose 1 (n=3): Grade 3 treatment-related adverse events (TRAEs) included dyslipidemia (n=1) and hyperglycemia (n=1). At Dose 2 (n=3): Grade 3 TRAEs included increased ALT (n=1). At Dose 3 (n=3): Grade 3 TRAEs included hypophosphatemia (n=1). Eight of 9 patients have discontinued treatment: 6 patients due to PD, 2 with SD opted to stop treatment due to drug-related Grade 2 AEs (pruritus, acneiform rash), and 1 with SD is still on therapy at Dose 3.

Conclusion: The primary objective has been met with no DLTs, the MTD was not reached and Dose 3 has been designated as the phase 2 dose of ABI-009 which is on-going.

Poster #194 3256430

RESPONDER ANALYSIS OF PATIENT-REPORTED OUTCOMES MEASUREMENT INFORMATION SYSTEM (PROMIS) PHYSICAL FUNCTION (PF) AND WORST STIFFNESS AMONG PATIENTS WITH TENOSYNOVIAL GIANT CELL TUMORS (TGCT) IN THE ENLIVEN STUDY

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Objective: The double-blind, randomized, placebo-controlled phase 3 ENLIVEN study in TGCT demonstrated a significant tumor response at week 25 by RECIST for pexidartinib (39% vs. 0% for placebo) and improvement in joint function and symptoms. The aim of this analysis was to identify a threshold score for responder definitions for PROMIS-PF scale and Worst Stiffness Numerical Rating Scale (WS-NRS) and compared responder rates for pexidartinib versus placebo.

Methods: Anchor- and distribution-based estimates were calculated, and cumulative distribution function (CDF) plots were generated to derive responder definition threshold estimates. Anchor- and distribution-based results and CDFs were evaluated through triangulation, following FDA PRO Guidance, to determine a single responder definition threshold (i.e., meaningful change) for each instrument. The proportion of responders at Week 25 between treatments was compared with Fisher's Exact Test (2-sided).

Results: 120 patients were randomized to pexidartinib (n = 61) and placebo (n = 59) and assessed through 25 weeks of treatment. Anchor-based analysis showed one-level improvement on the patient global rating of PF item was associated with a mean change of 4.0 on PROMIS-PF. Distribution-based estimates (0.5 SD and 1 SEM) for PROMIS-PF were 2.8 and 2.5, respectively. For WS-NRS, a response of "A little improved" by patients on the perception of stiffness item was associated with a mean change of 1.1. The distribution-based estimates for the WS-NRS item were 0.9 and 0.5, respectively. This resulted in the following responder definition thresholds: ≥3 points for PROMIS-PF and ≥1 for WS-NRS improvement. A greater proportion of pexidartinib as compared to placebo patients were responders by PROMIS-PF (30% vs. 5%, $p<0.001$) and WS-NRS (39% vs. 19%, $p=0.02$) at week 25, respectively.

Conclusion: Triangulation yielded responder definitions of ≥3 points for PROMIS-PF and ≥1 for WS-NRS. With these definitions, a greater proportion of patients treated with pexidartinib compared to placebo had meaningful improvement in physical function and stiffness.

Poster #195 3255349

DEVELOPMENT OF RAPID AND COST-EFFECTIVE ASSAY TO DETECT AMPLIFICATION OF CHROMOSOME 12Q13-15 IN WELL DIFFERENTIATED AND DE-DIFFERENTIATED LIPOSARCOMA

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Objective: Background: Liposarcomas are one of the most common mesenchymal tumors that occur in soft tissues. Well-differentiated and dedifferentiated liposarcomas (WDLS/DDLS) are characterized by an amplification of the chromosome 12q13-15 region, which contains *MDM2*, *CDK4* and numerous other genes. The current gold standard to differentiate WDLS from lipomas and DDLS from other pleomorphic sarcomas is FISH to detect *MDM2* amplifications; however, FISH is relatively costly and is often associated with lengthy turnaround times. The NanoString nCounter assay is a high-throughput hybridization technique using target-specific probes to assess the expression of multiple genes in a single assay utilizing RNA extracted from formalin-fixed paraffin-embedded (FFPE) material. This technique uses no enzymatic steps and is tolerant of low quality tissue specimens.

Objective: We report on the development and evaluation of a novel NanoString based molecular diagnostic assay to detect concurrent overexpression of multiple genes in the chromosome 12q13-15 amplicon to differentiate WDLS/DDLS from histologically similar tumors.

Methods: A set of 43 target genes was selected based on a literature review and available gene expression data for 56 WDLS/DDLS cases and 206 other sarcoma cases. The initial set included 40 genes from the chromosome 12q13-15 region. RNA was extracted from 4-6x 10 micron scrolls of FFPE samples of WDLS, lipoma and other sarcomas. 150ng RNA was hybridized overnight with gene specific barcoded probes. Unbound probes and RNA were removed and the remaining complexes of reporter probe/capture probe/RNA were bound to a streptavidin coated cartridge. The bound complexes were aligned and counted on a Nanostring Digital analyzer based on the fluorescent reporter probe barcode tags. We identified the top 20 differentially expressed genes ranked by p-value between lipoma and WDLS samples using a two-sided t-test. Using these 20 genes, we trained a random forest model in R that predicts the likelihood of WDLS on a set of 22 training samples (9 lipoma and 13 WDLS). A random forest model is a collection of decision tree models, each trained using a subset of lipoma vs WDLS samples and a subset of the 20 genes. Each tree was trained using 4 genes and 14 random samples out of the 22 training samples. 500 such trees were trained simultaneously and combined (ensemble of trees). At model run-time, each tree outputs a prediction, and the probability that the sample is WDLS is taken as the % of trees that vote for WDLS. To assess accuracy of the model, we used 5-fold cross validation repeated 5 times, and took the average for each fold.

Results: In the initial assay of 43 genes, differentially expressed genes included *MDM2*, *CCT2*, and *FRS2* (5.9x, 6.9x and 5.3x higher in WDLS). *MDM2* was the top gene for differential expression between WDLS and lipoma, and was sufficient to separate lipoma from WDLS samples (Figure 1). In a random forest model, the top 20 differentially expressed genes showed a prediction value of 99.2% on a test set of 9 Lipomas and 13 WDLS. To date, all 13 validation WDLS cases tested using this 20 gene expression cassette cluster could be clearly separated from the 12 lipoma and 24 other sarcoma samples assessed (Figure 2). The assay takes 36 hours to run from RNA extraction to result and costs less than USD$300 per case including reagents and technologist time.

Conclusion: We have developed a Nanostring assay to detect chromosome 12q13-15 amplification based on surrogate overexpression of a panel of 20 genes within this chromosomal region. This assay can be performed at low cost and with quick turnaround, and has the potential to replace FISH as a first-line molecular diagnostic assay for distinguishing WDLS from lipomas and other histologic mimics, as well as DDLS from other sarcomas. The assay may also have value for low grade osteosarcomas with *MDM2* amplifications, and more generally this strategy could also be adapted for the detection of other amplicons.

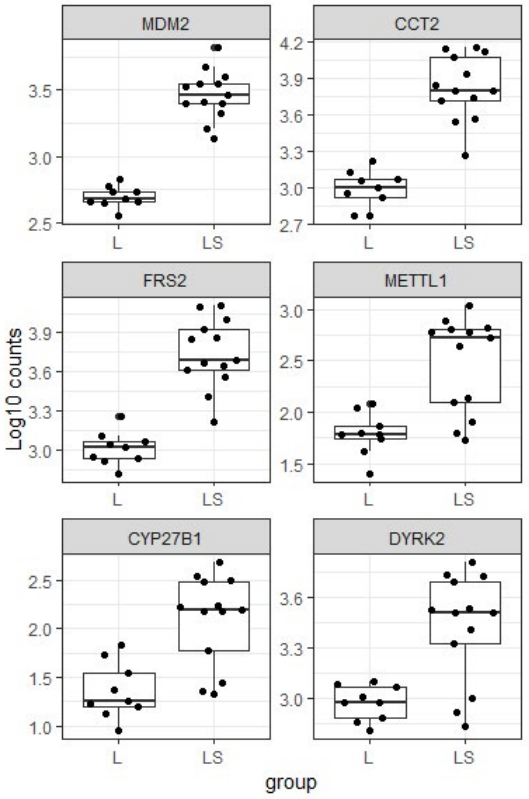

Figure 1: Top 6 differentially expressed genes between lipoma and WDLS samples, ranked by p-value

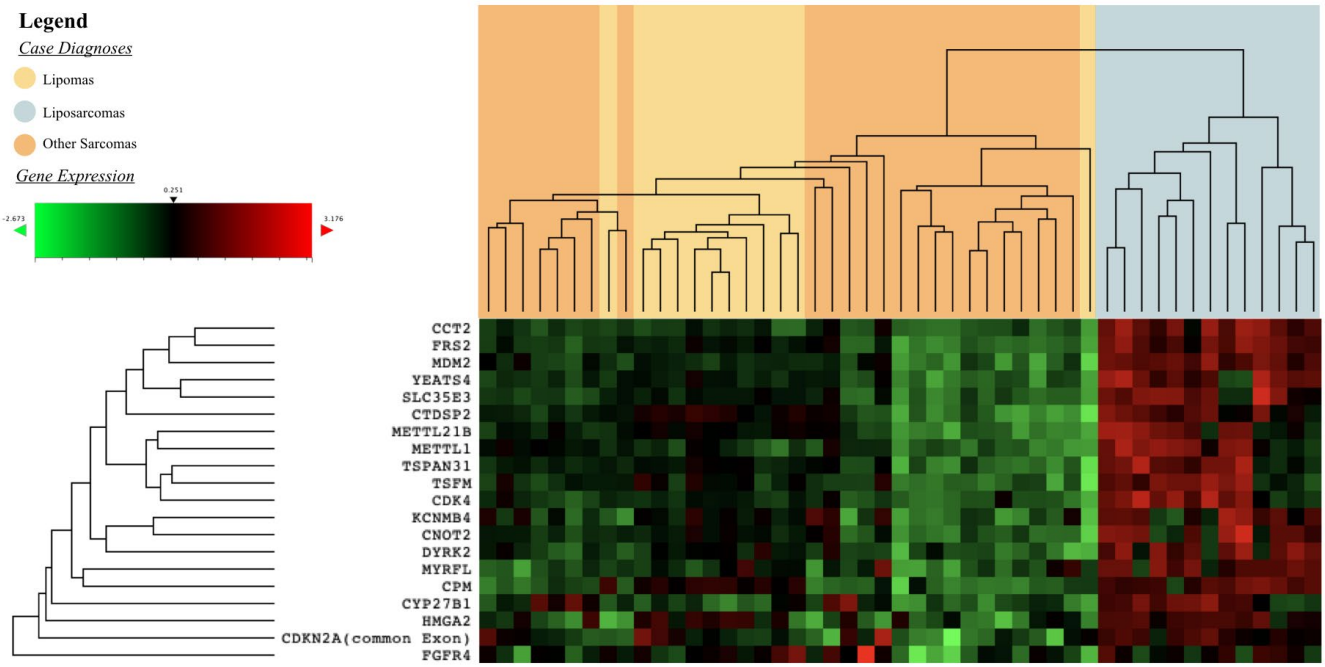

Figure 2. Gene Expression Heat Map

Poster #196 3255331

CLINICAL OUTCOMES IN THE SETTING OF MULTIMODALITY TREATMENT OF PRIMARY ANGIOSARCOMA AND RADIATION-INDUCED ANGIOSARCOMA OF THE BREAST

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Objective: The estimated incidence of primary angiosarcoma (PAS) of the breast is 0.002% to 0.05% per year, and the estimated incidence of radiation-induced angiosarcoma (RIAS) is 0.01% to 0.02% per year. To our knowledge, no studies to date have compared outcomes in PAS to RIAS in the setting of multimodality treatment (neoadjuvant chemotherapy and radiation therapy, surgery, and adjuvant chemotherapy and radiation therapy). This study evaluates clinical PAS and RIAS outcomes in the setting of multimodality treatment at a high-volume academic medical center.

Methods: Patients diagnosed with non-metastatic PAS or RIAS of the breast were identified from our tumor registry (2010-2017). Data was collected for patient demographics, tumor characteristics, systemic therapy, radiation, surgical treatment, and pathology. Primary outcomes werelocal recurrence (LR), distant recurrence (DR), and median overall survival (OS).

Results: Eleven patients met inclusion criteria. Five (46%) had RIAS. Compared to PA patients, RIAS patients were older (67.0 vs 42.8 years, p=0.009) and had more comorbidities (Charlson Comorbidity Index >2, 100% vs 16.7%, p=0.22). The average time from radiation to diagnosis was 7.4 years in the RIAS group. Tumor size did not differ significantly for those with RIAS compared to PAS. RIAS patients had a higher percentage of high-grade sarcoma (40% vs 0%, p=0.084). PAS patients were more likely to receive multimodality neoadjuvant treatment with chemotherapy (50% vs 30%, p=0.303) and radiation (33.3% vs 10%), p=0.154). The most common surgical procedure was total mastectomy or a modified radical mastectomy for both PA (83.3%) and RIAS (80.0%). Adjuvant chemotherapy was more likely to be given to those with PA (50% vs 30%, p=0.303) and adjuvant radiation was more likely to be given to those with RIAS (33.3% vs 20%, p=0.621). A greater percentage of RIAS patients had a LR (40% vs 16.7%, p=0.38), whereas a great percentage of patients with PAS had distant metastasis (50% vs 0%, p=0.064). Median OS was 103 months in those with PAS and 145 months in those with RIAS (p=0.866).

Conclusion: RIAS patients were older than the PAS patients, and the average time from radiation to diagnosis was 7.4 years, which is consistent with the literature. Median OS was higher for both PAS (103 months) and RIAS (145 months) than that described in the largest retrospective series in the literature (93 months for PAS and 32 months for RIAS). This study suggests that in the setting of multimodality treatment at a high-volume sarcoma academic center, long-term survival is achievable for PAS and RIAS. Multi-institutional and randomized control studies need to be conducted to further evaluate the benefit of multimodality treatment in the management of PAS and RIAS.

Table 1. Demographics, tumor characteristics, treatment and survival in patients with primary versus radiation-induced angiosarcoma

		Combined (n=11)		Primary (n=6)		RIAS (n=5)		
		%	n	%	n	%	n	p
Demographics								
Age (mean, SD)		54	71.3-36.7	42.8	29.6-55.9	67	52.7-82.1	0.009
Race	White	90.9	10	100	6	80	4	0.251
	Asian/Indian	9.1	1	0	0	20	1	
Ethnicity	Hispanic	36.4	4	50	3	20	1	0.303
	Non-Hispanic	63.6	7	50	3	80	4	
BMI (mean, SD)		24.9	21.3-28.5	24.4	20.6-28.2	25.6	20.7-30.5	0.608
CCI	0	27.3	3	50	3	0	0	0.022
	1-2.	18.2	2	33.3	2	0	0	
	>2	54.5	6	16.7	1	100	5	
Tumor Characteristics								
Tumor Size (cm)		4.9	2.4-7.4	5.3	2.7-7.9	4.6	1.1-8.1	0.668
Grade	1	27.3	3	50	3	0	0	0.084
	2	54.5	6	50	3	60	3	
	3	18.2	2	0	0	40	2	
Margin Status	R0	90.9	10	83.3	5	100	5	0.338
	R1	9.1	1	16.7	1	0	0	
Treatment								
Neoadjuvant chemotherapy		36.4	4	50	3	20	1	0.303
NAC Regimen	Doxorubicin/ifosfamide	50	2	33.3	1	100	1	0.248
	Gemcitabine/docetaxel	50	2	66.6	2	0	0	
Neoadjuvant radiation		18.2	2	33.3	2	0	0	0.154
Definitive surgical procedure	Total Mastectomy/ Modified Radical Mastectomy	81.8	9	83.4	5	80	4	0.402
	Partial mastectomy	9.1	1	16.7	1	0	0	
	Chest wall excision, removal of implant	9.1	1	0	0	20	1	
Adjuvant chemotherapy		36.4	4	50	3	20	1	0.303
AC Regimen	Doxorubicin/ifosfamide	27.3	3	75	3	100	1	0.395
	Gemcitabine/docetaxel	9.1	1	25	1	0	0	
Adjuvant radiation		27.3	3	33.3	2	20	1	0.621
Survival								
Local Recurrence		27.3	3	16.7	1	40	2	0.38
Distant Recurrence		27.3	3	50	3	0	0	0.064
Median Survival (months, 95% CI)		145	36.5-253.4	103	60-9-200.0	145	54.9-196	0.866

Poster #197 3255375

DETECTION OF TRANSLOCATION ASSOCIATED SARCOMAS BY EXON EXPRESSION IMBALANCE AND GENE OVER-EXPRESSION

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Objective: Background: The NanoString nCounter assay is a high-throughput hybridization technique using target-specific probes that can assess the expression of multiple gene target sites in a single assay utilizing RNA extracted from formalin-fixed paraffin-embedded (FFPE) material. This technique uses no enzymatic steps and is tolerant of low quality tissue specimens. Recently, we developed a clinically-validated assay using Nanostring probes that hybridize across fusion junction sequences that detects 178 sarcoma fusion variants with 96% sensitivity and 100% specificity, and does so at lower cost and faster turn-around than FISH or next generation sequencing (Chang KTE et al, J. Mol. Diagn. 2018). Despite the effectiveness of this assay to detect most sarcoma fusion types, there were several entities for which fusion junction probes were not suitable due to excessive variability at the junction sites. To complement our current fusion assay, we used a Nanostring-based gene expression approach to detect aberrant 5′/3′ exon expression imbalance as a surrogate marker for fusion gene rearrangement.

Objective: We report on the development of a NanoString-based assay to diagnose translocation-associated sarcomas via exon imbalance analysis and over-expression of genes involved in fusion transcripts.

Methods: Oligonucleotide probes targeting 6-8 exonic sites per gene were designed to assess exon expression imbalance across 25 sarcoma fusion genes, with focus on 3′-partner genes (Figure 1). Total gene expression was also analyzed for 5 additional genes previously shown to be consistently overexpressed in unison in *CIC*-rearranged sarcoma. RNA was extracted from 2-3x 10 micron FFPE scrolls. Up to 150ng RNA was hybridized overnight with a pool of barcoded gene specific oligonucleotide probes ("codeset"). Bound codeset/RNA complexes were counted on a NanoString Digital analyzer based on bound fluorescent reporter probe barcode tags. RNA sample quality was determined by expression of four housekeeping genes. A minimum positive exon imbalance ratio and expression ratio was set for each gene as the average background ratio plus 5x the standard deviation (Table 1).

Results: To date, 26 confirmed translocation-associated sarcoma samples and 24 non-fusion samples have been run on the assay. The single *CIC-DUX4* sample showed gene over-expression of 4 out of 5 genes (*CCDN2*, *CRH*, *ETV1*, *ETV4*, *ETV5*) ranging from 17-1181x the median expression for the corresponding gene for all other samples analyzed. 18 of the 19 exon imbalance genes assessed to date showed differential exon expression for the positive case(s) analyzed (Figure 2). Instead of differential exon expression, complete gene overexpression was detected for both cases with a *STAT6* translocation. The exon imbalance was detectable for the single case with a *TFE3* translocation at a lower stringency of background plus 4x standard deviation. This case also showed a marked decrease in overall *TFE3* expression. Nine of the genes showed detectable gene over-expression correlating with the exon imbalance for the respective positive cases. A *BCOR-CCNB3* case showed increased expression for both the *BCOR* and *CCNB3* genes, as expected. The assay takes 36 hours to run from RNA extraction to result and costs less than USD$300 per case including reagents and technologist time.

Conclusion: A Nanostring-based exon expression imbalance approach shows high sensitivity for detecting sarcoma fusions that are difficult to detect using other approaches and represents a rapid, low-cost and sensitive method to identify diagnostic sarcoma fusion events. In combination with our previously established fusion junction sequence assay, we are developing a combined assay that will have comprehensive coverage of all sarcoma fusion types. Given the coverage of fusion types seen in other malignancies (e.g. ALK, ROS, RET, NTRK and other kinase fusions), we also hope to utilize this assay strategy for screening non-sarcoma cases.

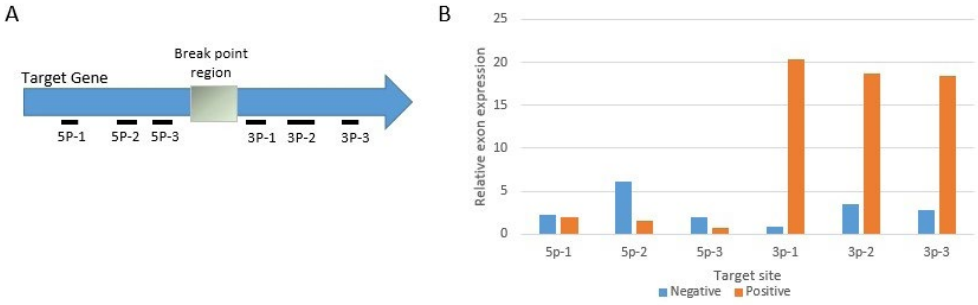

Figure 1. **Exon imbalance**. Exon expression imbalance was detected by comparing the normalized counts for the target sites upstream vs downstream of the translocation region for each gene.

Gene Target	Cases (detected/ expected)	Average negative exon imbalance (std. dev)	Positive case exon imbalance range	Average negative expression (std. dev)	Positive case over-expression range
ALK	2/2	1.34 (1.03)	3P/5P: **22.00 - 151.12**	1.36 (1.09)	**7.49 -184.24**
BCORL1	none	0.99 (0.15)		1.02 (0.44)	
BCOR	1/1	1.04 (0.14)		1.16 (0.56)	**86.67** (BCOR-CCNB3)
BRAF	1/1	0.97 (0.15)	3P/5P: **2.03**	1.23 (0.74)	0.73
CAMTA1	2/2	1.40 (1.14)	3P/5P: **9.32 - 13.39**	1.84 (2.42)	2.91 – 10.30
CCNB3	1/1	1.09 (0.52)	3P/5P: **1632.76**	1.24 (0.64)	**686.49**
CREB3L1	1/1	1.06 (0.15)	3P/5P: **5.00**	1.41 (1.29)	4.26
CREB3L2	1/1	0.98 (0.12)	3P/5P: **2.54**	1.07 (0.49)	2.44
CSF1	1/1	1.06 (0.16)	5P/3P: **6.60**	1.06 (0.75)	2.56
FOSB	none	1.00 (0.28)		2.38 (3.31)	
NFATC2	1/1	1.29 (0.73)	3P/5P: **8.73**	1.33 (1.30)	2.61
NRG1	none	1.40 (1.48)		3.04 (5.19)	
NTRK1	1/1	0.98 (0.24)	3P/5P: **15.00**	1.42 (1.08)	**6.96 -58.08**
NTRK2	2/2	1.09 (0.44)	3P/5P: **6.30 - 27.86**	1.45 (0.77)	**5.85 -9.66**
NTRK3	2/2	1.18 (0.80)	3P/5P: **10.13 - 101.30**	3.33 (5.61)	**16.26**
NUTM1	1/1	0.82 (0.48)	3P/5P: **11.05**	2.22 (4.18)	**33.56**
PATZ1	none	1.07 (0.24)		1.13 (0.68)	
PDGFB	1/1	0.93 (0.24)	3P/5P: **34.44**	1.09 (0.72)	**4.89**
PHF1	none	1.22 (0.44)		1.12 (0.47)	
PLAG1	1/1	1.16 (0.40)	3P/5P: **68.82**	1.18 (1.10)	**10.97**
RET	1/1	1.00 (0.23)	3P/5P: **10.48**	2.52 (4.49)	2.85
ROS1	1/1	1.00 (0.23)	**3.09**	2.66 (5.47)	0.84
STAT6	2/2	0.96 (0.09)	3P/5P: 0.91 - 1.09	1.00 (0.41)	**6.64 - 10.41**
TFE3	1/1	1.05 (0.15)	5P/3P: 1.66	1.20 (0.66)	0.30
USP6	2/2	1.29 (0.76)	3P/5P: **17.58 - 145.86**	2.22 (2.79)	**27.70 - 31.95**
CIC fusion panel					
CCDN2	1/1			1.33 (1.07)	2.43
CRH				1.82 (2.5)	**1181.71**
ETV1				2.53 (3.12)	**17.38**
ETV4				7.03 (15.53)	**822.05**
ETV5				1.50 (1.32)	**23.90**

Figure 2. Assay coverage

Poster #198 3255558

RETROSPECTIVE ANALYSIS OF CT VERSUS XR SURVEILLANCE FOR METASTASIS AFTER SURGICAL RESECTION OF LOCALIZED SOFT TISSUE SARCOMA

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Objective: There is no clear consensus on the best surveillance regimen after resection of soft tissue sarcomas (STS). As such, practices differ between institutions, countries and specialties. Further investigation of surveillance patterns and patient outcomes could reduce unnecessary testing in this population. Previous studies have shown no significant survival difference between patients followed with chest x-ray (XR) versus computed tomography (CT) scan after resection of bone or soft tissue sarcoma of the extremities. In this study, we aimed to examine whether there was a statistically significant difference between these modalities in patients who underwent resection of localized soft tissue sarcoma of any site including trunk and retroperitoneum. Additionally, we evaluated whether the frequency of Ct scan (three- versus six-month intervals) led to any difference in overall survival, time-to-detection, or time-to-biopsy of a pulmonary nodule.

Methods: We performed a retrospective cohort analysis of patients who underwent surgical resection of a localized soft tissue sarcoma at a US tertiary-referral sarcoma center between 1999-2016. The primary outcome was overall survival in patients followed with chest XR versus CT at three years, five years and overall, as assessed using the log rank test. Additionally, overall survival between patients who underwent CT scan every three months versus six months were compared in terms of overall survival, as well as the time-to-detection of pulmonary nodules and time-to-biopsy of these nodules.

Results: Of the 234 patients included in this study, 135 underwent post-operative surveillance with chest XR, while 99 were followed with chest CT. Of the latter group, 67 had scan every three to four months, while 32 underwent scan every 6 months. There were 64 fatalities related to recurrent or metastatic sarcoma, 28 in the CT scan group and 36 in the XR group. There were an additional 18 fatalities attributable to other causes or of unknown cause. There was no statistically significant difference in overall survival between the XR and CT scan group at 36 ($p=0.99$) and 60 months ($p=0.85$), as well as overall(time of death or last follow up) ($p=0.67$). There additionally was no statistically significant difference in overall survival between patients who underwent screening with CT scan at 3-month intervals vs 6-month intervals ($p=0.71$).

Conclusion: As demonstrated in previous studies of extremity STS, patients with surgically resected, localized tumors have no statistically significant difference in overall survival if they undergo post-operative surveillance for metastatic disease with XR vs CT scan. A randomized, multi-institutional trial would be beneficial to further examine the safety of less intensive regimens for surveillance for metastatic disease.

Poster #199 3255785

THE PROGNOSTIC INFLUENCE OF HYALURONIC ACID EXPRESSION IN RESECTED SOFT TISSUE SARCOMA

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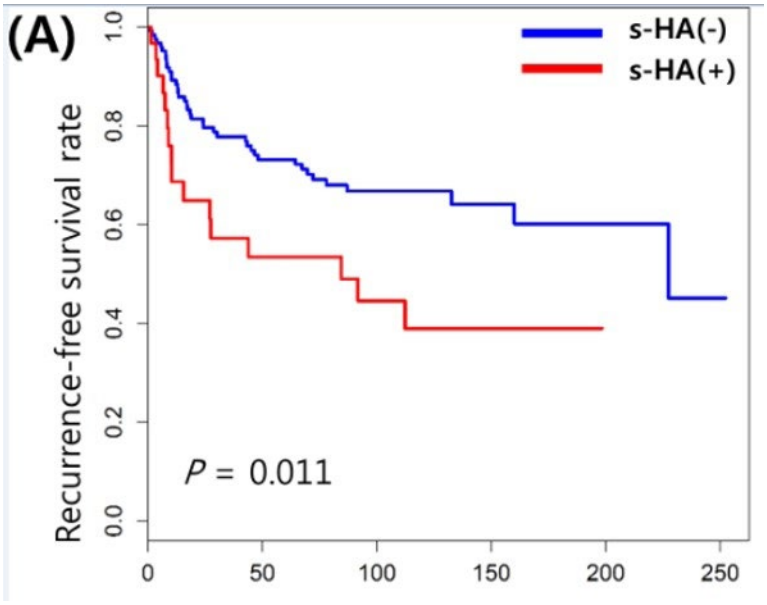
Objective: Hyaluronic acid (HA) is one of components of the extracellular matrix that plays a critical role in a various cellular processes. The regulations of HA include cancer cell adhesion, migration, and proliferation associated with the prognosis in numerous types of malignant tumors. However, the clinical prognostic significance of HA in soft tissue sarcoma (STS) has not been well evaluated.

Methods: Tissues from STS patients undergoing surgical resection were analyzed in tissue microarrays (TMAs) divided into stroma and cancer panels. Besides protein expression levels of HA, HA synthases, and hyaluronidases were also included to assess by immunohistochemistry.

Results: A total of 112 STS tissues collected between 2010 and 2018 were analyzed. Male patients were 59 (52.6%), female patients were 53 (47.4%). The median age was 60 (range 8~91). The most common type of STS was liposarcoma (23%, n=28), followed by leiomyosarcoma (20.5%, n=23), undifferentiated pleomorphic sarcoma (UPS, 17.8%, n=20). The clinicopathological characteristics showed non-significant difference based on stromal HA protein expression. However, the clinical outcome was significantly associated with stromal HA expression levels. The clinical outcomes of stromal HA expression was found to be an independent indicator of disease recurrence (hazard ratio [HR], 2.345; 95% confidence interval [CI], 1.187−4.875, P = 0.011, figure A) in the multivariate analysis, and the combined analysis of tumor and stromal expression of HA showed that STS patients with stroma-positive HA expression had significantly worse outcomes than those with other combinations (recurrence-free survival, P = 0.048; overall survival, P = 0.074).

Conclusion: Stromal HA expression may be independently correlated with poor prognosis in STS. Thus, HA expression in the stroma may serve not only as a prognostic marker, but also as a putative target for STS treatment.



Poster #200 3256055

EVALUATION OF DISTROFIN EXPRESSION BY INMUNOHISTOCHEMISTRY AS A PROGNOSTIC FACTOR IN LEIOMYOSARCOMAS

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Objective: Leiomyosarcomas (LMS) are soft tissue sarcomas with a complex karyotype that derive from smooth muscle and can arise anywhere in the body. The known clinical prognostic factors are location, size, stage at diagnosis and histological grade. However, the molecular factors influencing the patients prognosis are unknown. The *DMD* gene, that codifies for protein dystrophin, has been proposed as tumour suppressor gene in sarcomas with myogenic origin like LMS. We aimed to evaluate the expression of dystrophin in LMS and its correlation with the patients prognosis.

Methods: A total of 50 LMS patients were analysed. Clinical and pathological characteristics were obtained retrospectively from the patients' electronic record system. Dystrophin expression was analysed by immunohistochemistry (IHC) in paraffin embedded tissue LMS samples using the Novocastra NCL-DYS2 (Leica Biosystems). Semiquantitative assessment of the staining was classified from score 0 to 3, being 0 no dystrophin expression 1 low expression, 2 moderate expression and 3 high dystrophin expression.

Results: A total of 16 patients had metastatic disease at diagnoses. Fifteen LMS samples were located in the extremities, 11 in retroperitoneum, 12 were uterine, 7 were cutaneous and 5 were in other locations**.** All but 2 of the evaluated samples were grade 2 or 3 (FNCLCC).

Lost dystrophin expression (IHQ score 0 or 1) was more frequent in grade 3 samples (N=25, 73.5%) than grade 2 samples (N=8, 23.5%) ($p<0.05$). Dystrophin expression by IHC did not correlate with the risk of relapse in patients with localized disease: 57% (N=12/21) of the patients with IHC score 0-1 relapsed compared to 67% (N=8/12) of the patients with score 2-3 ($p>0.05$). However, the majority of patients with metastatic disease at diagnosis (N=16) had loss of dystrophin expression (12 patients, 75% score 0-1 vs 4 patients, 25% score 2-3).

Conclusion: Loss of dystrophin expression is a common event in high grade LMS. Dystrophin expression is more frequently lost in grade 3 LMS compared to grade 2, and in LMS with metastatic disease at diagnoses. Loss of dystrophin expression did not correlate with the risk of relapsed in localized LMS.

Poster #201 3256112

CLINICAL AND MOLECULAR CHARACTERISTICS AND OUTCOMES OF 59 PATIENTS WITH EXTRASKELETAL MYXOID CHONDROSARCOMA TREATED AT TWO INSTITUTIONS

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Objective: Extraskeletal myxoid chondrosarcoma (EMC) is an extremely rare histotype of sarcoma that usually arises in soft tissue; firstly described in 1972 by Enzinger, it has been recently identified to carry a NR4A3 reciprocal translocation. EMC is characterized by a quite indolent behaviour but despite optimal surgery it displays high rates of local recurrence and metastases even after many years from first treatment. EMC is considered among sarcomas resistant to chemotherapy (CHT).

Methods: Electronic health records of patients (pts) with a diagnosis of EMC treated at Istituto Oncologico Veneto (IOV) in Padova and at Institut Gustave Roussy (IGR) in Villejuif from 1980 to 2018 were retrieved from a prospectively maintained database. Demographics, histological data, treatment approach, response and oncological outcomes were collected. Statistical analysis was performed with Sigmaplot software v.14

Results: Data on 59 pts were retrieved, 37 male, with a M/F ratio of 1.6/1, median age at diagnosis 56 years (range 24-90); most frequent primary tumor sites were lower limb (34 pts), abdomen (7 pts), upper limb (5 pts), chest (3 pts), other sites (6 pts). Molecular data are available for 22 pts, all with NR4A3-EWSR1 translocation, for other pts analyses are ongoing. After primary treatment, thirteen pts (22%) had local recurrence and 25 pts (42.4%) developed distant metastases with the most frequent sites being lung (22 pts) and bone (4 pts). Six pts presented with metastastic disease at diagnosis. Overall survival (OS) for all pts was 18.3 years (IC 95%13.1-23.4), and OS for metastatic patients was 4.1 years (IC 95% 2.5-5.7) with a median time from diagnosis to metastases of 3.4 years. A trend for better survival was observed in pts with primary location in the limbs compared to other sites though not significant. Nineteen pts with metastatic disease, mean PS 1, were treated with first line CHT (11 anthracycline-based; 4 oral cyclophosphamide and 4 other regimens). Out of 16 pts evaluable for response, best response was stable disease (8 pts), progressive disease (7 pts), partial response (1 pt), with disease control rate of 69%. Second-line CHT was given to 13 patients (trabectedin in 4 pts, etoposide in 3 pts; anthracycline in 3 pts, other regimens in 3 pts) with a disease control rate of 45% (5 pts out of 11 pts evaluable). Six pts (mean PS 2) did not receive CHT for metastatic disease. No difference in survival was observed for patients treated with CHT compared to pts who did not receive CHT [mOS: 3.7 years (CI 2.1-5.3) and 4.7 years (CI 95% 1-8.3), respectively]. Drug holiday was undertaken for 8 pts with a median duration of 22.6 month (range 2-41month), still ongoing in three pts. Loco-regional treatments at relapse were frequently used, with 10 pts undergoing re-excision of relapsed mass; 22 pts palliative radiation; 4 pts pulmonary metastasectomy, and 2 pts radiofrequency ablation, with a mean of 1.56 treatment/pts (range 0-17).

Conclusion: This is a large series of EMC pts with molecular data available. Our data confirm the relative indolent behaviour of the disease, with survival rates for pts with metastastic disease of more than 4 years, with no proven efficacy of standard CHT. Compared to previous clinical series, these data show a globally better survival, and this could be due to higher use of loco-regional treatments for metastatic disease. A possible prognostic role of specific rare translocations cannot be ruled out as of now.

Patients Characteristics

CHARACTERISTICS	N.	%
INSTITUTION	-	-
IOV	31	52.5
IGR	28	47.5
SEX	-	-
M	37	62.7
F	22	37.3
PRIMARY SITE:	-	-
Lower limb	34	57.6
Upper limb	5	8.4
Abdomen	7	11.9
Chest	3	5
Other	6	10.2
Not available	4	6.9
FIRST TREATMENT	-	-
Surgery	40	67.8
Radiation therapy	3	5
Chemotherapy	10	17
Not available	6	10.2
METASTATIC SITE	-	-
Lung	22	-
Bone	4	-
Other	11	-
TRANSLOCATION	-	-
EWSR1-NR4A3	22	37.3
Analyses ongoing	37	62.7
NEOADJUVANT/ADJUVANT CHEMOTHERAPY	9	15.3
NEOADJUVANT/ADJUVANT RADIATION THERAPY (RT)	15	25.4
METASTASES	25	-
At diagnosis	6	-
Metastatic relapse	19	-
PALLIATIVE CHEMOTHERAPY	19	76
LOCOREGIONAL TREATMENT	-	-
RT	22	-
Lung metastasectomy	4	-
Excission of recurrence	10	-
Radiofrequency	2	-
LINES OF PALLIATIVE CT	1-6	-

Poster #202 3256175

NY-ESO-1 TCR T (GSK3377794)– CASE STUDIES – SARCOMA AND MRCLS – CORRELATES OF PREDICTABLE RESPONSE CHARACTERISTICS

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Objective: Genetically engineered NY-ESO-1 specific T cells (NY-ESO-1 TCR T Cells; GSK3377794) are autologous CD4+ and CD8+ T cells transduced with a self-inactivating lentiviral vector to express an affinity-enhanced NY-ESO-1-specific T-cell receptor. Ongoing Phase 1 and 2 trials are evaluating GSK3377794 in solid tumors and hematologic malignancies. This is a case study review of clinical observations and biomarker data for 8 patients from two ongoing Phase 1/2 pilot studies of GSK3377794 in SS and MRCLS (NCT01343043 and NCT02992743, respectively) who showed extended duration of response and stable disease.

Methods: Patients who were progression free for at least 4 months after the first T-cell infusion were selected: seven patients from Cohort 4 of the ongoing SS trial and one patient from the ongoing MRCLS trial. All patients were treated with the same lymphodepletion regimen (30 mg/m^2 x3D Fludarabine, 600 mg/m^2 x3D Cyclophosphamide) prior to the first NY-ESO-1 TCR T-cell infusion. Six of the seven patients with SS were eligible for a second NY-ESO-1 TCR T-cell infusion and received higher-dose lymphodepletion (30 mg/m^2 x4D Fludarabine, 1800 mg/m^2 x2D Cyclophosphamide) prior to the second infusion. Pre-treatment tumor biopsies were analyzed for CD3 infiltration by RNAScope. Persistence of transduced cells in the peripheral blood was measured by quantitative PCR of transgene vector copies in DNA extracted from PBMCs. Expression of cytokines in the serum was measured by Meso Scale Discovery immunoassay and PBMC phenotypes were characterized by flow cytometry.

Results: Basic demographic data is presented in Table 1 for the 8 patients. Five of 7 patients with SS had SD, and 2/7 had PR/CR per RECIST1.1. Duration of stable disease for these patients ranged from 17.8 weeks to 105 weeks. The one patient with MRCLS had a PR per RECIST1.1 which lasted for 8.8 months. Six of 7 SS patients received a second infusion, with 2/7 having a SD to second infusion, and 3/7 having a PR, and 1/7 having a CR. Patients had high expression of NY-ESO-1 as determined by immunohistochemistry, at least ≥ 50% of cells that are 2+ or 3+, and expression was maintained prior to second infusion (if applicable). Baseline tumor samples before first infusion consistently showed <2% CD3 T-cell infiltration. In 3/6 patients with SS receiving a second infusion after a high-dose lymphodepletion, peak persistence was increased >10 fold over the first infusion peak persistence; of these three patients, two had a PR and CR. Increases in cytokines reflecting immune cell activation, such as IFNg, IL-6, and IL-2Ra were observed within four to seven days post first and second T-cell infusion. Transduced T cells within the manufactured product showed increased expression of activation markers (such as CD28, ICOS, and CD40L) as compared to T cells from apheresis. In patients 5 and 6, transduced CD8 cells within the manufactured product primarily had a T effector memory RA+ (TEMRA; CD45RA+CCR7-) and T effector memory (TEM; CD45RA-CCR7-) phenotype. In the product for patient 7, the majority (34.3%) of transduced CD8 cells had a T stem cell memory (TSCM; CD45RA+CCR7+) phenotype.

Conclusions: SS and MRCLS tumors initially show low immune cell infiltration. Upon infusion of GSK3377794, increased expression of activated immune cell cytokines was observed in serum from all prolonged stable disease and responding patients. Analysis of individual cases of prolonged response can provide important insights into clinical response characteristics and facilitate in identifying potentially predictive biomarkers.

Clinical trial ID: NCT01343043 and NCT02992743
Acknowledgment: These studies (NCT01343043 and NCT02992743) were funded by GlaxoSmithKline (GSK).Table 1

Table 1:

Patient ID	Diagnosis	Age at Consent	Sex	Infusion Date 1	Total Transduced Dose (x10^9)	Best Response (1st Infusion)	Infusion Date 2	Total Transduced Dose (x10^9)	Best Response (2nd Infusion)
1	SS	48	Male	16-Jan-17	3.4010	SD	1-Aug-18	5.0000	SD
2	SS	68	Female	12-Dec-16	1.6000	PR	Not Applicable		
3	SS	33	Male	9-Jan-17	3.8000	SD	12-Mar-18	2.7900	SD
4	SS	58	Male	24-Apr-17	2.1000	SD	25-Apr-18	1.3140	SD
5	SS	46	Male	10-Jul-17	1.0022	SD	26-Mar-18	2.2000	PR
6	SS	36	Female	14-Jul-17	1.8000	PR	11-Apr-18	2.0000	CR
7	SS	31	Female	14-Aug-17	4.9536	SD	29-May-18	4.9876	SD
8	MRCLS	46	Female	4-Oct-17	5.0190	PR	Not Applicable		

CR, complete response; PR, partial response; SD, stable disease

Poster #203 3256364

PHASE 1 TRIAL OF NY-ESO-1-SPECIFIC ADOPTIVE T-CELL THERAPY WITH GSK3377794 IN PATIENTS WITH ADVANCED SYNOVIAL SARCOMA

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Objective: Genetically engineered NY-ESO-1 specific T-cells (NY-ESO-1 TCR T Cells; GSK3377794) are autologous CD4+ and CD8+ T-cells transduced with a self-inactivating lentiviral vector to express an affinity-enhanced NY-ESO-1-specific T-cell receptor. Ongoing Phase 1 and 2 trials are evaluating GSK3377794 in solid tumors and multiple myeloma. Study NCT01343043 (208466) is a Phase 1 clinical trial assessing GSK3377794 in pts with previously treated, advanced metastatic synovial sarcoma stratified into 4 cohorts (**Table 1**). Of the 12 patients who received GSK3377794 infusions in Cohort 1, responses were observed in 6 patients (1CR and 5PRs), yielding an overall response rate of 50% (95% CI: 0.21-0.79). The median PFS for this cohort was 15.2 weeks (95% CI: 7.6-37.9) and the median DOR was 30.9 weeks (95% CI: 14-72). As of 15 October 2018, the median OS is 105 weeks (95% CI: 37-NA). This abstract focuses on data from Cohorts 2 and 4.

Methods: Pts with unresectable, metastatic, or recurrent synovial sarcoma were enrolled to cohorts based on NY-ESO-1 tumor expression determined by immunohistochemistry (IHC). Cohort 2 included patients with low expression of NY-ESO-1 and cohort 4 included patients with high expression of NY-ESO-1 (**Table 1**). Pts received lymphodepleting chemotherapy prior to GSK3377794 infusion (**Table 1**). Response was investigator-assessed as per RECIST v1.1. Persistence of transduced cells in peripheral blood was measured by qPCR of transgene vector copies in DNA extracted from PBMCs. Progression-free survival (PFS) was defined as the interval between first GSK3377794 infusion and first documented disease progression or death. Safety was monitored throughout the study. The study was not designed or powered to compare results between cohorts.

Results: We report data from April 12, 2019 data cut-off. 50 pts were enrolled; 14 and 10 pts received a GSK3377794 infusion in Cohorts 2 and 4, respectively. ORR (95% confidence interval [CI]) was similar for cohorts 2 and 4 (30.8% [0.09, 0.61] and 26.7% [0.08, 0.55], respectively) **(Table 2)**. Median DOR (95% CI) was 9.1 weeks (8.0, 13.0; cohort 2) and 16.4 weeks (14.3, 93.6; cohort 4). Stable disease (SD) was observed in 53.8% (cohort 2) and 66.7% (cohort 4) of pts. Median duration of SD (95% CI) was 13.1 weeks (7.9, 17.6; cohort 2) and 22.4 weeks (11.3, 26.6; cohort 4). Median PFS (95% CI) was 13.1 weeks (7.9, 13.9; cohort 2) and 22.4 weeks (11.3, 26.6; cohort 4). A median peak (range) persistence of ~64,712 DNA copies/µg (13,364–197,546) was achieved in cohort 2 in the first week after infusion vs ~16,468 DNA copies/µg (163–131,175) in Cohort 4. No statistically significant correlation was observed between peak persistence and BOR in Cohorts 2 and 4 (logistic regression p>0.05). Grade 3 and 4 adverse events occurring in ≥40% of pts in both cohorts were leukopenia, neutropenia, anemia, thrombocytopenia, lymphopenia and hypophosphatemia. Guillain-Barré syndrome-like symptoms were reported in two pts; when infused T-cells were low or minimally detectable, not at time of T-cell expansion.

Conclusion: In this phase 1 trial of GSK3377794 in pts with previously treated, advanced metastatic synovial sarcoma, cohort 2 and cohort 4 showed similar ORRs, but more durable responses were observed in cohort 4 (pts with higher NY-ESO-1 expression and lower-dose lymphodepletion), with prolonged median DOR, duration of SD, and PFS. Median peak persistence of GSK3377794 was higher in cohort 2, most likely due to higher-dose lymphodepletion, but unlike data previously reported in other cohorts, this did not correlate with response. Further development in synovial sarcoma will be based on previously reported data from cohort 1 (high NY-ESO-1 expression, high-dose lymphodepletion).

Clinical trial Id: NCT01343043

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Table 1. Antigen expression and lymphodepleting regimen for each cohort in study 208466

	NY-ESO-1 expression	Lymphodepletion regimen
Cohort 1 **n=12**	**HIGH** • IHC score 2+ or 3+ in ≥50% of tumor cells	**HIGH** doses of fludarabine and cyclophosphamide • 30 mg/m^2 IV fludarabine on Days –5 to –2 and 1800 mg/m^2 IV cyclophosphamide on Days –3 and –2
Cohort 2 **n=13**	**LOW** • IHC score ≥1+ in ≥1% cells but not exceeding 2+ or 3+ in ≥50% cells	**HIGH** doses of fludarabine and cyclophosphamide • 30 mg/m^2 IV fludarabine on Days –5 to –2 and 1800 mg/m^2 IV cyclophosphamide on Days –3 and –2
Cohort 3 **n=5**	**HIGH** • IHC score 2+ or 3+ in ≥50% of tumor cells	**HIGH** doses of cyclophosphamide only • 1800 mg/m^2 IV cyclophosphamide on Days –3 and –2
Cohort 4 **n=15**	**HIGH** • IHC score 2+ or 3+ in ≥50% of tumor cells	**LOW** doses of fludarabine and cyclophosphamide • 30 mg/m^2 IV fludarabine and 600 mg/m^2 IV cyclophosphamide on Days –7 to –5
IHC, immunohistochemistry; IV, intravenous.		

Table 2. Summary of response rates, time to responses, and response durations: Cohorts 2 and 4

	Cohort 2 (n=13)	Cohort 4 (n=15)
Overall response rate, n (%) 95% CI	4 (30.8) 0.09, 0.61	4 (26.7) 0.08, 0.55
Best overall response, n (%) Complete response Partial response Stable disease Progressive disease Not evaluable	 0 4 (30.8) 7 (53.8) 1 (7.7) 1 (7.7)	 0 4 (26.7) 10 (66.7) 1 (6.7) 0
Median time to response, weeks (95% CI)	4.5 (4.1, 6.0)	6.6 (3.7, 12.1)
Median duration of response, weeks (95% CI)	9.1 (8.0, 13.0)	16.4 (14.3, 93.6)
Median duration of stable disease, weeks (95% CI)	13.1 (7.9, 17.6)	22.4 (11.3, 26.6)
Median time in study, days (min, max)	107.0 (3, 534)	242.0 (33, 739)
CI, confidence interval; NA, not available		

Poster #204 3256543

OUTCOME AFTER SURGICAL TREATMENT OF DERMATOFIBROSARCOMA PROTUBERANCE (DFSP): DOES IT REQUIRE ALL THIS FOLLOW-UP? WHAT IS AN ADEQUATE RESECTION MARGIN?

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Objective: To Assess patient outcomes following DFSP +/- FS-DFSP resection by Quantifying the radial margins, Local recurrence, Distant metastases, and devise a f/u protocol for both DFSP and FS-DFSP.

Methods: All patients treated for DFSP at a single sarcoma center were identified from a prospective database, consents were obtained from patients at the time of referral to our sarcoma clinic and prospective follow-up data was collected. Patients with and without prior surgery, and patients with Fibrosarcoma-DFSP were included. Each patient underwent resection with the goal of achieving a wide negative margin, to ensure complete removal of the tumor. But how "wide" a margin is necessary to prevent local recurrence? We defined an R0 margin as no tumor at the inked resection margin. Patients were followed after surgery to monitor complications, local recurrence, transformation and/or metastasis. Minimum follow-up was one year.

Results: N=196 patients (mean age=44.1, standard deviation= 13.7) were included with a minimum follow up of one year. 136 (69.4%) patients had a prior "whoops" procedure before referral. 60 patients (30.6%) had a primary presentation. In the DFSP group, 9/166 patients had a positive resection margin. One DFSP patient had multiple local recurrences and ultimately developed a high-grade sarcoma. In the FS-DFSP group (n=30 patients), there were 6 positive margins, 4 patients had local recurrence, and 7 developed metastasis. The 5 and 10-year metastasis-free survival rates for DFSP and FS-DFSP were 98.2%, 72.7% respectively. The 5 year LR-free survival was 99.2% for DFSP and 84.9% for FS-DFSP. Our closest radial resection margin for DFSP ranged from 0 (i.e. positive, 9/166, 5.4%) to 3.7 cm (mean 1.2 cm), and 75 % of the margins were at least 0.4 cm. In comparison, for the FS-DFSP group, the closest margin ranged from 0 (i.e. positive, 6/30, (20%) to 2.2 cm (mean 0.78 cm), and 75 % of the margins were at least 0.4 cm.

Conclusion: Local recurrence was extremely rare for DFSP patients (1/166), while it was higher in the FS-DFSP group (4/30). There were no lung metastases associated with DFSP, but 7/30 patients with FS-DFSP developed metastases. Therefore, achieving a negative as opposed to a wide margin may be sufficient to avoid local recurrence of most DFSP. Radiation and/or Imatinib may improve local control in DFSP/FS-DFSP. There is currently no histological sub-classification of FS-DFSP in the literature. However, we are currently grading FS-DFSP adopting the FNCLCC system (Maki et al., AnnSurgOncol 2013). In our institution we have developed a modified follow-up protocol for DFSP patients based on these results: No follow-up is needed for DFSP cases after wound healing due to the extremely low risk of LR & metastases; for grade I FS-DFSP, annual follow up with chest x-rays for five years; and for grades II and III FS-DFSP, follow-up should be as for similar high-grade STS.

Poster #205 3257861

THE ROLE OF NEOADJUVANT CHEMOTHERAPY IN THE MANAGEMENT OF ANGIOSARCOMA

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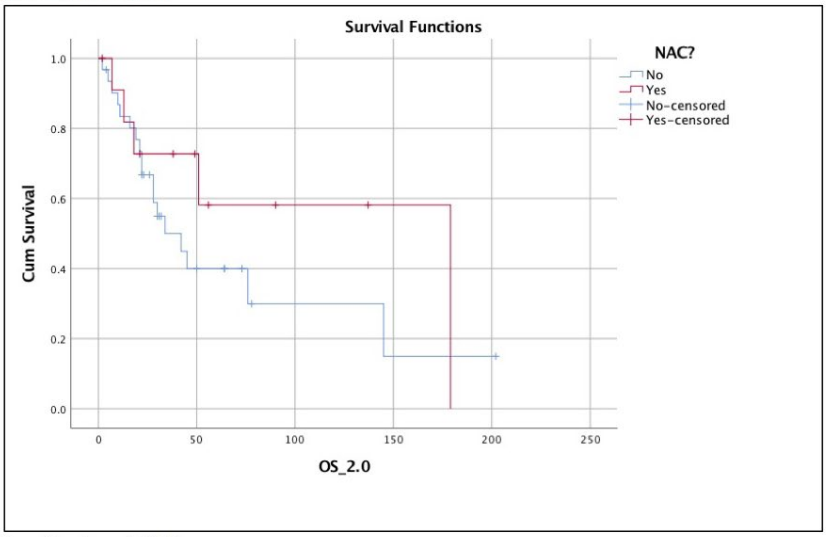
Objective: Angiosarcomas represent 1-3% of all sarcomas. There is a paucity of recent data evaluating multimodal therapy and survival outcomes for patients with this rare tumor. Our investigation evaluates clinical outcomes in the setting of multimodal treatment for a large group of patients treated at a single academic medical center.

Methods: Patients diagnosed with angiosarcoma were identified from a local tumor registry (2010-2017). Data was collected for patient demographics, tumor characteristics, systemic treatment, radiation, surgical management, and pathology. Primary outcomes were overall survival (OS) and recurrence-free survival (RFS).

Results: Sixty-six patients were identified. The average age was 63 years (53-68), 56.1% were female, and 84.8% were Caucasian. The most common tumor sites were intraabdominal (19.7%), head and neck (16.7%), extremity soft tissue (16.7%), primary breast (12.1%), and radiation-induced breast angiosarcoma (RIAS) (10.6%). Twelve patients (18.2%) had a prior history of radiation to the relevant site. Patients were diagnosed predominantly with localized disease (72.7%). Two-thirds (66.7%) underwent curative intent surgery, of which 64.3% had an R0 resection. 40.5% were classified as high grade (grade 3). Of those undergoing surgery, 31.8% underwent neoadjuvant chemotherapy and 11.4% had neoadjuvant radiation; 50.0% had adjuvant chemotherapy and 38.6% had adjuvant radiation. Median OS was 28 months and median RFS was 5 months. One-year OS was 68% and 5-year OS was 30%. OS was lowest among patients with angiosarcomas of the scalp, bone and extremity soft tissue, and highest among those with angiosarcomas of the head/neck, thorax, and RIAS (Table 2). Among non-metastatic patients (n=53), RFS was lowest among patients with angiosarcomas of the abdominal viscera, thorax, and extremity soft tissue; and highest among those with angiosarcomas of the head/neck, breast (primary and radiation-induced) and scalp (Table 3). In addition, median OS and RFS were improved among resected patients who received neoadjuvant chemotherapy compared to those who did not (179 vs 34 months, p=0.310, and 15 vs 7 months, p=0.018, respectively).

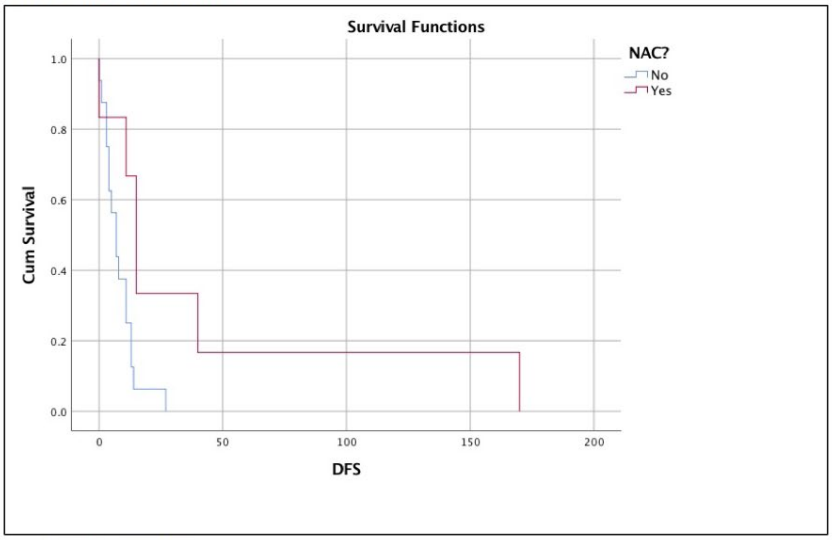
Conclusion: Limited data exists on the multimodal management of angiosarcoma. Analysis of angiosarcoma cases at our sarcoma center reveals improved RFS in patients undergoing neoadjuvant chemotherapy and a trend towards improved OS in patients undergoing neoadjuvant chemotherapy. However, further studies are needed to adequately power risk stratification and survival analysis to evaluate the benefit of multimodal treatment to manage this rare disease.

Figure 1. Overall survival in resected patients who received neoadjuvant chemotherapy versus those who did not



Log Rank p=0.310

Figure 2. Recurrence-free survival in resected patients who received neoadjuvant chemotherapy versus those who did not



Log Rank p=0.018

Table 1. Demographics, tumor characteristics, and treatment in patients with angiosarcoma

Demographics			
		n	%
Age (mean, SD)		63.2	53-68
Sex	Male	29	43.9
	Female	37	56.1
Race	White	56	84.8
	Black	8	12.1
	Asian/Indian	1	1.5
	Other	1	1.5
Ethnicity	Hispanic	23	34.8
Charlson Comorbidity Index	0	9	13.6
	1 to 2	13	19.7
	>2	44	66.7
History of Radiation		12	18.2
Tumor Characteristics			
Location	Intraabdominal	13	19.7
	Scalp	5	7.6
	Head/Neck	11	16.7
	Bone	3	4.5
	Thoracic	6	9.1
	Extremity/Soft Tissue	11	16.7
	Primary Breast	8	12.1
	Radiation Induced Breast	7	10.6
	Abdominal Wall Muscle	2	3
Group Stage	Localized	48	72.7
	Regional	5	7.6
	Distant	13	19.7
Margin Status	R0	27	64.3
	R1	13	31
	R2	2	4.8
Grade	1	7	16.7
	2	11	26.2
	3	17	40.5
	Unknown	7	16.7
Treatment			
Neoadjuvant Chemotherapy		14	31.8
Neoadjuvant Radiation		5	11.4
Curative Intent Surgery		44	66.7
Adjuvant Chemotherapy		22	50
Adjuvant Radiation		17	38.6

Table 2. Median overall survival, all patients, all sites

		95% CI	
Site	OS (months)	Lower	Upper
Head/Neck	51	9.2	92.8
RIAS	45	0	114.0
Thoracic	42	0	98.9
Primary Breast	31	23.6	38.4
Intraabdominal	19	13.5	24.5
Abdominal wall muscle	11	.	.
Extremity Soft Tissue	8	3.7	12.3
Scalp	7	0	24.6
Bone	7	0	15.0
Overall	28	17.8	38.2

Table 3. Median recurrence-free survival among non-metastatic patients

		95% CI	
Site	RFS (months)	Lower	Upper
Head/Neck	13	7.1	18.9
Primary Breast	7	0	18.2
RIAS	7	0.6	13.4
Scalp	5	0	11.4
Intraabdominal	0	.	.
Thoracic	0	.	.
Extremity Soft Tissue	0	.	.
Overall	5	1.0	9.0

Poster #206 3257892

ITALIAN SARCOMA GROUP (ISG) - SPANISH SARCOMA GROUP (GEIS) - FRENCH SARCOMA GROUP (FSG) - POLISH SARCOMA GROUP (PSG) CLINICAL TRIAL ON NEO-ADJUVANT CHEMOTHERAPY IN HIGH-RISK SOFT TISSUE SARCOMAS (STS): RESULTS OF NON-RANDOMIZED GROUP OF PATIENTS

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Objective: The ISG in collaboration with the GEIS, the FSG and the PSG carried out an international, randomized, phase III, clinical trial in localized, high-risk, STS, comparing a conventional chemotherapy with epirubicin plus ifosfamide (EI) versus an histology-tailored regimen (HT), in neo-adjuvant setting, in 5 histological subtypes: high-grade myxoid liposarcoma, leiomyosarcoma (LMS), synovial sarcoma (SS), malignant peripheral nerve sheath tumour (MPNST) and undifferentiated pleomorphic sarcoma (UPS). Final results of this study were recently presented at 2019 ASCO annual meeting. In the context of this study, a group of patients (pts) were not randomized to receive EI or HT, but were just registered and treated with EI. We report on the results in this group of pts.

Methods: Pts aged 18 years or older with localized high-risk (high malignancy grade, >5 cm, deeply located) STS of extremities or trunk wall were eligible for this trial. Pts with a diagnosis of myxofibrosarcoma, pleomorphic liposarcoma, pleomorphic rabdomyosarcoma, unclassified spindle cell sarcoma were not randomized but just registered and treated with neo-adjuvant EI. Radiation-therapy (RT) could be delivered either in pre-operative (with concomitant chemotherapy, from the second cycle) or in post-operative setting. Pts with a diagnosis of high-grade myxoid liposarcoma, LMS or UPS requiring a pre-operative RT were not randomized but just registered and treated with neo-adjuvant EI. Pts received 3 cycles of full-dose chemotherapy with epirubicin (60 mg/m2 per day, days 1 and 2) plus ifosfamide (3 g/m2 per day, days 1, 2, and 3). The Kaplan-Meier method was used to estimate Relapse-Free-Survival (RFS) and Overall Survival (OS).

Results: Between May 2011 and May 2016, 148 pts were registered in this study (myxofibrosarcoma 55 pts; pleomorphic liposarcoma: 14 pts; pleomorphic rabdomyosarcoma: 6 pts; unclassified spindle cell sarcoma: 6 pts; high-grade myxoid liposarcoma: 23 pts; LMS: 8 pts; UPS: 35 pts; other: 1 pt). Male were 101, female 47. Median age was 55 years (range: 20-75 years). Median size was 11 cm (range 10-35 cm). One hundred thirty-one pts (88%) completed chemotherapy treatment and 17 pts (12%) did not completed chemotherapy (chemotherapy interruptions reasons were: progression disease in 6 pts, toxicity in 7 pts, consent withdrawn in 2 pts, other in 2 pts). Chemotherapy dose reductions were made in 45 pts (31%); median epirubicin and IFX dose intensity were 93% and 91%, respectively. One hundred twenty-eight pts (86.5%) received RT; 71 pts (48%) in pre-operative setting, concomitantly with chemotherapy. In the group of pts treated with pre-operative RT, chemotherapy interruptions because of toxicities were observed in 6 pts (8%), dose reductions in 27 pts (38%); median epirubicin and IFX dose intensity were 91% and 90%, respectively. At a median follow-up of 37 months (IQR 29 months), 62 events of relapse and 37 deaths were recorded. Five-years RFS was 54% for the entire group of pts (95% CI 45-64), being 65% in myxofibrosarcoma; 40% in pleomorphic liposarcoma; 33% in pleomorphic rabdomyosarcoma; 62% in unclassified spindle cell sarcoma; 80% in high-grade myxoid liposarcoma; 25% in LMS; 36% in UPS. Five-year OS was 71% for the entire group of pts (95% CI 63-80), being 73% in myxofibrosarcoma; 56% in pleomorphic liposarcoma; 83% in pleomorphic rabdomyosarcoma; 86% in unclassified spindle cell sarcoma; 100% in high-grade myxoid liposarcoma; 53% in LMS; 59% in UPS.

Conclusion: Risk of recurrence and death varied widely among the different histological subtypes. Future studies will have to stratify therapies taking this into account. The concurrent administration of chemotherapy and radiation-therapy in the pre-opertaive setting is confirmed to be feasible and safe. Detailed toxicities will be provided. This combination may be of help when tumors are of borderline resectability or function preservation is a goal.

Poster #207 3245645

GENETIC ANALYSIS OF SOFT TISSUE SARCOMAS REVEALS HISTOTYPE-SPECIFIC PATHWAY ALTERATIONS AND POTENTIAL PREDICTORS OF IMMUNOTHERAPY RESPONSE

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Objective: A hallmark of sarcomas is genetic and clinical heterogeneity, which poses a challenge for preclinical investigation of therapeutic targets, clinical trial design, and patient care. Because sarcoma is a rare disease with over 70 different histotypes, a broad comparative genetic analysis of histotypes has been lacking and in-depth sarcoma genetic studies have by necessity largely focused on one or a few histotypes. Thus, we sought to address this unmet need.

Methods: Here, we retrospectively analyzed the genetics of 557 soft tissue sarcoma samples representing 36 distinct pathologic entities using an institutional tumor sequencing platform (MSK-IMPACT) to deconvolute the genetic heterogeneity of soft tissue sarcoma. We assessed this cohort for histotype-specific mutations or copy number variation in pathways in which there are clinical or preclinical therapeutic targets. By analyzing pathways instead of individual genes, we sought to identify potential functional convergence of genetic alterations in one or more sarcoma subsets. Pathway analysis was performed in histotypes with 5 or more samples and in the case of mutation assessment, only on samples with matched normal tissue. In addition, testing for microsatellite instability was performed using the MSIsensor score and tumor mutation burden was determined based on the genome coverage in the MSK-IMPACT panel in evaluable samples. Both approaches have been previously validated in the MSK-IMPACT cohort.

Results: Significant (FDR ≤ 0.05) alterations were found in the telomere maintenance pathway in intimal sarcoma (*TERT* amplifications in 54% of cases) and *TERT* mutations were identified in 87% myxoid liposarcoma and in 42% of solitary fibrous tumor samples. The epigenetic pathway was significantly mutated in undifferentiated pleomorphic sarcoma (e.g. *ATRX*:27.4%; *ASXL2*:5.8%; *KDM6A*:3.9%; *SMARCB1*:3.9%) and well-differentiated/de-differentiated liposarcoma (e.g. *ATRX*:3.5%; *EP300*:2.3%; *MLL2*:2.3%; *NSD1*:2.3%). Epigenetic copy number changes were found to be significant in soft tissue leiomyosarcoma (e.g. *NCOR1*:13.7%; *ATRX*:7.8%; *DNMT1*:3.9%; *KDM6A*:3.9%; *SMARCA4*:3.9%), and the DNA damage response (DDR) pathway was significantly mutated in synovial sarcoma (e.g. *ATM*:2.6%; *FANCC*:2.6%; *PALB2*:2.6%; *PARP1*:2.6%; *POLE*:2.6%). Microsatellite instability (MSI-H; defined as MSIsensor ≥ 10) and elevated tumor mutation burden (TMB ≥ 10 mut/Mb), predictive biomarkers for immune checkpoint blockade in other solid tumors, were determined for each histotype. While the overall rate of MSI-H samples was 4.2% across the cohort, MSI-H tumors accounted for 14.2% of pleomorphic liposarcoma (1 of 7 samples) and 10.5% of myxoid-round cell liposarcoma (2 of 19 samples). The rate of high TMB was 3.3% across the entire cohort. Pleomorphic liposarcoma had the greatest rate of high TMB (16.6%; 1 of 6 samples) followed by angiosarcoma (12.1%; 4 of 33 samples), undifferentiated pleomorphic sarcoma (5.5%, 2 of 36 samples), and myxoid-round cell liposarcoma (5.5%, one of 18 samples).

Conclusion: We anticipate our findings will motivate further preclinical analyses of histotype-specific pathways as potential therapeutic targets and will inform efforts to understand whether these genetic factors, as well as potential predictors of immune checkpoint response, correlate with outcomes in sarcoma clinical trials. Analysis of a validation cohort of approximately 1,000 additional cases is ongoing and is important to confirm these results.

Poster #208 3253973

THE ASSOCIATION OF CHEMOTHERAPY AND SURVIVAL IN PATIENTS WITH PRIMARY, LOCALIZED, HIGH-GRADE, EXTREMITY AND TRUNK SOFT TISSUE SARCOMA

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Objective: The role of chemotherapy for primary, localized, high-grade extremity and trunk soft tissue sarcoma patients is debated. In a recent phase 3 study, standard multi-agent chemotherapy resulted in better survival when compared to histotype-tailored chemotherapy. We examined the effect of chemotherapy on survival in a similar patient population treated in 'real-world' clinical practice at Commission on Cancer accredited facilities across the United States.

Methods: Using the National Cancer Database, we identified 7,736 patients ≥18 years of age who underwent surgical resection for localized, high-grade, extremity and trunk STS (including myxoid liposarcoma, synovial sarcoma, MPNST, leiomyosarcoma, and UPS) from 2004-2016, to mimic the population of patients from a modern phase 3 study. We examined the association between chemotherapy use and overall survival using Kaplan-Meier analysis and a Cox Proportional-Hazards model. Co-variates included clinical, patient, demographic, and facility characteristics. We repeated this survival analysis by comparing single versus multi-agent chemotherapy as well as neoadjuvant versus adjuvant chemotherapy in patients treated after 2006, as neoadjuvant chemotherapy data was only available starting in 2006.

Results: Chemotherapy was administered to 22% (n = 1,679) of the study population. Median follow-up time for surviving and censored patients was 60.5 months. After adjustment for tumor characteristics, chemotherapy use was significantly associated with a 10% improvement in survival (adjusted HR 0.90; Table 1). After adjustment for radiation treatment and surgical margins, the benefit of chemotherapy was no longer statistically reliable (adjusted HR 0.91; $p<0.10$). Of patients in each sub-analysis, 89% (n = 1,347) received multi-agent chemotherapy and 56% (n = 657) received neoadjuvant chemotherapy, respectively. The use of multi-agent chemotherapy (KM curve in Figure 1) was associated with improved survival (adjusted HR 0.62±0.08; Table 1), but there was no association between the use of neoadjuvant chemotherapy and survival (adjusted HR 0.98±0.11).

Conclusion: The use of multi-agent chemotherapy is associated with a survival advantage for patients with localized, high-grade, extremity and trunk STS. These results highlight the importance of appropriate chemotherapy utilization in this patient population. Further studies will evaluate the differential effect of chemotherapy on subgroups of patients based on factors such as tumor size, depth and histology.

Table 1. The impact of chemotherapy on survival in primary, localized, high-grade, extremity and trunk STS in the NCDB from 2004-2016.

	Chemotherapy - Yes	Multi-agent Chemotherapy	Neoadjuvant Chemotherapy
	(ref = no)	(ref = single-agent chemotherapy)	(ref = adjuvant chemotherapy)
Models	HR (95% CI)	HR (95% CI)	HR (95% CI)
Model 1: unadjusted	***0.84 (0.75, 0.93)	***0.58 (0.46, 0.72)	1.02 (0.92, 1.12)
Model 2: age, sex, race, & Charlson comorbidity adjusted	**1.16 (1.04, 1.29)	***0.68 (0.54, 0.85)	1.08 (0.97, 1.19)
Model 3: Model 2 + insurance type & income adjusted	**1.19 (1.07, 1.31)	***0.68 (0.54, 0.86)	1.04 (0.93, 1.15)
Model 4: Model 3 + facility location, type, volume, & distance adjusted	**1.18 (1.06, 1.30)	**0.68 (0.53, 0.88)	1.06 (0.95, 1.11)
Model 5: Model 4 + histology, tumor site, size, & depth adjusted	*0.90 (0.80, 1.00)	**0.65 (0.50, 0.84)	1.18 (1.05, 1.31)
Model 6: Model 5 + surgical margins & radiation adjusted	†0.91 (0.82, 1.01)	***0.62 (0.47, 0.80)	1.12 (1.00, 1.24)

Multivariable Cox Regression models presented. Standard errors corrected for clustering by facility. Multiagent analysis is among those who received chemotherapy. Neoadjuvant analysis is among those who received chemotherapy, excluding single-agent chemotherapy. HR=Hazzard Ratio; CI=Confidence Interval; †p<0.001.

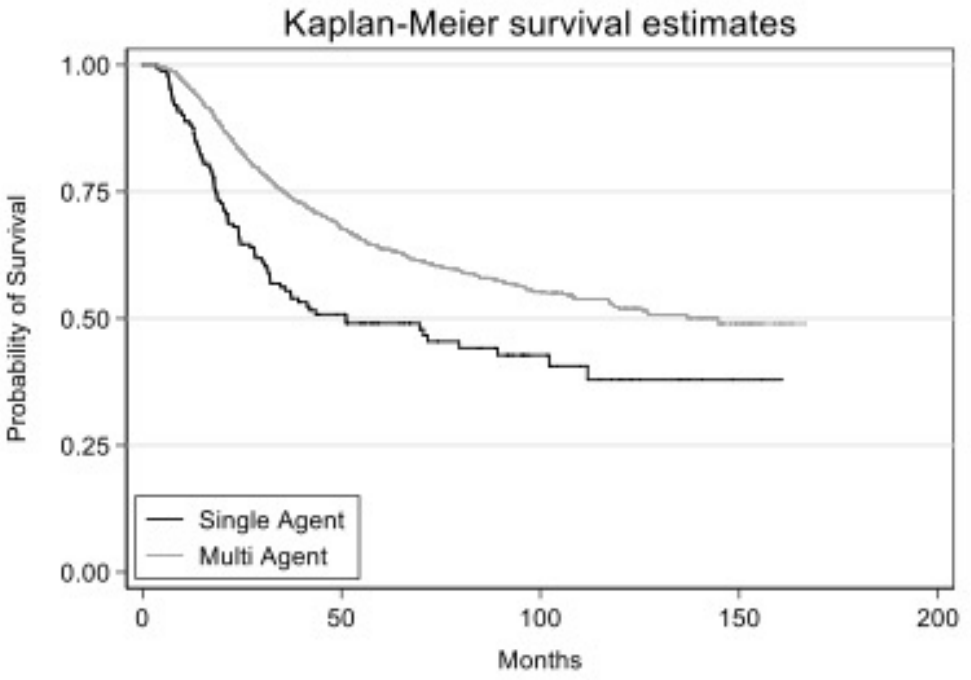

Figure 1. Kaplan-Meier survival estimates comparing single- and multi-agent chemotherapy for the treatment of primary, localized, high-grade STS in the NCDB from 2004-2016.

Poster #209 3254426

SAFETY AND EFFICACY OF TAZEMETOSTAT, A FIRST-IN-CLASS EZH2 INHIBITOR, IN PATIENTS WITH EPITHELIOID SARCOMA (ES) (NCT02601950)

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Objective: ES is a rare soft tissue sarcoma that metastasizes in approximately 30% to 50% of cases. More than 90% of ES tumors lack expression of INI1, an important component of epigenetic regulation. Loss of INI1 function allows another epigenetic modifier, EZH2, to become an oncogenic driver in tumor cells. Tazemetostat, a first-in-class, selective, oral inhibitor of EZH2, has demonstrated tumor regression and favorable safety in phase 1/2 trials. Here, we report data from a phase 2 open-label, multicenter trial of patients with locally advanced or metastatic ES treated with tazemetostat.

Methods: Efficacy was assessed with primary and secondary endpoints including objective response rate (ORR) by RECIST 1.1, disease control rate (DCR; objective confirmed response of any duration or stable disease [SD] lasting ≥32 weeks), duration of response (DOR), progression-free survival (PFS), overall survival (OS); safety and tolerability were also evaluated.

Results: As of September 17, 2018, 62 INI1-negative ES patients were enrolled and treated with tazemetostat 800 mg BID. The median number of prior lines of therapy was 1 (range: 0-9). There were 9/62 (15%) confirmed partial responses (PRs) with an ORR of 15% and DCR of 26%. The DOR ranged from 7.1+ weeks to 103.0+ weeks (median: not reached) with a median OS of 82.4 weeks (95% CI: 47.4, not estimable) for all 62 patients. Tazemetostat was generally well tolerated. Treatment-emergent adverse events (TEAEs) were generally mild to moderate with the most commonly reported adverse events (AEs; ≥10% incidence) regardless of attribution being fatigue (24/62; 39%), nausea (22/62; 35%), and cancer pain (20/62; 32%). Any treatment-related TEAEs of grade ≥3 were reported in 10/62 (16%) patients. TEAEs grade ≥3 reported in ≥2 patients included anemia (6%) and decreased weight (3%). There were no drug-related deaths and a low discontinuation rate (1.7%).

Conclusion: In the largest prospective clinical trial of ES to date**,** tazemetostat achieved disease control in 26% of patients with advanced ES who entered this study. Durable clinical response of the drug was documented. Tazemetostat demonstrated favorable safety with few patients with treatment-related AEs grade ≥3.

Poster #210 3220904

PLOCABULIN, A NOVEL TUBULIN INHIBITOR, HAS ANTITUMOR ACTIVITY IN A PATIENT-DERIVED XENOGRAFT (PDX) MODEL OF *CIC*-REARRANGED SARCOMA

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Objective: *CIC*-rearranged sarcomas are aggressive tumors sharing partial morphologic overlap with Ewing sarcoma. Despite the morphological resemblance, they lack the pathognomonic *EWSR1/ETS* fusions seen in classical Ewing sarcoma. Although often managed similarly to Ewing sarcoma, *CIC*-rearranged sarcoma have a more aggressive clinical course, a higher metastatic rate and are more often resistant to established chemotherapeutic agents, which all results in worse prognosis. Currently, the standard treatment for these 'Ewing-like sarcomas', including *CIC*-rearranged disease, has not been defined yet. We explored the activity of plocabulin (PLO; PM060184, PharmaMar), a potent cytotoxic tubulin-dynamics modifier, in a PDX model of *CIC*-rearranged sarcoma.

Methods: Female NMRI *nu/nu* mice (n=20) were transplanted bilaterally with human xenografts of *CIC*-rearranged sarcoma UZLX-STS134p.10, a model established in our laboratory. The tumor originates from a patient with *CIC*-rearranged sarcoma prior to systemic treatment with vincristine, ifosfamide, doxorubicin and etoposide, cisplatin, ifosfamide, which resulted in a partial response. Xenografted animals were randomly assigned to three treatment groups: 1) vehicle (20% hydroxypropyl □-cyclodextrin) 6.4ml/kg once weekly (QW) intravenously (i.v.), 2) doxorubicin (DOXO) 3.0 mg/kg QW i.v., or 3) PLO 16 mg/kg QW i.v. Treatment lasted 22 days and antitumor activity was assessed by tumor volume analysis, histopathology and Western blotting. Tumors with volumes smaller than 100mm^3 at start of experiment were excluded from the volumetric analysis. However, all tumors in which a sufficient number of high-power fields could be evaluated were included in the histopathological assessment. Kruskal-Wallis test with Dunn's multiple comparisons test as *post hoc*, non-parametric test was used for statistical analysis with $p < 0.05$ considered as significant.

Results: PLO treatment resulted in a reduction of tumor volume to 40% as compared to baseline, while DOXO treated tumors increased in size to 227%. Response obtained with PLO was characterized by necrosis, similar to what we have recently reported on PLO in PDX models of gastrointestinal stromal tumors. None of the PLO treated *CIC*-rearranged sarcoma tumors could be evaluated histologically due to the extensive necrosis induced. The experimental drug was well tolerated throughout the experiment at the dose administered.

Conclusion: PLO is a novel anti-tubulin agent showing potent antitumor activity in a PDX model of *CIC*-rearranged sarcoma. The drug induces cytotoxicity through necrosis and is more active than DOXO. This study provides strong arguments to study PLO further in this aggressive disease and to explore the compound in clinical trial.

Poster #211 3232641

INDIVIDUALIZATION OF FOLLOW-UP IN PATIENTS WITH HIGH-GRADE SOFT TISSUE SARCOMA

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Objective: Extremity soft-tissue sarcomas (eSTS) are followed up via a heuristic approach, with the aim to detect local recurrences (LR) or distant metastases (DM) at early stages. However, this "one-size-fits-it-all" strategy may not be appropriate, considering that risk factors for recurrent disease include grade, size, histological subtype, chemo- and radiotherapy (CTX/RTX) as well as surgical margins.

The aim of the present study was to further individualize eSTS aftercare applying flexible parametric competing risk regression modeling (FPCRRM).

Methods: In this retrospective, multicentre study, 3016 patients with high G2/3 eSTS (1931 test cohort, 1085 validation cohort) were included, treated with curative intent (median age 59 years; 54% male; 49 months median follow-up). Risks of LR and DM were estimated applying two FPCRRM allowing for adjustment of time-varying covariates, changes in hazards over time and incorporation of death as competing event.

Results: Altogether, 242 (12.5%) and 603 (31.2%) of patients in test cohort developed LR and DM, respectively, as did 110 (10.1%) and 373 (34.4%) of patients in validation cohort. In the FPCRRM for LR, margins, size, gender, histology, adjuvant CTX, neoadjuvant and adjuvant RTX were significantly associated with development of LR, whilst grading was non-significant. Risk factors associated with development of DM were grading, margins, gender, size, neoadjuvant RTX and histological subtype. Subdistribution hazard functions for LR and DM are provided in Image 1 and 2, respectively. C-statistics were computed for internal (C-index for LR: 0.705; for DM: 0.723) and external cohort (C-index for LR: 0.683; for DM: 0.772).

Conclusion: The estimates of the present FPCRRMs will be implemented in the PERSARC app, further improving individualization of STS-aftercare in practice.

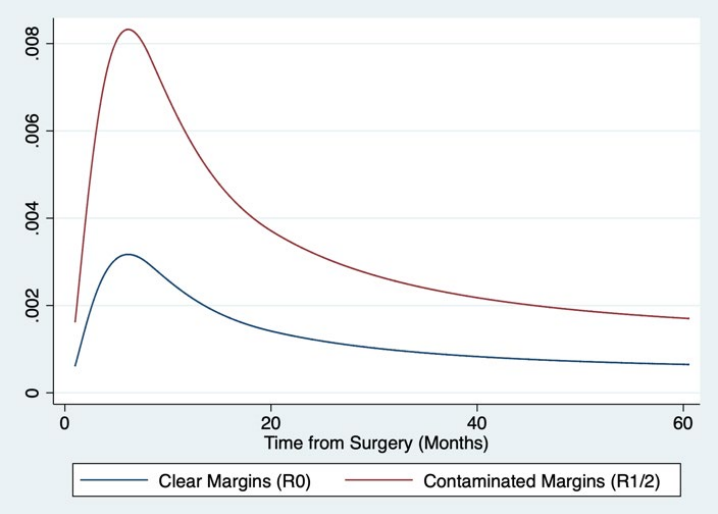

Image 1. Subdistribution hazard function for LR separated by margins with FPCRRM.

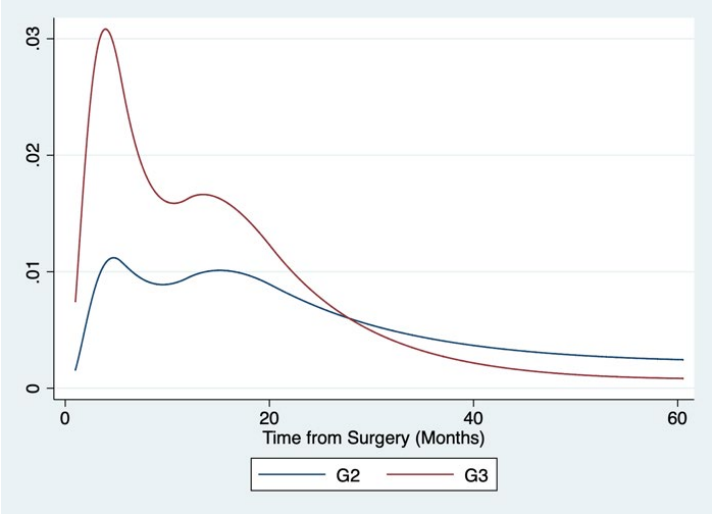

Image 2. Subdistribution hazard function for DM separated by grading with FPCRRM.

Poster #212 3241036

A PHASE II STUDY OF PAZOPANIB AS FRONT-LINE THERAPY IN PATIENTS WITH NON-RESECTABLE OR METASTATIC SOFT TISSUE SARCOMAS WHO ARE NOT CANDIDATES FOR CHEMOTHERAPY

Angela Hirbe, MD, PhD[2]*; Vanessa Eulo*[1]*; Jingqin Luo*[1]*; Chang In Moon*[2]*; Mahesh Seetharam*[4]*; Jacqui Toeniskoetter*[2]*; Tammy Kershner*[2]*; Mark Agulnik*[6]*; Varun Monga*[3]*; Mohammad Milhem*[3]*; Amanda Parkes*[5]*; Steven Robinson*[8]*; Scott Okuno*[7]*; Steven Attia*[8]*; Brian A. Van Tine*[2]

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Objective: Soft-tissue sarcomas constitute approximately 1% of adult malignancies and encompass approximately 70 different histologic subtypes. Cytotoxic chemotherapy remains the standard of care first line treatment for advanced and metastatic disease. In some instances, patients may not be a candidate for chemotherapy based on age or other comorbidities leaving no viable treatment option. Pazopanib is a multi-targeted tyrosine kinase inhibitor that is FDA approved as a second line and beyond treatment for metastatic soft tissue sarcoma. We proposed a phase II study to evaluate pazopanib as a first-line agent in patients with non-resectable or metastatic disease who are not candidates for cytotoxic chemotherapy.

Methods: Eligible patients were at least 18 years old, not a candidate for chemotherapy and had not received prior systemic therapy for sarcoma. Initial starting dose of pazopanib was 200mg BID daily titrated to 800mg daily. The primary endpoint was clinical benefit rate (CBR) (CR + PR + SD per RECIST 1.1) at 16 weeks. The sample size of 56 evaluable patients was calculated to provide 80% power to test a hypothesized CBR of ≥ 35% against an unfavorable CBR of ≤20%. If ≥17 patients achieved benefit, the null CBR of 20% would be rejected at a nominal 5% alpha level (actual alpha=0.043). Secondary endpoints included PFS rate, OS, quality of life, and serum biomarkers.

Results: 56 patients are included in the intention-to-treat analysis. Currently 52 patients are evaluable for CBR. Data from the final 4 patients will be added at the time of presentation. Median PFS was 12 (8.29~24.14) weeks and PFS rate at 16 weeks was 40% (CI 0.2893-0.5617). Median OS was 8.6 months, CBR=36.5% (19/52), 95% CI=0.2362~0.5104, 2-sided exact binomial test p=0.00507. No new or unexpected adverse events were seen. The most common Grade I-II adverse events were diarrhea, nausea, and anemia. The most common grade III-IV adverse events were hypertension and liver function test (LFT) abnormalities. Longitudinal quality of life analysis will be added at the time of presentation as well.

Conclusion: Given that the primary endpoint was met, these data suggest that there is a benefit to front-line pazopanib in patients who are not candidates for cytotoxic chemotherapy.

Poster #213 3242737

CONCURRENT PACLITAXEL AND RADIATION THERAPY FOR THE TREATMENT OF CUTANEOUS ANGIOSARCOMA

Prashant Gabani, MD[1]*; Peter Oppelt*[2]*; Ryan Jackson*[3]*; Jason Rich*[3]*; Jeff Michalski*[1]*; Brian A. Van Tine*[2]*; Matthew Spraker*[1]
[1]Radiation Oncology, Washington University in Saint Louis, Saint Louis, MO, USA; [2]Medical Oncology, Washington University in Saint Louis, Saint Louis, MO, USA; [3]Otolaryngology, Washington University in Saint Louis, Saint Louis, MO, USA

Objective: Cutaneous angiosarcoma is a rare and an aggressive form of soft tissue sarcoma. Even with sequential multimodality therapy including surgery, radiation therapy (RT) and chemotherapy, most patients develop metastatic disease within 2 years after diagnosis with less than 50% surviving greater than 5 years. Recently, our institutional practice for the treatment of cutaneous angiosarcoma has changed to use induction paclitaxel followed by concurrent paclitaxel-based chemoradiotherapy followed by surgical resection. This retrospective study compared outcomes in patients receiving induction paclitaxel followed concurrent paclitaxel and RT versus patients receiving other treatment paradigms for cutaneous angiosarcoma.

Methods: Patients with cutaneous angiosarcoma between the years 2008 and 2017 were retrospectively reviewed. Patients with metastatic disease, visceral angiosarcoma, and primary angiosarcoma of the breast were excluded. Patient were divided into two groups: those receiving induction paclitaxel followed by paclitaxel-based concurrent chemoradiation (CRT), and those receiving other treatment paradigms (non-CRT). In the CRT cohort, patients were treated with induction paclitaxel followed by paclitaxel-based chemoradiation with or without surgery; however, in the non-CRT cohort, inoperable patients were excluded. As such, non-CRT cohort was defined as surgery followed by RT and/or chemotherapy, but not concurrent chemoradiation. Paclitaxel was delivered once weekly at 80 mg/m^2 during both induction and chemoradiation for up to 12 cycles. In the CRT cohort, the intention was to treat with 6 weekly cycles of induction paclitaxel then 6 weeks of chemoradaition for a total of 12 cycles of paclitaxel. RT dose was at least 50 – 50.4 Gy delivered in 1.8 – 2 Gy per fraction. An additional boost of 10 – 16 Gy was allowed for patients not undergoing surgery or with positive margins. A *t*-test was used to compare the baseline characteristics of the CRT and the non-CRT groups. Kaplan-Meier and log-rank statistics were used to compare the outcomes between the two groups. P<0.5 was considered significant.

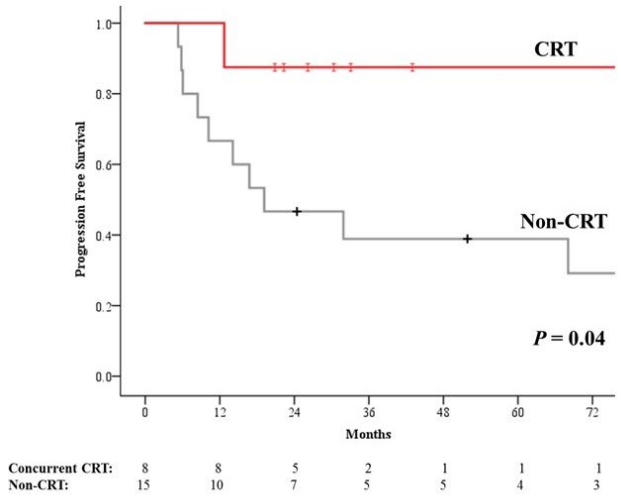
Results: A total of 23 patients were included: 8 in the CRT and 15 in the Non-CRT cohort. The median age at diagnosis was 70.9 (40.1 – 87.7) years. The median follow up was 26.2 (5.8 – 115.3) months. The anatomic sites treated as part of this study were scalp (n = 8, 34.8%), extremity (n = 6, 26.1%), trunk (n = 5, 21.7%), and head and neck (n = 4, 17.4%). The baseline patient characteristics including age, gender, tumor location, and tumor size between CRT cohort and Non-CRT cohort were well balanced between the two groups (Table 1). In the CRT cohort, concurrent paclitaxel and RT was administered as a definitive treatment in 4 (50%) patients and as neoadjuvant treatment prior to surgery in 4 (50%) patients. In the Non-CRT cohort, 9 (60%) patient were treated with surgery + RT, 3 (20.0%) patients with surgery + chemotherapy, and 3 (20.0%) patients with surgery + sequential RT + chemotherapy. The 2-year OS in the CRT cohort was significantly higher compared to the non-CRT cohort (100% vs. 64.6%, p = 0.03; Fig 1). Similarly, the 2-year PFS in the CRT cohort was also significantly higher compared to the non-CRT cohort (87.5% vs. 46.7%, p = 0.04; Fig 1).

Conclusion: The use of induction paclitaxel followed by concurrent paclitaxel-based CRT was associated with improved overall survival compared with sequential therapy, and had 2-year outcomes that are substantially better than other published series. Induction paclitaxel followed by CRT may therefore represent the best available therapy for this aggressive disease. A prospective trial evaluating the safety and efficacy of this regimen is currently ongoing (NCT03921008).

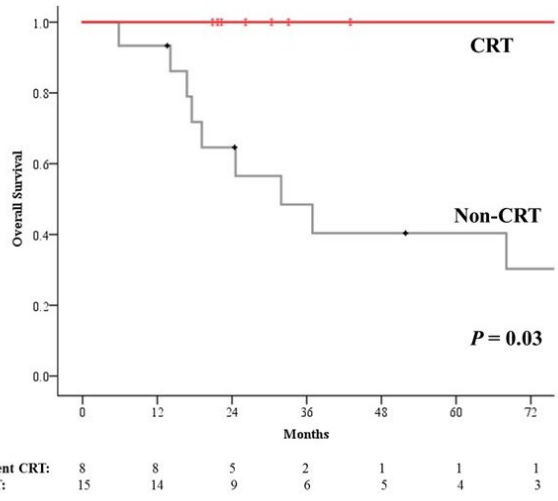
Baseline Characteristics

		Concurrent Paclitaxel + RT n (%)	Other Treatment n (%)	P-Value
Age	<60	0 (0)	5 (33.3)	0.12
	>60	8 (100)	10 (66.7)	
Gender	Male	6 (62.5)	8 (53.3)	0.67
	Female	3 (37.5)	7 (46.7)	
Tumor Location	Scalp	5 (62.5)	3 (20.0)	0.08
	Head and Neck	2 (25.0)	2 (13.3)	
	Trunk	1 (12.5)	4 (26.7)	
	Extremity	0 (0)	6 (40.0)	
Tumor Size	< 5 cm	2 (25.0)	8 (53.3)	0.42
	> 5 cm	4 (50.0)	5 (33.3)	
	Unknown	2 (25.0)	2 (13.3)	
Surgical Margin	Negative	1 (12.5)	10 (66.7)	0.01
	Positive	3 (37.5)	5 (33.3)	
	No Primary Surgery	4 (50.0)	0 (0.0)	
Paclitaxel Cycles	Median No. of Cycles (Range)	12 (5 - 12)	6 (2 - 12)	0.03
Radiation Therapy	No	0 (0.0)	3 (20.0)	0.53
	Yes	8 (100.0)	12 (80.0)	
Radiation Dose (cGy)	Median (Range)	6000 (4600 - 6480)	6600 (6000 - 7200)	0.01
Treatments	Surgery + RT	0 (0.0)	9 (60.0)	0.01
	Surgery + Paclitaxel	0 (0.0)	3 (20.0)	
	Surgery + RT + Paclitaxel (Sequential)	0 (0.0)	3 (20.0)	
	Concurrent RT + Paclitaxel + Surgery	4 (50.0)	0 (0.0)	
	Definitive Concurrent RT + Paclitaxel	4 (50.0)	0 (0.0)	

Figure 1.
First Panel = Progression Free Survival



Second Panel = Overall Survival



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Maria Thomas, MD, PhD
Wade L. Thorstad, MD
Christina I. Tsien, MD
Gregory Vlacich, MD
Imran Zoberi, MD

June 10, 2019

Re: Prashant Gabani, MD

Dear Members of the Connective Tissue Oncology Society:

It is with great enthusiasm that I nominate Prashant Gabani, MD for the 2019 Young Investigator Award for the 2019 Annual CTOS Meeting. Prashant is currently a PGY-5 radiation oncology resident at Washington University School of Medicine in St. Louis/Barnes Jewish Hospital. He has completed his three years of radiation oncology residency with outstanding reviews from his supervising physicians, colleagues, and patients.

While in training, Prashant has also developed an immense interest in clinical research, specifically studying sarcoma and breast cancer. He has published multiple research papers on these topics in highly reputable journals. In his submitted abstract for the meeting, he has analyzed our institutional outcomes of combining concurrent paclitaxel and radiation therapy for the treatment of cutaneous angiosarcoma. He has even gone beyond this analysis and written a prospective phase II clinical trial (NCT03921008) to confirm the findings of his retrospective project. He also independently secured clinical trial funding of $30,000 to run this trial at our institution.
Prashant has a strong potential to become a leader in the field of oncology. The Young Investigator Award would help accelerate his early promising academic career. I give him my highest recommendation for this award and support his attendance at the annual meeting.

Sincerely,

Stephanie M. Perkins, MD
Associate Professor
Chief, Pediatrics Radiotherapy Service
Residency Program Director

Washington University School of Medicine at Washington University Medical Center, Mail Stop #90-38-635, Campus Box 8224,
4921 Parkview Place – Lower Level, St. Louis, Missouri 63110 USA, (314) 747-4405, Fax (314) 362-8521, www.wustl.edu

Poster #214 3245787

GLO1 AS NOVEL POTENTIAL TARGET TO OVERCOME TRABECTEDIN RESISTANCE IN SOFT TISSUE SARCOMAS

Francesco Pantano; Sonia Simonetti; Giulia Ribelli; Michele Iuliani; Andrea Napolitano; Daniele Santini; Giuseppe Tonini; ***Bruno Vincenzi***

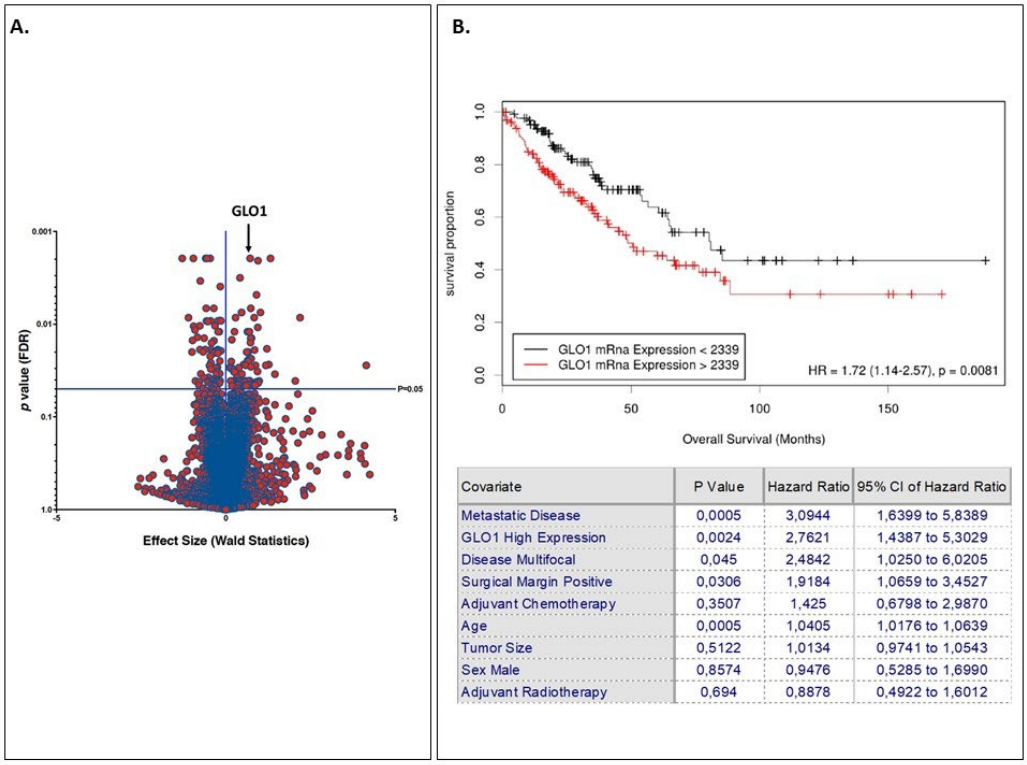
Campus Bio-Medico University, Rome, Italy

Objective: To identify new potential therapeutic targets in Soft Tissue Sarcomas (STS), an explorative bioinformatics analysis was performed. We screened a public mRNA expression data from the TCGA Sarcoma database to find mRNAs associated with differential prognosis (Fig. 1A). Data showed that STS patients with over-expression of glyoxalase 1 (Glo1) mRNA had significantly shorter OS compared to Glo1 low-expressed patients. Moreover, in a multivariate analysis, Glo1 mRNA expression retained its significant association to worse prognosis (Fig 1B). Glo1 is involved in the detoxification of the endogenous reactive metabolite, methylglyoxal (MG), whose abnormal accumulation increases adduct levels and induce cell apoptosis. Several preclinical studies demonstrated that increased Glo1 expression was associated with cancer chemotherapy resistance.
On the bases of these evidences, we investigated the potential role of Glo1 expression as biomarker of tumor growth and drug resistance in STS.

Methods: Trabectedin and MG cytoxicity was evaluated by MTT viability assay measured at spectrofluorometer (Tecan M200). Apoptosis was analyzed by flow cytometry (CytoFlex) using Annexin V antibody and propidium iodide. Glo-1 expression analysis was performed by Western Blot using a mouse monoclonal anti-human Glo-1 antibody (NBP1-19015). Synergy analysis was calculated using Combenefit software and statistical analysis was performed by Student t test using the program GraphPad Prism.

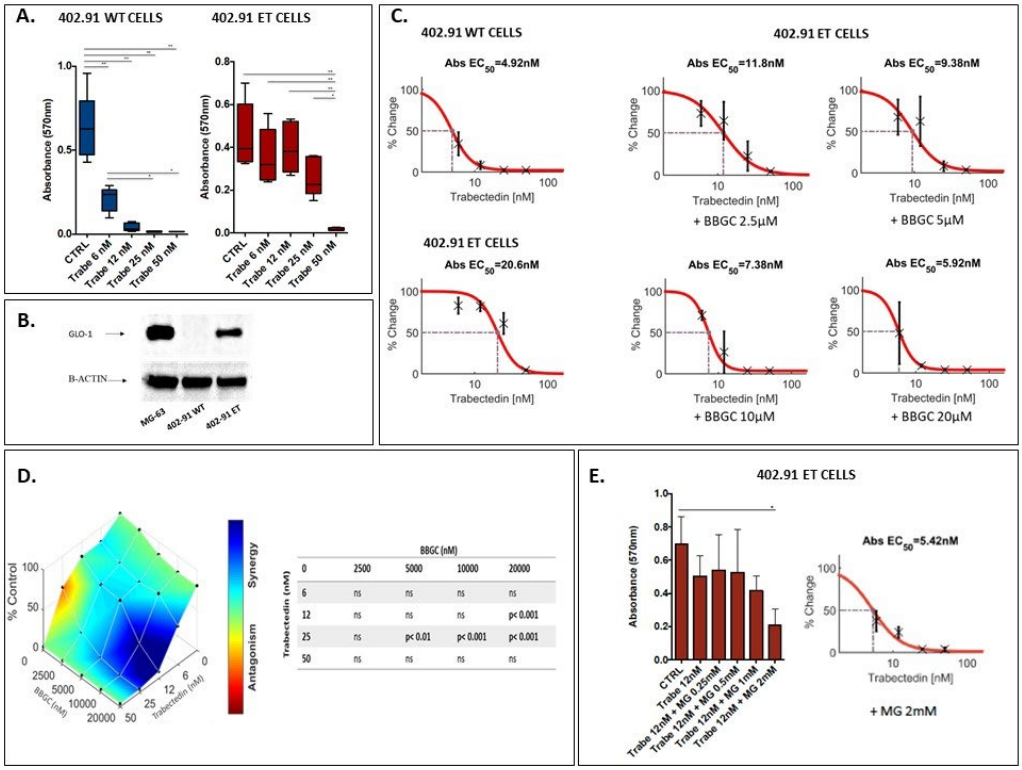
Results: As STS trabectedin resistant model, we used a myxoid liposarcoma cell line (402-91 ET cells) that are not responsive to clinical doses of trabectedin contrary to the parental sensitive cell line (402-91 WT cells) (fig 2A). Intriguingly, we found higher Glo1 protein levels in 402-91 ET cells compared to 402-91 WT cells (Fig. 2B). The treatment of 402-91 ET cells with the specific Glo1 inhibitor S-p-bromobenzylglutathione cyclopentyl diester (BBGC, Sigma Aldrich) in combination with trabectedin (PharmaMar) significantly inhibited cell viability than trabectedin alone. In particular, the addition of BBGC reduced trabectedin EC50 (half-maximal effective concentration) from 20.4nM to 5.92nM in 402-91 ET cells, restoring the trabectedin sensitivity, similar to that observed in 402-91 WT cells (4.92nM) (Fig.2C). The maximum drug combination synergy between trabectedin and BBCG was achieved with trabectedin 12nM + BBGC 20μM (Fig. 2D), which also promoted an increase of late apoptotic cell percentage (data not shown). To investigate if cell death was induced by MG accumulation following Glo1 inhibition, we evaluated 402-91 ET cell viability after treatment with different doses of MG in combination with trabectedin. The addition of MG (Sigma Aldrich), at 2mM dose, restored sensitivity to trabectedin in 402-91 ET cells as well as BBGC (Fig. 2E).

Conclusion: Our results highlight a new potential mechanism of trabectedin resistance mediated by Glo-1 over-expression. The use of the specific Glo-1 inhibitor, BBGC, restores trabectedin sensitivity in resistant cells leading to MG accumulation that, in turn, promotes cell death and apoptosis. These data provide a strong rationale to investigate Glo-1 inhibition strategy, in combination with trabectedin, in STS *in vivo* models.



Covariate	P Value	Hazard Ratio	95% CI of Hazard Ratio
Metastatic Disease	0,0005	3,0944	1,6399 to 5,8389
GLO1 High Expression	0,0024	2,7621	1,4387 to 5,3029
Disease Multifocal	0,045	2,4842	1,0250 to 6,0205
Surgical Margin Positive	0,0306	1,9184	1,0659 to 3,4527
Adjuvant Chemotherapy	0,3507	1,425	0,6798 to 2,9870
Age	0,0005	1,0405	1,0176 to 1,0639
Tumor Size	0,5122	1,0134	0,9741 to 1,0543
Sex Male	0,8574	0,9476	0,5285 to 1,6990
Adjuvant Radiotherapy	0,694	0,8878	0,4922 to 1,6012

Fig. 1 A. Volcano plot of mRNAs whose expression is associated to differential prognosis in STS patients. The vertical axis (FDR) is the base-10 negative logarithm of the adjusted P value; the horizontal axis quantifies association to differential prognosis (genes with positive values are overexpressed in patients with poor prognosis, genes with negative values are under-expressed in patients with poor prognosis). The horizontal line at 1.3 divides significant genes (adj P ≤ 0.05, top) from non significant genes (adj P > 0.05, bottom). **B. Comparison between Kaplan-Meier curves was performed using the log-rank test.** The optimal cutoff point to dichotomize into low (n=172) and high (n=78) GLO1 expression levels was evaluated by use of the receiver operating characteristic method.



BBGC (nM)	0	2500	5000	10000	20000
6	ns	ns	ns	ns	ns
12	ns	ns	ns	p< 0.001	
25	ns	p< 0.01	p< 0.001	p< 0.001	
50	ns	ns	ns	ns	ns

Fig. 2. A. Cytotoxic assay (MTT) on 402-91 WT and ET cells treated or not with trabectedin (6nM, 12nM, 25nM, 50nM). *p**B.** Western Blot analyses of GLO1 protein levels. MG63 osteosarcoma cell line represents the positive control. **C**. EC50 values in 402-91 WT and ET cells treated with trabectedin alone or in combination with BBGC calculated by Combenefit Software. **D**. Synergism analysis of trabectedin and BBGC in 402-91 ET cells using Combenefit Software (LOEWE Analysis). **E.** Cytotoxic assay (MTT) on 402-91 ET cells treated or not with trabectedin (12nM) and MG (0,25mM, 0,5mM, 1mM, 2mM) *p

Poster #215 3247828

CIRCULATING TUMOR DNA LEVELS PREDICT PARTIAL RESPONSE IN A COHORT OF RELAPSED LEIOMYOSARCOMA PATIENTS

Laura Madanat-Harjuoja[1]; Kelly Klega[1]; Yao Lu[2]; Karla Ballman[2]; David S. Shulman[1]; Denise Reinke[3]; William D. Tap[4]; Suzanne George[5]; ***Brian Crompton***[1]

[1]Pediatric Oncology, Dana-Farber Cancer Institute/ Boston Children's Cancer and Blood Disorders Center, Boston, MA, USA; [2]Weill Cornell Medicine, New York, NY, USA; [3]Sarcoma Alliance for Research through Collaboration, Ann Arbor, MI, USA; [4]Sloan Kettering Cancer Center, New York, NY, USA; [5]Harvard Medical School, Boston, MA, USA

Objective: Previous studies have suggested liquid biopsy may be a useful prognostic biomarker for patients with leiomyosarcoma (LMS) but this has never been tested prospectively in a patient cohort receiving uniform therapy. The aim of the study was to explore whether the detection and level of circulating tumor DNA (ctDNA) prior to the start of therapy is associated with outcomes or treatment response after 2 cycles in a cohort of patients with relapsed leiomyosarcoma.

Methods: Our cohort consisted of a total of 75 patients with relapsed LMS who were treated on the prospective SARC021 study, an open-label, randomized, phase 3, multicenter trial testing the efficacy of adding evofosfamide to doxorubicin compared to treatment with doxorubicin alone for patients with advanced soft-tissue sarcomas. Plasma samples were collected from patients prior to initiating therapy and after completion of 2 cycles of chemotherapy. LMS was the most frequent diagnosis of patients enrolled on this study, presenting a unique opportunity to evaluate the prognostic significance of ctDNA levels in patients with relapsed LMS receiving chemotherapy. Ultimately, evofosfamide did not improve outcomes.

Ultra-low passage whole genome sequencing (ULP-WGS) was used to detect ctDNA in plasma samples collected from enrolled patients prior to starting therapy. We assessed the association between ctDNA detection and the level of ctDNA in pre-treatment blood samples with measures of clinical outcome and radiographic response. Kaplan Meier curves were used to estimate survival in patients with or without detectable ctDNA and the log-rank test was used to estimate the significance of the difference between these two groups. We also tested for an association between disease response, stage and number of metastatic sites with the presence or absence of ctDNA with Fisher's exact test and with ctDNA levels by Student t test.

Results: ctDNA was detectable in 40 out of 75 (53%) patients with relapsed leiomyosarcoma. Stage of disease was not associated with ctDNA detection nor the level of ctDNA. However, patients with detectable ctDNA were more likely to have more than 5 metastatic sites compared to patients with no ctDNA (56.7% vs. 36.4%, p=0.0112). Patients with detectable ctDNA had a median overall survival (OS) of 388 days compared to patients with undetectable ctDNA who had a median OS of 572 days, however the difference did not achieve significance (p=0.06). Patients with a partial response after 2 cycles were less likely to have detectable ctDNA prior to treatment by ULP-WGS (23.5%; 95% CI 9.6-47.3%) compared to patients with either stable or progressive disease (61.1%; 95% CI 47.8-73%; p= 0.0112). Patients with a partial response also had significantly lower mean ctDNA levels (2.26%, 95% CI 0-5.1%) expressed as a percentage of overall cell free DNA compared to patients with stable or progressive disease (15.10%; 95% CI 9.7-20.5%; p= 0.011). No patients achieved complete response.

Conclusion: Low or undetectable levels of ctDNA prior to treatment appear to be associated with better response to chemotherapy in patients with LMS. Patients with undetectable ctDNA prior to therapy may have longer overall survival although this could not be determined conclusively from this cohort. Ongoing work focuses on identification of ctDNA features, such as copy-number alterations or changes in ctDNA levels over time, that may also be associated with disease progression or response to therapy.

Poster #216 3249535

THE PROGNOSTIC IMPACT OF PULMONARY METASTASECTOMY IN SOFT TISSUE SARCOMA PATIENTS

Teruya Kawamoto[1]*; Toshihiro Akisue*[2]*; Masayuki Morishita*[3]*; Hitomi Hara*[1]*; Naomasa Fukase*[1]*; Yohei Kawakami*[1]*; Ikuo Fujita*[3]*; Takuya Fujimoto*[3]*; Toshiyuki Takemori*[1]*; Shuichi Fujiwara*[1]*; Kazumichi Kitayama*[1]*; Shunsuke Yahiro*[1]*; Ryosuke Kuroda*[1]

[1]Orthopaedic Surgery, Kobe University Graduate School of Medicine, Kobe, Japan; [2]Rehabilitation Science, Kobe University Graduate School of Health Sciences, Kobe, Japan, Japan; [3]Orthopaedic Surgery, Hyogo Cancer Center, Akashi, Japan

Objective: Soft tissue sarcomas (STSs) are rare heterogeneous malignancies of mesenchymal origin. The lungs are the primary sites of distant spread, with over 50 % of patients developing metastatic lesions, and surgical treatment of pulmonary metastasis in STS patients has been reported to result in the long-term survival. The purposes of this study were to describe factors associated with survival in a series of STS patients, and to reveal the benefit of surgical treatment of metastatic lung lesions for the prognosis of the patients.

Methods: We retrospectively reviewed 113 STS patients with pulmonary metastasis, who were treated in our institutions between January 2000 and December 2017. Uni- and multi-variate analyses were used to identify factors associated with clinical outcomes, and post-metastasis survival was estimated using Kaplan-Meier survivorship curves and Cox-regression hazard models.

Results: This study included 70 men and 43 women, with a median age of 60.0 years at a diagnosis of primary lesion (range 15-88). The histologic results of the primary tumor were: 25 leiomyosarcomas, 25 UPS/MFHs, 15 synovial sarcomas, 10 liposarcomas, 10 myxofibrosarcomas, 7 MPNSTs, 4 extraskeletal Ewing/PNETs, and 17 others. Metastasis in other sites developed in 45 patients (39.8%), including 16 bone, 13 skin/soft tissue, 12 lymph node, 6 liver, etc. For pulmonary metastasis, 42 patients (37.2%) underwent surgical treatment, and chemotherapy was performed in 52 patients (46.0%). One-, three- and five-year post-metastasis survival in all 113 patients were 64.3%, 32.0%, and 22.5%, respectively. Those survival rates in 42 patients with the pulmonary metastasectomy were 89.9%, 68.8% and 57.3%, and were significantly better than in 71 patients without the surgery (48.7%, 9.8% and 0%) ($p<0.0001$). Univariate analyses revealed that pulmonary metastasectomy ($p<0.0001$), number of metastatic nodules in the lung ($p<0.0001$), bilateral involvement ($p<0.0001$), surgery for primary lesion ($p=0.0003$), synchronous lung metastasis ($p=0.007$), metastasis-free interval ($p=0.001$), age at diagnosis ($p=0.016$) and size of primary tumor ($p=0.037$) had a significant correlation with the prognosis of the patients. Among the factors, pulmonary metastasectomy was the only independent factor, significantly associated with an improved post-metastasis survival in a multivariate analysis (HR: 5.263, 95%CI: 2.659-10.419) ($p<0.0001$). In the current study, site or depth of the primary tumor, metastasis in other sites, chemo- or radio-therapy for pulmonary metastasis did not influence the prognosis of the patients.

Conclusion: The treatment for pulmonary mestastasis in STS patients is complex, and should be considered individually to each patient. In the current study, we retrospectively reviewed the factors associated with the post-metastasis survival in STS patients with the pulmonary metastasis. A multivariate analysis using the Cox regression hazard models identified that pulmonary metastasectomy is the most important independent prognostic factor, and seems to prolong a post-metastasis survival in the STS patients with pulmonary metastasis. Although we should carefully weigh the risks and the benefits of the patients, surgical treatment for the pulmonary metastasis could be a means of achieving long-time survival.

Poster #217 3253397

A PHASE IB STUDY OF THE SAFETY AND PRELIMINARY EFFICACY OF LENVATINIB (LENV) PLUS ERIBULIN (ERI) IN ADVANCED ADIPOCYTIC SARCOM (LPS) AND LEIOMYOSARCOM (LMS)(NCT03526679)

Tom Wei-Wu Chen[1]*; Ruey-Long Hong*[1]*; Rong-Sen Yang*[2]*; Chueh-Chuan Yen*[3]*; San-Chi Chen*[1]*; Jhe-Cyuan Guo*[1]*; Meng-Chi Hsu*[1]*; Ting-Fang Kung*[3]

[1]Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan; [2]Department of Orthopedic Surgery, National Taiwan University Hospital, Taipei, Taiwan; [3]Department of Oncology, Taipei Veterans General Hospital, Taipei, Taiwan

Objective: Lenv, an anti-angiogenic multi-kinase inhibitor, has anti-tumor activity in various caner types. The safety and efficacy of lenv and eri combination has not been explored in LMS and LPS.

Methods: Advanced LMS and LPS with no more than 2 lines of systemic chemotherapy were eligible. The starting dose was lenv 18mg/day daily and eri 1.1mg/m2 D1, D8 in a 21-day cycle. The primary endpoint of the phase Ib study was to assess the dose-limiting toxicity (DLT) in the first 21 days. A rule-based 3+3 design was implemented to determine the recommended phase II dose (RP2D) after the first 6 pts.

Results: From 2018 Jul 24 to 2019 Jan 8, a total of 6 pts (4 LMS, 1 dedifferentiated LPS, 1 myxoid LPS) were enrolled. The median age was 56 (range 30-70), female: male 3:3. Only 1 pt had a DLT, which was < 75% of the planned dosage. Within all (27) cycles, common grade (gr) 3 or higher adverse events (AE) included hypertension (HTN, n=4), hand-foot syndrome (HFS, n=3), and neutropenia (n=4). However, 4 pts had gr3 or multiple coexisting gr2 AEs that necessitated dose reduction(s) (dr) for lenv (7 dr) or eri (2 dr) after the DLT assessment period (see table). The median time to 14 mg/day, 10mg/day of lenv, and eri 0.7mg/m2 was 22, 28 (after starting lenv 14mg/day), and 69 days, respectively. In terms of preliminary anti-tumor efficacy, 3 (50%) and 3 (50%) pts had PR (1 confirmed) and SD as best response according to RECIST 1.1.

Conclusion: Late onset AEs after cycle 1 leading to dose reduction was notable for lenv + eri. The RP2D is thus determined at a lower starting dose of lenv 14mg/day and eri 1.1mg/m2. The safe and efficacy of lenv + eri for LMS and LPS will continue to be explored in phase II study.

AEs leading to dose reduction	Incidences	Attributed drug
Gr3 HFS	1	Lenv
Gr3 diarrhea	1	Lenv
Gr3 arthritis	1	Lenv
Gr2 HTN + gr2 myalgia + gr2 bilirubin	1	Lenv
Gr3 HTN + gr3 HFS	1	Lenv
Gr2 HTN + gr2 AST + gr2 ALT	1	Lenv
Gr3 HTN + gr2 epigastralgia	1	Lenv
Gr4 neutropenia	2	Eri

Poster #218 3253883

SYNERGISTIC ACTIVITIES OF THE HISTONE DEACETYLASE INHIBITORS WITH CONVENTIONAL CYTOTOXIC CHEMOTHERAPIES IN ANGIOSARCOMAS

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Objective: Angiosarcoma (AS) is a rare aggressive malignant tumour typically arising from skin or viscera. The incidence of AS appears more common in Asia, as compared with the West. The prognosis of patients (pts) advanced/inoperable AS remains poor. Taxanes and anthracyclines remain the commonest used cytotoxic agents. The median PFS of first line systemic treatments of 3.8months and OS of <12 months. Histone deacetylases inhibitors (HDACi) are epigenetic agents which have shown anti-tumour effects as single-agents, as well as synergism with cytotoxics in a variety of solid and haematological malignancies. The effect of HDACi in angiosarcomas have yet been studied. We explored Panobinostat (LBH589) and Vorinostat (SAHA), two pan-HDACi which can induce cell apoptosis and cell-cycle arrest in a time and dose-dependent manner, as single-agents and in combination with cytotoxics in angiosarcomas.

Methods: We investigated the potential effects of LBH589 and SAHA in an angiosarcoma cell line (ISO-HAS-B). A synovial sarcoma cell line (SW982) was used as comparison control. Anti-tumour activities of two pan-HDACi as single agents were studied in both cell lines, followed by synergism studies in combination with conventional cytotoxics including doxorubicin, paclitaxel and gemcitabine. Synergy effects were calculated by synergy-finder and evaluated by synergy score as follow scale: < -10 (antagonistic); -10 to 10 (additive); > 10 (synergistic).

Results: LBH589 and SAHA were shown to have anti-tumour effect in both cell lines (Table1). Synergy score of LBH589 and SAHA in combination with conventional cytotoxics were calculated to evaluate the synergy effects (Table 2). The combination of two pan-HDACi with doxorubicin and gemcitabine showed synergistic growth inhibition and induced a higher level of cell death than each agent alone in the two cell lines. However, synergy effects of two pan-HDACi and paclitaxel can be observed only when paclitaxel is in a low dose.

Conclusion: LBH589 and SAHA can enhance the sensitivity of chemo drugs in AS in different degree, in which LBH589 + Doxorubicin is the best combination while both LBH589 + Paclitaxel and SAHA + Paclitaxel showed poor synergism in AS. In-vivo experiments to validate these findings are currently on-going. Molecular mechanisms of synergy effects need to be further explored in this study.

Table 1. IC50 (nM) of LBH589 and SAHA in both cell lines.

	ISO-HAS-B	SW982
LBH589	21	880
SAHA	2212	10138

Table 2. Synergy score of different combinations in both cell lines.

	ISO-HAS-B	SW982
LBH589 + Doxorubicin	14.79	12.95
SAHA + Doxorubicin	12.21	16.34
LBH589 + Gemcitabine	12.26	8.09
SAHA + Gemcitabine	14.12	20.36
LBH589 + Paclitaxel	0.51	0.78
SAHA + Paclitaxel	4.41	-2.94

Poster #219 3254568

XENOSARC: PATIENT-DERIVED XENOGRAFT MODELS OF SOFT TISSUE SARCOMA – AN UPDATE ON A PRECLINICAL PLATFORM FOR EARLY DRUG TESTING

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Objective: Soft tissue sarcoma (STS) constitutes a rare family of mesenchymal tumors with more than 70 subtypes classified by WHO (2013). The limited treatment options available for advanced STS underline the need for reliable preclinical models, especially from ultra-rare subtypes, to test novel therapeutic strategies. We aimed at creating a panel of patient-derived xenograft (PDX) models of STS to be used for *in vivo* drug testing.

Methods: A panel of PDX models was established by subcutaneous implantation of fresh tumor specimens in immunodeficient, athymic nude NMRI mice. Once tumor growth was observed, pieces of tumor were re-transplanted to next generations of mice. At each passage tumor fragments were collected for histopathological and molecular characterization. A model was considered "established" after observing stable histological and molecular features for at least two passages. Furthermore, *ex*-mouse tumor tissue samples were stored, further characterized by immunocytology and flow cytometry and cultured to be used for *in vitro* drug testing.

Results: Between September 2011 and June 2019, 329 STS samples from 301 consenting patients treated at the University Hospitals, Leuven, Belgium have been transplanted. A total of 56 PDX models were established, maintaining the histopathological and molecular features of the original tumor. Detailed clinical information about the donor patient and tumor characteristics (including sensitivity to standard and experimental agents), is known for every model. At present the XenoSarc platform includes ready to use models of dedifferentiated liposarcoma (10 models), gastrointestinal stromal tumor (8), myxofibrosarcoma (8), leiomyosarcoma (7), malignant peripheral nerve sheath tumor (4), synovial sarcoma (2), pulmonary artery intimal sarcoma (2), CIC - rearranged round cell sarcoma (1), epithelioid hemangioendothelioma (1), mesenchymal chondrosarcoma (1), pleomorphic rhabdomyosarcoma (1), teleangiectatic extraskeletal osteosarcoma (1), myxoid liposarcoma (1), myxoinflammatory fibroblastic sarcoma (1), rhabdomyosarcoma NOS (not otherwise specified) (1) and high-grade undifferentiated pleomorphic sarcoma (7). These models are well-characterized, including molecular information on copy number changes (by low-coverage whole genome sequencing) and gene expression profile (by RNA-Seq). In addition, we have constructed tissue microarrays (TMA) from the xenografts which are used for target identification and model selection for preclinical studies. We are using the xenografts for *in vivo* testing of novel agents, including targeted and cytotoxic (pro-)drugs, and results already served as rationale for a number of prospective clinical trials.A total of 16 other xenografts are still in early stages of engraftment, not yet fulfilling our criteria of an "established" model.

Conclusion: The XenoSarc platform offers a lot of opportunities for studying the biology of a variety of important sarcoma subtypes including ultra-rare entities, and has proven efficiency for early drug screening in STS in preparation of clinical testing of novel compounds. The platform is well maintained and continuously expanded, and available to collaborators from academia and industry.

Poster #220 3254669

INVESTIGATING THE CIRCULATING TUMOR DNA AS A BIOMARKER OF CANCER PROGRESSION AND RECURRENCE IN SARCOMA

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Objective: Circulating tumor DNA (ctDNA) is an active area of research in many types of cancer due to its value as a non-invasive diagnostic tool. Despite making up a small fraction of total cell-free DNA (cfDNA) (approximately 0.1%), detection of ctDNA has been made possible given advances in next generation sequencing and Digital Droplet PCR (ddPCR).

While needle biopsy will likely remain the gold standards for diagnosis, ctDNA testing has some key advantages including repeated testing compared to tissue biopsy, which allows ease of repetition to provide a means of real-time monitoring of treatment response and signs of recurrence in cancer. This has specific relevance in sarcoma, where early detection of recurrence may provide an opportunity for faster intervention and can potentially lead to better prognostic outcomes. The evaluation of the ctDNA in sarcoma has been not extensively studied.

The purpose of this study is to determine if ctDNA is detectable in plasma samples collected from sarcoma patients and to validate our pre-analytical procedures and to identify opportunities to optimize our protocols for future use.

Methods: 20 milliliters of peripheral blood samples were collected into EDTA tubes from 200 soft tissue sarcoma and osteosarcoma patients with or without pre-operative adjuvant treatment and processed within 1 hour of collection to separate the plasma. Cell-free DNA was isolated from 2ml of plasma using QIAamp circulating nucleic acid extraction kit. The concentration of purified plasma DNA was determined by quantitative qPCR using an 81 base pair amplicon of the *EIF2C1* gene on chromosome 1 and a dilution series of placenta DNA. Quality assessment of cell free DNA was performed by capillary electrophoresis using 2100 Bioanalyzer.

Whole exome sequencing (WES) was performed on 6 matched tumor-blood DNA samples to identify tumor specific single nucleotide alterations. The two sequence variations identified from WES analysis of 2 patients were used to design primers and probes to detect the tumor specific alterations in the corresponding ctDNA in those 2 cases using Droplet Digital PCR (ddPCR).

Results: Of the 58 patient samples analysed, the majority were positive for cell-free DNA at levels above 5ng per ml plasma. Quality assessment of 41cell free DNA by capillary electrophoresis showed peaks corresponding to small DNA fragments of approximately 170 bp in size, characteristic of cfDNA (Figure 1).

WES of two patients' matched tumor-blood samples identified G1252A and T1584G variations in the COL19A1 and SMAD4 genes, respectively. The mutant allele frequency was found to be 57% for G1252A and 86 % for T1584G. The COL19A1 sequence alteration was further validated by Sanger sequencing, which confirmed that the mutant allele frequency was 50%, similar to the value observed in WES data.

We performed ddPCR to investigate the sensitivity of this assay by generating a series of DNA mixtures containing different fractions of mutant and wild-type DNA. We were able to detect mutant alleles at 0.5 % of the wild type genome (Figure 2).

To investigate the minimum input DNA for the detection of the mutant allele, we performed a serial dilution of the mutant tumor DNA with water. We were able to detect the mutant alleles for both variations at a level of 0.5ng of DNA. We further showed the presence of G1252A and T1584G alterations in their corresponding ctDNAs using 10 nanograms of total cfDNA (Figure 3).

Conclusion: Our ongoing study to evaluate the use of ctDNA as a biomarker in sarcoma monitoring shows promise related to the efficiency of our protocols and assays. Further testing will be required to confirm the sensitivity of the detection level of ctDNA in sarcoma and to make more definitive assertions regarding its use in this cancer.

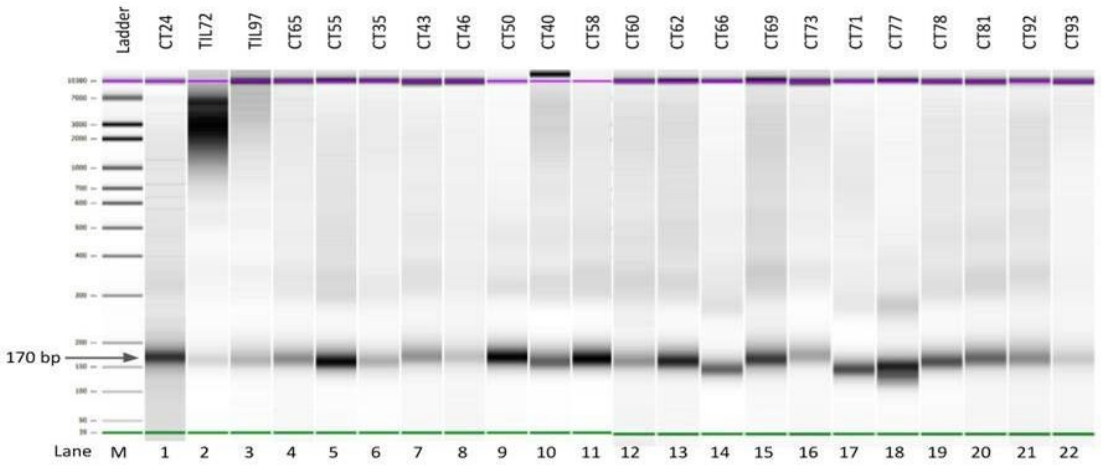

Figure 1. CfDNA fragment size assessment by capillary electrophoresis.
CfDNA isolated from samples was assessed for quality by capillary electrophoresis. Lane M contains molecular weight ladder; Lanes 1-22 contain extracted DNA samples as indicated by sample ID at top of electropherogram. All samples tested contained signal peaks corresponding to DNA fragments of approximately 170 bp.

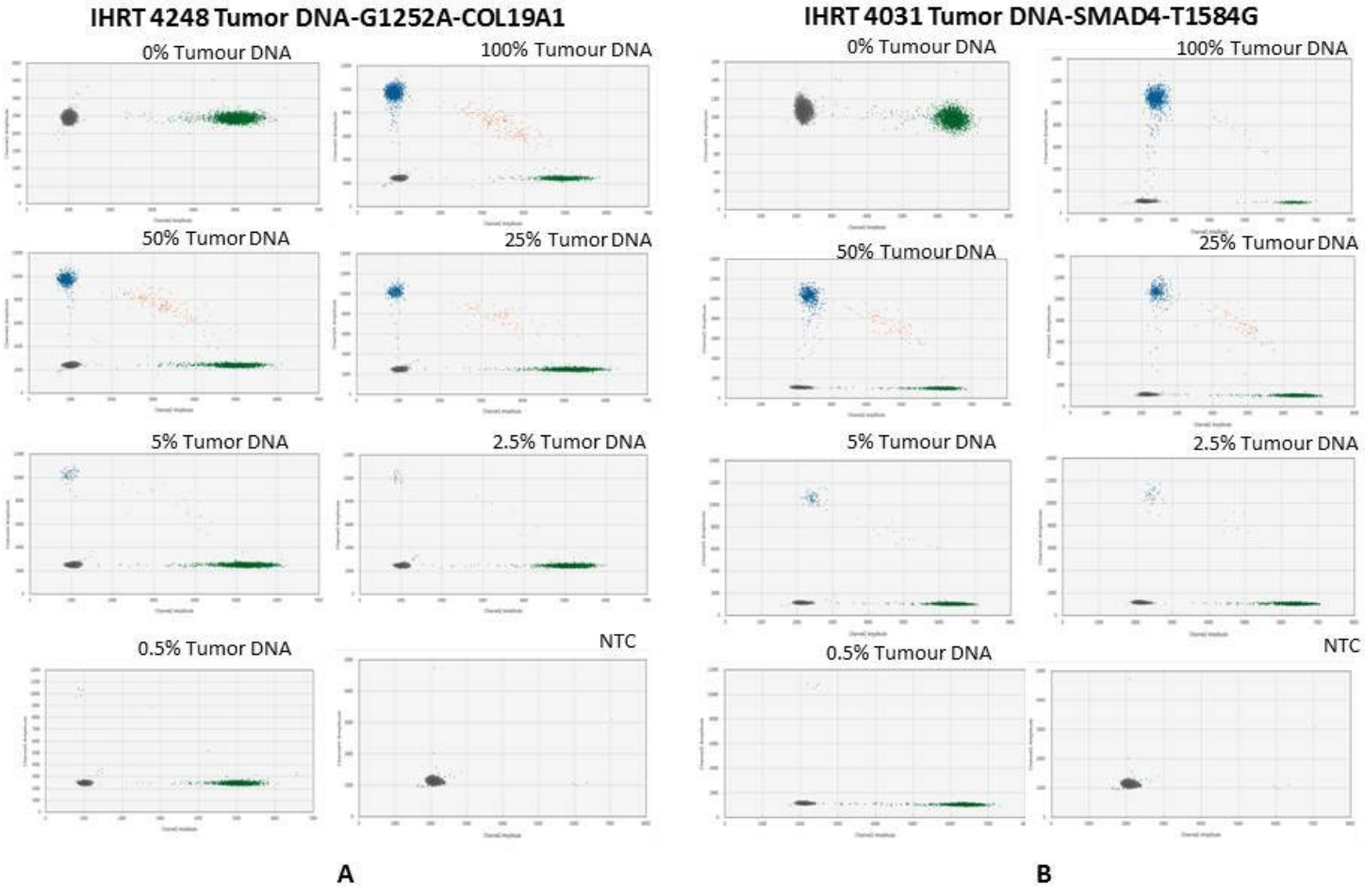

Figure 2. The fractional representation of the detected mutation in the tumor DNA. Tumor DNA was mixed with different fractions of wild type DNA. A) G1252-COL19A1 mutation. B) T1584G-SMAD4 mutation.

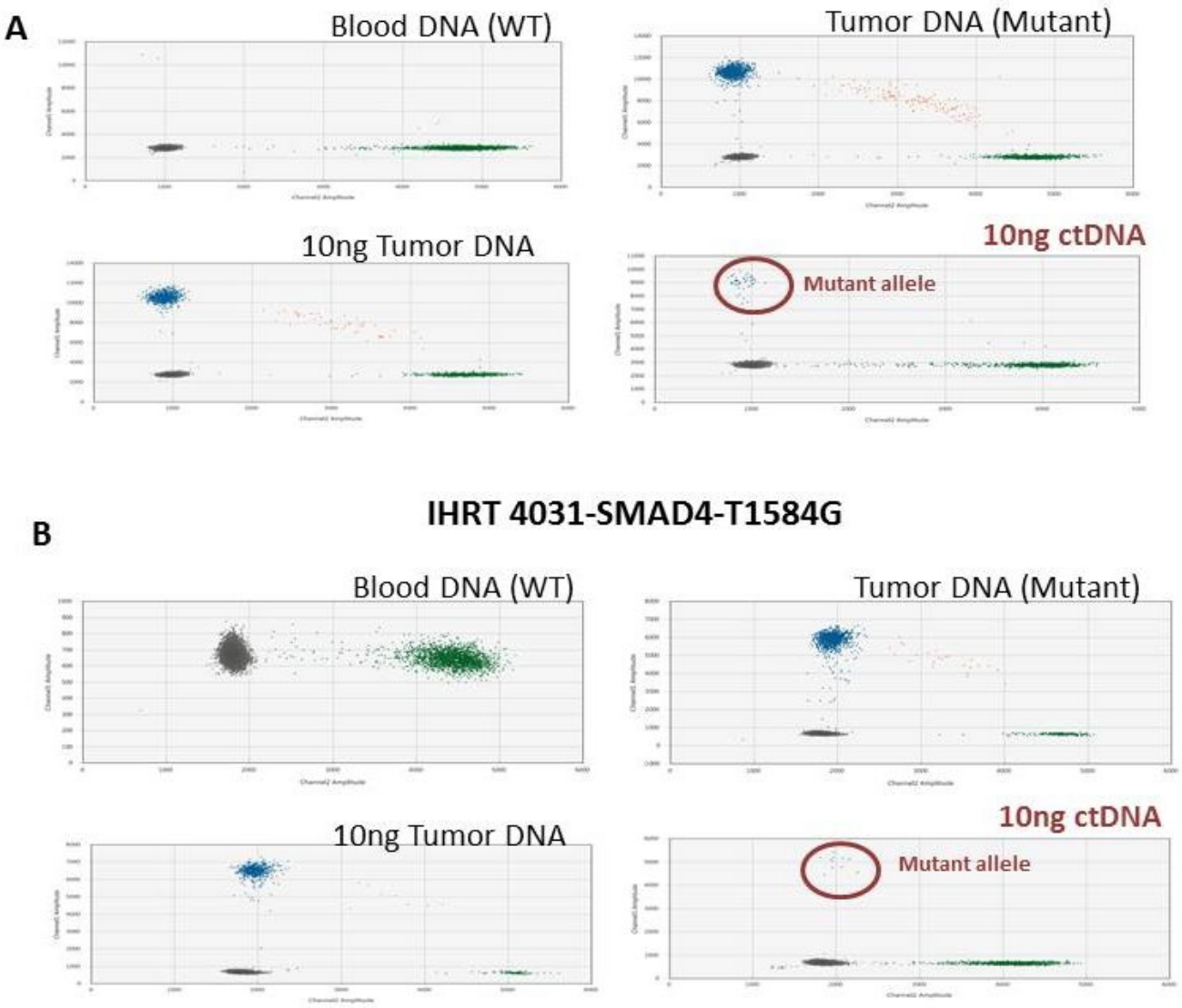

Figure 3. Detection of **A**. G1252A-COL19A1, **B**. SMAD4-T1584G mutations in sarcoma ctDNA.

Poster #221 3254681

DURABLE RESPONSES TO COMBINATION ANTI-CTLA-4 AND ANTI-PD-1 THERAPY AMONG PATIENTS WITH CHEMOTHERAPY/TYROSINE KINASE INHIBITOR RESISTANT SOFT TISSUE AND BONE SARCOMAS

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Objective: The primary objective was to evaluate the biologic activity including objective tumor responses and response durations of combination anti-CTLA-4 and anti-PD-1 therapy in patients with chemotherapy and tyrosine kinase inhibitor-resistant soft tissue and bone sarcomas segregated by histologic subtype. The secondary objective was to assess immune-mediated toxicity.

Methods: We conducted a comprehensive medical record review of patients with advanced chemotherapy and tyrosine kinase inhibitor-resistant soft tissue and bone sarcomas from 1/1/2016 to 5/1/2018 cared for at the John Theurer Cancer Center. Categorical variables were summarized as frequencies (percentages). Continuous variables were summarized using mean (SD) or median (interquartile range), depending on whether data are normally distributed, an assumption checked by Shapiro-Wilk test. Time to event endpoint analysis including survival and progression were evaluated using Kaplan-Meier plots. Comparison of time to treatment events between groups was examined using two-sided log rank test. Data analysis was performed using SAS 9.4 (SAS Institute Inc. Cary, N.C.).

Results: Twenty seven patients with chemotherapy and tyrosine kinase inhibitor refractory soft tissue and bone sarcoma with a median age of 51.9 (IQR 35.1-70.9) years received combination anti-CTLA-4 (Ipilimumab 1-3 mg/kg) and anti-PD-1 (Nivolumab 1-3 mg/kg) for 4 cycles followed by anti-PD-1 (Nivolumab 240 mg Q 2 weeks) and anti CTLA-4 (Ipilimumab 1 mg/kg Q 6 weeks) until progression, severe toxicity or complete response. Among the twenty-seven patients, there were 12 histologic subtypes (Table-1: 20 patients with soft tissue and 7 with bone sarcomas). Ten patients (37%) had Royal Marsden Hospital (RMH) prognostic score of 0-1 (good prognosis), while 17 (63%) had RMH scores of 2-3 (poor prognosis). Median duration of therapy was 25 weeks. Best response (Table 1) included 4 complete responses (1/3 Ewings, 1/3 liposarcoma and 2/5 leiomyosarcoma), 1 partial response (1/1 MFH) and 4 stable disease (1/2 alveolar soft parts, 1/1 epitheliod, 1/1 pleomorphic, 1/1 uterine carcinosarcoma). 18/27 (67%) patients did not respond and progressed. Median treatment-failure free survival for the entire group was 9.0 months (95% CI: 4 months-not reached). RMH score 0-1 patients had a median survival of 13 months (95% CI 3 months-not reached) compared to RMH score patients 2-3 of 10 months (95% CI 4 months-not reached). Among responders including stable disease patients, median duration of response was 23 months (range 3-40 plus months). 59.3% of patients experienced immune adverse events including skin rash (22%), hepatitis, colitis and hypophysitis (all 14.8%). Less common adverse immune events included diabetes, arthritis and pneumonitis. There were no immune related fatalities.

Conclusion: In a cohort of chemotherapy and tyrosine kinase inhibitor-resistant relapsed advanced soft tissue and bone sarcoma patients combination anti-CTLA-4 and anti-PD-1 therapy led to meaningful and durable response in one third of patients with a variety of histology. Combination therapy was generally well tolerated in this population with an expected incidence and severity of immune adverse events associated with the combination. Further study is warranted and efforts to receive regulatory approval for these indications should be considered.

Table 1: Best response to I-O Therapy for Advanced Sarcoma

Type of sarcoma	n	Complete Response (CR)	Partial Response (PR)	Stable Disease	Progressive Disease
Leiomyosarcoma	5	2	0	0	3
Osteosarcoma	4	0	0	0	4
Ewing	3	1	0	0	2
Liposarcoma	3	1	0	0	2
Alveolar Soft-Part Sarcoma	2	0	0	1	1
Pleomorphic Sarcoma	2	0	0	1	1
Synovial Cell Sarcoma	2	0	0	0	2
Embryonal Rhabdomyosarcoma	1	0	0	0	1
Epitheloid Sarcoma	1	0	0	1	0
Malignant Fibrous Histiocytoma	1	0	1	0	0
Rhabdomyosarcoma	1	0	0	0	1
Spindle Cell Sarcoma-Peripheral Nerve Sheet Tumor	1	0	0	0	1
Uterine Carcinosarcoma	1	0	0	1	0

Poster #222 3254823

LOW-DOSE PREOPERATIVE RADIATION THERAPY, RESECTION, AND REDUCED-FIELD POST-OPERATIVE RADIATION THERAPY FOR SOFT TISSUE SARCOMA

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Objective: For soft tissue sarcoma (STS), preoperative radiation therapy (PreRT) permits treatment to a lower dose and smaller field than post-operative RT (PORT) with equivalent oncologic outcomes. In some circumstances, such as urgency of surgery or concerns for wound healing, a full course of PreRT may not be feasible. We hypothesized that, in such situations, low-dose PreRT (LD-PreRT) would decrease the risk of intra-operative tumor seeding and thus permit PORT to a reduced target volume while preserving oncologic outcomes.

Methods: In a single-institution cohort of patients (pts) with non-metastatic STS treated from 1980-2018, 77 pts underwent LD-PreRT (range: 10-30 Gy), resection, and PORT, while 484 underwent resection and PORT without PreRT. In LD-PreRT pts, PORT fields were generally similar to standard PreRT fields.

Results: LD-PreRT pts were median 51 y old (range: 14-88 y) and 51% male. Histology was 27% undifferentiated pleomorphic sarcoma (UPS), 13% liposarcoma, 10% leiomyosarcoma, 9% synovial sarcoma, 9% malignant peripheral nerve sheath tumor, and 31% other. Tumors were 82% grade 2-3, 52% extremity, 62% >5cm (median 9.0 cm, range 1.5-49 cm), 77% deep, and 82% primary (18% recurrent after prior treatment).

Median LD-PreRT dose was 20 Gy (range 10-30 Gy). LD-PreRT technique was 90% photon (52% 2D, 22% 3D, 16% IMRT/VMAT), 5% proton, 3% electron, and 2% mixed modality. All pts underwent resection with 58% R0, 27% R1, and 8% R2 margins. 12% (9 pts) received intra-operative RT, 8 with electrons (median 10 Gy, range 9-15 Gy) and 1 with ^{32}P dural plaque (10 Gy). 80% received PORT via external beam RT (EBRT) (median 40 Gy, range 20-56 Gy) and 20% via interstitial brachytherapy (IBT) (median 40 Gy, range 23-50 Gy). Median total RT dose was 61 Gy (range 38-82 Gy). 27% received systemic therapy.

With a median follow-up of 8.1 y, the 8-y overall survival (OS) was 66.0% [95% CI: 53.2%-76.1%], disease-free survival (DFS) 50.5% [38.0%-61.7%], and local control (LC) 77.8% [65.0%-86.4%] among pts receiving LD-PreRT. On univariate analysis, margin status was associated with LC (86.4% [70.0%-94.2%] R0 vs 64.8% [42.1%-80.5%] R1/2, p=0.046) and grade with OS (100% grade 1 vs 58.4% [43.9-70.3%] grade 2/3, p=0.017); in addition, tumor size trended towards association with OS (per cm, HR 1.04 [1.00-1.07] p=0.071). LC at 8 y was 92.3% [56.6%-98.9%] among LD-PreRT pts receiving PORT via IBT vs 73.4% [58.0%-83.9%] via EBRT (p=0.170). Both before and after propensity score adjustment for larger size, more UPS histology, and more negative margins among LD-PreRT pts, there was no significant difference in OS (unadjusted hazard ratio [uHR] 0.97 [0.62-1.51], p=0.888 adjusted hazard ratio [aHR] 0.89 [0.59-1.34], p=0.565), DFS (uHR 0.91 [0.64-1.31], p=0.619, aHR 1.07 [0.78-1.46], p=0.681), or LC (uHR 0.73 [0.42-1.26], p=0.253, aHR 1.19 [0.77-1.84], p=0.424) between pts receiving LD-PreRT vs PORT alone.

Conclusion: In STS pts for whom full-course PreRT is not an option, LD-PreRT may enable PORT to a reduced target volume. Oncologic outcomes of this approach appear comparable to those achieved with standard-field PORT alone.

Poster #223 3254961

HIGH-THROUGHPUT ANALYSIS OF TRANSCRIPTIONAL STARTING POINT AND IDENTIFICATION OF PROMOTER

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Objective: Recently, mutation and expression analyses of DNA, RNA and protein have clarified to some extent the tissue-specific genetic/proteiomic changes in soft tissue sarcomas; however, in spindle cell sarcomas, many unclear points remain, hampering the diagnosis and treatment of such lesions. Recently, cap analysis gene expression (CAGE) for high-throughput analysis of transcriptional starting point and identification of promoter usage were developed.In this study, we conducted comprehensive gene expression profiling including analyses of the transcription start points, promoters and enhancers associated with each gene by CAGE in order to elucidate the histological and biological behavior of spindle cell sarcomas.

Methods: We performed a CAGE of 34 high-grade spindle cell sarcomas (high-grade myxofibrosarcoma [MFS], pleomorphic leiomyosarcoma [pLMS], conventional leiomyosarcoma [cLMS]) managed at our hospital from 2014 to 2017. Frozen samples were examined using an mRNA extraction kit. The gene expression profiles were statistically analyzed and compared among the tissue types using the edgeR system.

Results: The CAGE requires high mRNA quality (≥5 μg), therefore 14 of the 34 samples (41.2%) were thus deemed suitable to be analyzed. Finally, we acquired the gene expression profiles 14 cases including five cases of MFS, five cases of pLMS and four cases of cLMS. Hierarchical clustering analyses (HCA) were performed using these acquired gene expression profiles with the unsupervised method to clarify the correlation among the histological subtypes. With respect to comparisons among three histological subtypes including cLMS, pLMS and MFS, HCA demonstrated pLMS to have a gene expression which was similar to that of cLMS. On the other hand, there were significant differences between pLMS and MFS. Regarding the details of such gene differences, a difference in the expression was observed between cLMS and pLMS for 17 genes (p-value<0.01, FDR<0.1), including PRDM16, a tumor suppressor gene involved in muscle differentiation (Andrew H B, et al. Oncogene. 2010). There were differences in the expression of 110 genes between cLMS and MFS (p-value<0.01, FDR<0.01) and 84 genes between pLMS and MFS (p-value<0.01, FDR<0.01). Both lists include GPR64 and TNXB, which have recently been reported to be over-expressed in MFS compared to other spindle cell sarcomas (Jun K, et al. Genetics Research International. 2011).

Conclusion: We identified genes with different expressions in high-grade spindle cell sarcomas using a novel CAGE method. We believe that further statistical analyses and functional studies might elucidate various biological behaviors based on the genes functions in spindle cell sarcomas.

Poster #224 3255113

TRABECTEDIN WITH CONCURRENT LOW-DOSE OF RADIATION THERAPY FOR METASTATIC SOFT TISSUE SARCOMAS (TRASTS): A MULTICENTER EUROPEAN, SINGLE ARM PHASE II TRIAL OF SPANISH, FRENCH AND ITALIAN SARCOMA GROUPS

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Objective: The capacity of inducing tumor shrinkage in advanced soft tissue sarcomas (STS) is an unmet need beyond the first line of systemic therapy. Pivotal studies of approved drugs reported RECIST response rates below 10%. Thus, it is challenging to relieve symptoms related to tumor volume in patients progressing to anthracycline-based schemes. Besides that, the overall response rate (ORR) is an appropriate surrogate for overall survival (J Clin Oncol 34:1469-1475, 2016). This phase II trial explores the combination of trabectedin and concurrent radiotherapy (RT) in the metastatic setting and is supported by preclinical experiments and previous phase I trial.

Methods: Patients received Trabectedin 1.5 mg/m^2 in 24-h infusion and started RT (30 Gy, 3 Gy/day) within 1 hour after the end of the first Trabectedin perfusion. Most relevant inclusion criteria were metastatic progressing STS, initially restricted to lung metastasis and later amended to allow up to two different metastatic sites, a maximum of two previous systemic lines for advanced disease with at least one previous anthracycline-based line. Neither all the lesions nor all the sites were required to be irradiated. The main endpoint was ORR by RECIST 1.1. A Simon 2-stage was used to estimate 35% ORR of interest for further investigation (α=0.1, power 90%; P0= 0.10). Central pathology and radiological review were mandatory.

Results: From 10/2017 to 11/2018, 27 patients were enrolled. Histologies were: leiomyosarcoma 7 (26%), synovial sarcoma 6 (22%), liposarcoma 4 (15%) and other 10 (37%). The median of previous lines was 2, and ECOG was 0 in 19 (70%) patients and 1 in 8 (30%) patients. With a median follow-up of 6 months (1-12), there were 9 events of progression and 3 events of death. The 6-month PFSR was 75% and the 6-month OSR was 86%. From 26 evaluable patients by RECIST, there were 16 PR (57.7%), 7 SD (26.9%) and 4 PD (15.4%). One G3 and 3 G1 pneumonitis were observed. One toxic death occurred (sepsis) being G3-4 neutropenia observed of 7 (26%) while febrile neutropenia was reported in 2 (7.4%) cases.

Conclusion: Trabectedin concurrent with low-dose RT showed a relevant activity in progressing metastatic setting in a wide range of STS types, giving options for tumor shrinkage beyond the first line of advanced STS. The RECIST ORR of 57.7% and 6-m PFSR of 75% confirm the synergy of Trabectedin+RT.

Poster #225 3255195

ACTIVITY OF CHEMOTHERAPY IN INFLAMMATORY MYOFIBROBLASTIC TUMOUR (IMT): RETROSPECTIVE ANALYSIS WITHIN EUROPEAN REFERENCE CENTRES

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Objective: Few data are available on the role of chemotherapy in inflammatory myofibroblastic tumour (IMT). We report on a retrospective study on cytotoxic chemotherapy in patients (pts) with IMT treated at nine European sarcoma reference centres.

Methods: Pts of any age with a histologically confirmed diagnosis of IMT and treated with anthracycline-based and/or methotrexate (MTX) plus vinorelbine/vinblastine chemotherapy and/or other antitumor medical treatments between 5/1996 and 12/2018 were retrospectively reviewed. Diagnosis was reviewed and confirmed by sarcoma expert pathologists. ALK status was evaluated by immunohistochemistry and/or FISH. Response was assessed by RECIST 1.1. Progression-free survival (PFS), relapse-free survival (RFS) and overall survival (OS) were computed by Kaplan-Meier method. The correlation between ALK status (positive versus negative) and outcome was evaluated.

Results: 39 pts were retrospectively identified, ALK positive/negative = 25 (64%)/ 14 (36%); median age = 30 (IQR 19-46) years; males/ females = 21 (54%)/ 18 (46%); primary tumour site = abdomen 13 (34%), lung/thoracic wall 11 (28%), other 15 (38%); pts with local disease treated with curative intent = 6 (15%), advanced disease = 33 (85%; locally advanced = 14 (36%), metastatic = 19 (49%)). Twenty-five (64%) pts received an anthracycline-based regimen, 13 (33%) MTX plus vinorelbine/vinblastine, 11 (28%) other regimens (1 carboplatin plus paclitaxel, 1 oral etoposide, 1 pazopanib, 2 docetaxel plus gemcitabine, 2 trabectedin, 4 oral cyclophosphamide). Ten (26%) pts received more then one line of treatment. In the anthracycline-based group, 9/25 (36%) pts were treated for localized disease with a curative intent, 16/25 (64%) for advanced disease. 21 pts were evaluable for response. Median number of cycles = 6 (range 1-6). Best RECIST response was: 10 partial response (PR) (48%), 6 stable disease (SD) (28%), 5 progressive disease (PD) (24%) (overall response rate (ORR) 48%; 95% CI: 26-70%). For pts with localized disease, median RFS was 137 (IQR: 26-137) months, median OS was not reached. For pts with advanced disease, at a median FU of 71 months (IQR 39-89), median PFS and OS were 6 (IQR 2-12) and 17 (IQR: 6-37) months, respectively. In the MTX plus vinorelbine/ vinblastine group, 6/13 (46%) pts were treated for localized disease with a curative intent, 7/13 (54%) for advanced disease. Median number of cycles = 38 (range 3-50). All pts were evaluable for response. Best RECIST response was: 2 CR (15%), 5 PR (39%), 3 SD (23%), 3 PD (23%) (ORR = 54%; 95% CI: 25-81%). For pts with advanced disease, at a median FU of 57 months (IQR 28-130), median PFS was 25 months (IQR 3.2-NE); median OS was 83 months (IQR 83-NE). Two pts with locally advanced disease achieved a CR and were still disease free at the time of this analysis. In the other-regimen group, all pts were treated for advanced disease. 9/11 (82%) were evaluable for response. Responses were seen with oral cyclophosphamide (1 CR, 2 PR of 3 treated pts) and docetaxel plus gemcitabine (1 PR). No correlation was found between response and ALK status in any of the subgroups.

Conclusion: In this retrospective series on the activity of chemotherapy in IMT pts, anthracycline-based and MTX plus vinorelbine/vinblastine chemotherapy were clearly active in IMT, with an ORR of roughly 50%. Interestingly, MTX plus vinorelbine/vinblastine was associated with prolonged PFS (>2 yrs). Anecdotal responses were also seen with other chemotherapy regimens (e.g., oral cyclophosphamide and docetaxel plus gemcitabine). Cytotoxic chemotherapy is an option in both localised disease, when tumour shrinkage is needed, and in advanced disease. The value of MTX plus vinorelbine/vinblastine should be prospectively studied.

Poster #226 3255203

IMPROVEMENT IN PATIENT-REPORTED PAIN IN A PHASE III TRIAL OF PEXIDARTINIB (PLX3397) AMONG PATIENTS WITH TENOSYNOVIAL GIANT CELL TUMOR (TGCT)

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Objective: Tenosynovial giant cell tumor (TGCT) is a rare, locally aggressive, usually non-metastatic neoplasm of the synovial lining of joints and tendon sheaths. In the recently completed Phase III Trial (ENLIVEN), pexidartinib, a novel systemic agent developed for the non-surgical treatment of TGCT, demonstrated efficacy in reducing tumor size and improving patient report outcomes. The objective of this report is to provide in-depth analysis and results on pain.

Methods: ENLIVEN was a double-blind, randomized, placebo-controlled Phase III study of pexidartinib in subjects with locally advanced TGCT with a primary objective of comparing the response rate based on RECIST 1.1 at Week 25. One of the secondary efficacy objectives included evaluation of pain (Brief Pain Inventory: Worst Pain Numeric Rating Scale – BPI Worst Pain NRS). The proportion of responders on the BPI (subjects with a decrease of at least 30% in the BPI Worst Pain NRS and did not have a 30% or greater increase in narcotic analgesic use; BPI-30) was evaluated in the intent to treat (ITT) population. Subjects who do not provide sufficient data for the endpoint determination (either BPI or analgesic data) were defined as non-responders. The proportions of BPI-30 responder at Week 25 in the two treatment groups were compared using one-sided Fisher's exact test at the alpha = 0.025 level of significance. As pre-specified exploratory analysis, BPI responders under two other BPI response criteria were also examined: a decrease of at least 50% in the mean BPI Worst Pain NRS item (BPI-50), and a decrease of at least 2 points in the mean BPI Worst Pain NRS item (BPI-2p), who did not have a 30% or greater increase in analgesic use. In addition, mean change from baseline in the BPI Worst Pain NRS was compared between treatment groups using a mixed model with repeated measures (MMRM). Additional post hoc sensitivity analyses were performed to address the potential concern of informative missing data, using the pattern mixture model multiple imputation methods, under conservative missing not at random assumptions.

Results: The ITT population comprises a total of 120 patients. As reported elsewhere, results for RECIST response (placebo: 0%; pexidartinib: 39.3%) and tumor volume score response (placebo: 0%; pexidartinib: 55.7%) show significant tumor response favoring pexidartinib (both $p<0.0001$). BPI responder analysis was limited by missing data for this endpoint (41% and 46% missing for placebo and pexidartinib, respectively) due to various reasons including early discontinuation, site issues and eDiary device issues/subject non-compliance. The response rate at Week 25 for the BPI-30 was higher in pexidartinib (n = 19, 31.1%) compared with placebo (n = 9, 15.3%) by a difference of 15.9 percentage points (95% CI: 0.7, 30.2), though this did not reach statistical significance (p = 0.0320; 1-sided). The response rate based on BPI-50 and BPI-2p was higher at Week 25 in the pexidartinib group (n = 16, 26.2% and n = 19, 31.1%, respectively) compared with the placebo group (n = 6, 10.2% and n = 8, 13.6%, respectively). The difference between the two groups significantly favored pexidartinib by 16.1 percentage points (95% CI: 2.1, 29.4, p=0.0198) and 17.6 percentage points (95% CI: 2.6, 31.6, p=0.0177) for the BPI-50 and BPI-2p, respectively. Mean change of BPI Worst Pain NRS from baseline also significantly favored pexidartinib (LS Mean Change: -2.5 vs -0.6, $P<0.0001$). Sensitivity analyses showed that results from MMRM analysis are credible and robust.

Conclusion: Though ENLIVEN did not establish statistically significant improvement in pain based on the BPI-30 responder analysis, several pre-specified exploratory endpoints and sensitivity analyses consistently showed that TGCT patients treated with pexidartinib experienced improvement in pain compared to placebo patients.

Poster #227 3255213

LONG NON-CODING RNA NEAT1 PROMOTES SARCOMA METASTASIS BY REGULATING RNA SPLICING PATHWAYS

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Objective: Soft tissue sarcomas (STS) are malignant tumors from diverse mesenchymal tissues. 50% STS patients develop fatal lung metastasis with a median survival of 15 months. There are no effective therapeutics developed for treating these patients over the past decades because the mechanisms driving the development of lung metastasis in sarcoma patients are still poorly understood.

Methods: Our lab has developed a genetically engineered mouse model (GEMM) of high-grade primary STS with conditional mutations in *Kras* and *Trp53* (KP) where 50% of mice tumors develop lung metastasis. This KP model recapitulates human patients with Undifferentiated Pleomorphic Sarcoma (UPS), one of the most common subtypes of STS diagnosed in adults. RNA sequencing (RNA-Seq) was performed on paired primary and lung metastases to identify differentially expressed lncRNAs. Real time PCR (qPCR), RNA in situ hybridization (ISH), CRISPR/Cas9 technology, RNA pull down assay with mass spectrometry analysis as well as tail vein injection were applied to determine the functional roles of lncRNA *Neat1* in sarcoma metastasis.

Results: *Neat1* is significantly increased in lung metastases compared to paired primary mouse KP sarcomas. In addition, RNA ISH on tissue microarrays (TMA) of human primary UPS and lung metastases determined that the expression of *NEAT1* is upregulated in lung metastases. Next, CRISPR/Cas9 technology was applied to delete *Neat1* in primary mouse sarcoma cells and loss of expression of *Neat1* was confirmed by qPCR and northern blot in knockout (KO) clones. In addition, loss of *Neat1* significantly reduced lung metastasis *in vivo* following tail vein injection of these modified cells into nude mice. Furthermore, RNA pull down assay with mass spectrometry analysis determined *Neat1* interacting proteins, such as *Khsrp*, were mainly involved in RNA splicing pathways which was also shown to be dysregulated in lung metastases and *Neat1* KO cells. Finally, CRISPR/Cas9 mediated knockout of *Khsrp* significantly reduced lung metastasis *in vivo* following tail vein injection of these modified cells into nude mice.

Conclusion: These results suggest that upregulation of *Neat1* promotes lung metastasis of soft tissue sarcoma through regulating RNA splicing pathways and *NEAT1* is a potential target to prevent or treat lung metastasis in sarcoma patients.

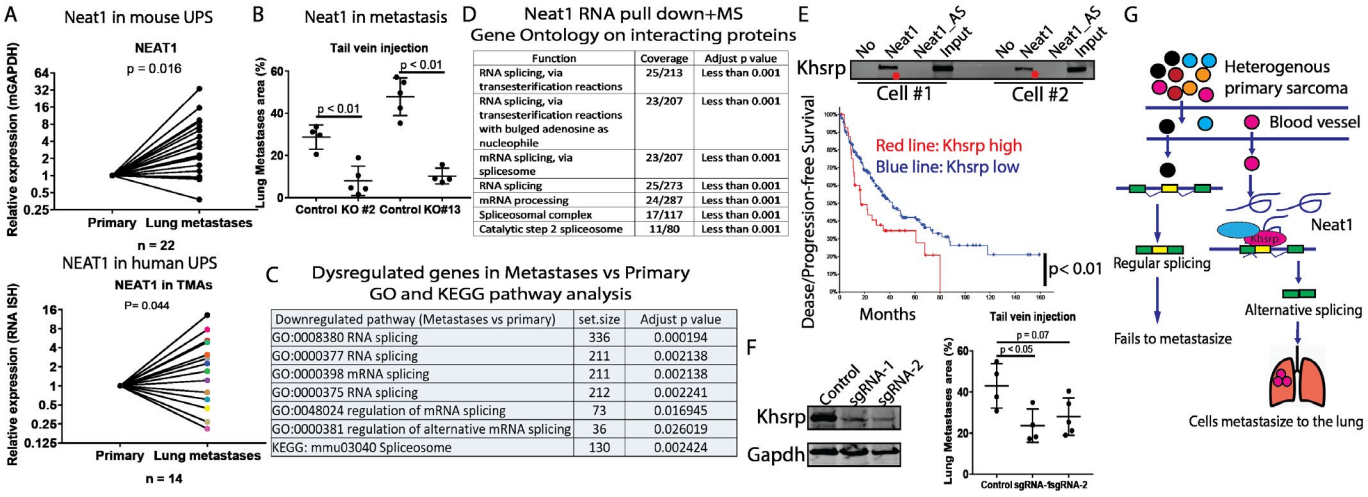

Figure. Long non-coding RNA *Neat1* drives sarcoma metastasis through RNA splicing pathways. (A) LncRNA Neat1 is upregulated in mouse and human lung metastases compared to their paired primary tumors. (B) Loss of lncRNA Neat1 suppresses lung metastasis. (C) RNA splicing pathways are downregulated in lung metastases compared to primary KP sarcomas. (D) LncRNA Neat1 interacts with a large group of RNA splicing regulators, such as Khsrp. (E) RNA pull down assay with western blot confirms that Khsrp interacts with Neat1 and upregulation of Khsrp is positively correlated with poor prognosis of human sarcomas. (F) Knockdown of Khsrp suppresses lung metastasis. (G) Schematic showing the hypothesis that Neat1 drives sarcoma metastasis through regulating RNA splicing pathways.

Poster #228 3255242

ARE THERE PATIENTS WITH SOFT TISSUE SARCOMA OF TRUNK OR LIMBS WHO MAY NOT BENEFIT FROM RADIATION THERAPY? A LARGE RETROSPECTIVE STUDY OF THE FRENCH SARCOMA GROUP

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Objective: To analyze the outcome and assess the prognostic impact of radiation therapy (RT) in patients with a localized extremity or trunk wall soft tissue sarcoma in a French national cohort.

Methods: Data from 738 patients ≥ 18 years treated between April 2000 and November 2016 were reviewed. Patients with incomplete margins after first surgery (R1 or R2) without surgical revision were excluded. Clinical data were retrospectively gathered on a national database (Conticabase) until April 2018. Margins have been defined as large if ≥ 5mm or after re-excision without residue, and close if < 5mm.
Survivals were estimated by the Kaplan-Meier method from surgery, using the following first event definitions: death for overall survival (OS), recurrence or death for disease free survival (DFS) and local recurrence for time to local recurrence (TLR). Comparisons between groups were assessed using Logrank test. Multivariable analyses were performed using the Cox proportional hazards model.

Results: Median age at diagnostic was 57 (range 18; 93). The characteristics of the tumors are as follows: the median size was 55 mm (range 6; 400), 66.7 % were deep tumors, 405 were grade 1 or 2 (56.1%). The margins were <5 mm in 242 patients (45.1%), and ≥5mm in 295 patients (54.9%), and 201 patients had R0 surgery without more precision. 495 patients received RT (67.1%), with a median dose of 50Gy (range 20;70).
With a median follow-up of 83.7 months (95%CI: 76.5-88.1), the 5 and 10-year OS are 81% (95%CI: 77.7-83.89) and 68% (95%CI: 63.47-72.68), and the 5 and 10-year DFS are 65.6% (95%CI: 61.9-69.1) and 51% (95%CI: 46.26-55.7). At 10 years, 80.7 % of patients are local recurrence free (95%CI: 76.2-84.4).
Independent prognostic factors for DFS and OS were age >60 (HR 1.87, 95%CI: 1.38-2.52, p<0.001 for DFS and HR 2.27 95%CI: 1.52-3.39, p<0.001 for OS), tumor size ≥5 cm (HR 2.08 (1.47-2.95), p<0.001 and HR 2.13 (1.29-3.50), p=0.003), grade 3 (HR 1.60 (1.18-2.17), p=0.003, and HR 2.09 (1.37-3.20), p=0.001), deep tumors (HR 1.44 (1.02-2.05), p=0.040 and HR 2.13 (1.25-3.63), p=0.006).
Large margins ≥ 5mm were significantly associated with OS (HR 0.64, (0.43-0.95), p=0.027), but not with DFS (HR 0.79 (0.58-1.06), p=0.11). RT was significantly associated with better DFS (HR 0.60 (0.44-0.83), p=0.002), but not with OS (HR 0.91 (0.56-1.46), p=0.694).
RT was associated in the whole cohort with a better TLR (HR 0.44, 95%CI: 0.30-0.66, p<.001). Similar results were observed in subgroup analysis regardless of margin: HR 0.37, (0.19-0.71), p=0.002 in patients with margin <5mm, and HR 0.45, (0.24-0.86), p=0.013 in patients with margin ≥5 mm.
After adjustment for other prognostic factors (age, grade, size, margin), RT remained significantly associated with TLR (HR 0.32, 95%CI: 0.20-0.52, p<.001).
Conversely, in subgroup of patients with a grade 1-2 tumor (N=284), RT was significantly associated with better TLR and DFS when margins were <5mm (respectively HR 0.15, 95%CI: 0.05-0.42, p<0.0001 and HR 0.50, 95%CI: 0.25-0.99, p=0.04), but not when margins were ≥ 5mm (a trend with TLR: HR 0.46 (0.20-1.04), p=0.054, and no significant impact on DFS: HR 0.92 (0.52-1.64, p=0.78).

Conclusion: In R0 patients, RT is associated with a better TLR and DFS, whatever margins size. In the case of low-grade tumors with wide margins, the impact of radiotherapy does not reach significance, which raises the question of the place of radiotherapy in this population. Further in-depth analyses and a prospective study are desirable to define more precisely the criteria for postponing irradiation.

Poster #229 3255266

PRIMARY CUTANEOUS SARCOMAS - A RETROSPECTIVE ANALYSIS OF A 10-YEAR PERIOD AT A TERTIARY TEACHING HOSPITAL

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Objective: Cutaneous sarcomas are a heterogeneous and rare group of tumors. The diagnosis is frequently delayed, with a negative impact in the prognosis. Management of cutaneous sarcomas should be carried out by a multidisciplinary team involving dermatologists, pathologists, oncologists and radiotherapists.

The aim of this study is to review and characterize the histopathological and clinical features of 32 patients presenting with the diagnosis of sarcoma of the skin, during a ten-year period at a tertiary teaching hospital.

Methods: The patients with a histological diagnosis of cutaneous sarcoma between January 1st, 2009 and December 31st, 2018, at Hospital de Santa Maria (Lisbon, Portugal) were included. Data was obtained by reviewing dermatopathology registries and the clinical records of dermatology and oncology visits. Kaposi sarcoma and metastatic sarcoma tumors were excluded.

Results: Thirty-two patients with a cutaneous sarcoma were identified. The mean age at the diagnosis was 65.6 years (+- 17.1), with a range of 30-90 years. Patients with dermatofibrosarcoma protuberans were significantly younger (*M*= 50.9 *vs* 73.3; $p<0.001$). A male predominance was observed (n=21; 65.6%). The most common diagnosis was dermatofibrosarcoma protuberans (n=11; 34.4%), followed by undifferentiated pleomorphic sarcoma (n=9; 28.,1%), atypical fibroxanthoma (n=6; 18.8%), angiosarcoma (n=4; 12.5%) and leiomyosarcoma (n=2; 6.3%). Apart from dermatofibrosarcoma protuberans which did not show a preferential location, most tumors presented in the head and neck area (n=17; 53.1%). Distant metastasis (lung) were only identified in one patient with angiosarcoma at initial staging. Wide margin excision was the preferential modality of treatment. Five patients were submitted to adjuvant radiotherapy. One patient with angiosarcoma was submitted to neoadjuvant chemotherapy with paclitaxel. Mean follow-up was 47.9 months (+- 40.6), with a range of 4-119 months. Four patients had a local recurrence and a patient with an undifferentiated pleomorphic sarcoma presented with cerebral metastasis.

Conclusion: Cutaneous sarcomas are a rare and challenging group of malignancies. Most are associated with a good prognosis, with the exception of angiosarcoma, if adequate wide margin excision is performed.

Poster #230 3255287

EFFICACY AND SAFETY OF ANLOTINIB IN REFRACTORY METASTATIC SOFT-TISSUE SARCOMA: A RETROSPECTIVE STUDY IN CHINA

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Objective: Anlotinib, a new, orally administered multi-targeted tyrosine kinase inhibitor, has been reported to be effective in a phase II trial in patients with selective subtypes of refractory metastatic soft-tissue sarcoma (STS). The efficacy of anlotinib in Chinese STS patients deserves further investigation. The aim of this study was to investigate the clinical characteristics and prognosis of anlotinib in Chinese patients with refractory metastatic soft-tissue sarcoma.

Methods: Patients with refractory metastatic STS treated with anlotinib in real life practice at Sun Yat-sen University Cancer Center were retrospectively analyzed. The clinical characteristics, pathologic features, and prognostic factors were analyzed using the SPSS software standard version 16.0. Also, we utilized an integrative method for the gene-panel sequencing data to explore valuable prognostic biomarkers.

Results: Sixty-nine patients were identified, including 40 males and 29 females. The main histological subtypes were liposarcoma (n=12), leiomyosarcoma (n=8) and undifferentiated sarcoma (n=7). The objective response rate (ORR) and disease control rate among all the subtypes was 7.2% and 55.1%, respectively. The response rate might be related to age, pathological type, FNCLCC grade and first-line therapy. The median progression-free survival (PFS) was 5.8 months. The most common grade 3 or higher adverse events were hypertension and hand-foot skin reaction. We used gene sequencing to find a panel of mutants, amplified and deleted genes for predicting the response to anlotinib.

Conclusion: Anlotinib showed broad-spectrum anti-tumor effect in Chinese patients with refractory metastatic soft-tissue sarcoma.

Poster #231 3255311

EFFICACY AND SAFETY OF BEVACIZUMAB COMBINED WITH CHEMOTHERAPY IN REFRACTORY METASTATIC SOFT-TISSUE SARCOMA: A RETROSPECTIVE STUDY IN CHINA

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Objective: Soft-tissue sarcomas (STS) are a heterogeneous group of relatively rare mesenchymal neoplasms and chemotherapy is currently the first-line treatment for refractory metastatic STS. Bevacizumab, an anti-angiogenesis agent, has been reported to be effective in angiosarcoma and malignant solitary fibrous tumors. The aim of this study was to investigate the clinical characteristics and prognosis of bevacizumab combined with chemotherapy in Chinese patients with refractory metastatic soft-tissue sarcoma.

Methods: Patients with refractory metastatic STS treated with bevacizumab combined with chemotherapy in real life practice at Sun Yat-sen University Cancer Center were retrospectively analyzed. The clinical characteristics, pathologic features, and prognostic factors were analyzed using the SPSS software standard version 16.0.

Results: Eight-five patients were identified, including 41 males and 44 females. The main histological subtypes were carcinosarcoma (n=16), rhabdomyosarcoma (n=14) and angiosarcoma (n=11). The objective response rate (ORR) and disease control rate among all the subtypes was 18.8% and 68.2%, respectively. The response rate might be related to pathological type, FNCLCC grade and first-line therapy. The median progression-free survival (PFS) was 4 months. The most common grade 3 or higher adverse events were myelosuppression.

Conclusion: The combination of bevacizumab and chemotherapy showed effective anti-tumor activity in Chinese patients with refractory metastatic soft-tissue sarcoma.

Poster #232 3255449

PERIVASCULAR EPITHELIOID CELL TUMOR (PECOMA) TREATMENT: 20 YEARS OF EXPERIENCE IN ONE REFERENCE SARCOMA CENTER

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Objective: Perivascular epithelioid cell tumors (PEComas) are rare sarcomas with known tuberous sclerosis complex gene mutations and resultant up-regulation of mTOR. Aim of this study is to evaluate long-term efficacy of multidisciplinary PEComa treatment. Until now surgery is the only curative treatment for these patients with poor outcomes in metastatic cases. This study evaluates the results of multidisciplinary practice in large PEComa series treated in the Maria Sklodowska-Curie Institute-Oncology Center in Warsaw – a reference sarcoma center in Poland.

Methods: We retrospectively reviewed all consecutive pts with PEComa NOS, as well as epithelioid angiomyolipoma (EAML), ekstrapulmonary lymphangioleiomyomatosis (LAM), but not clear cell "sugar" tumours (CCST) of lung or clear cell myomelanocytic tumour of the falciform ligament/ligamentum teres (CCMMT) or pulmonary LAM treated in our Center between 01/1999 and 05/2019. Histopatology of PEComa was reviewed and confirmed in all cases by a designated sarcoma pathologist. Any surviving progression-free patients were censored at last follow-up (30.05.2019) Survival curves were calculated according to Kaplan-Meier method and compared with the log-rank test or a Cox proportional hazard model, with R package.

Results: 26 (19 females and 7 males) consecutive PEComa patients (pts) were diagnosed and treated. The median age was 42 (range: 21-67) years. PEComas were located in retroperitoneal space (8/19) and in uterus (6/19) in females and retroperitoneal space in males (4/7). The main histotypes were PEComa NOS (65%), EAML (19%), and retroperitoneal LAM (15%). 3 patients presented unresectable tumor at diagnosis, 14 underwent biopsy or resection before reference to our center. 8 patients were operated primaryli in our center, including 75% R0 and 25% R1 resections. Only two patients received adjuvant radiation therapy prior tumor resection. Neoadjuvant or adiuvant systemic treatment was not employed. 3 pts experienced local relapse and 9 developed distant metastases. Local relapse free survival (LRFS) was 35 months (95% CI: 35-NA). In 4 cases metastatic tumors were resected, in 1 case surgery was the only treatment modality and enabled complete disease control. The median age of patients treated systemically was 43 years. The tumor size, primary localization or pts' gender did not affect DFS or LRFS. 2-year DFS rates reached 100% when the primary surgery was performed in reference center, 41% (95% CI: 20%-87%) if it took place in regional hospital and 67% (95% CI:42%-100%) if after primary resection in regional hospital radicalization in reference center was performed. 6 pts developed metastases (5 PEComa NOS, 1 EAML) - in the abdomen 6/6 cases and lungs (1/6). 9 patients were treated with sirolimus up-front, while 4 received at the first line doxorubicin-based chemotherapy and sirolimus as the second line therapy. Median progression free survival (PFS) was 5.8 months (95% CI: 4.0-NA) for doxorubicin-based chemotherapy and 42.6 months (95% CI: 42.0-NA) for sirolimus – both as first line therapy. There was one case of objective response (OR) in doxorubicin group. The OR rate reached was 67% (6/9 cases) for sirolimus, with additional clinical benefit in 3 cases. 3 patients died due to disease progression after 29, 32 and 54 months since metastastic disease diagnosis. After a median follow-up of 33 (range: 3.2-220) months, the 5-yr-RFS was 36% (95% CI 16-81) and 5-year OS rate was 88% (95% CI 74-100).

Conclusion: Current data supporting an optimal treatment of patients with advanced PEComa is limited. Our study, the second largest single institution report on PEComa NOS patients helps to fill the gap in this field by exploring the care of patients with advanced PEComa. It also provides further evidence of mTOR inhibitor - sirolimus effectivenes in unresectable and metastatic presentation of PEComa.

Poster #233 3255705

SURGICAL RESULTS AND INFLUENTIAL FACTORS FOR COMPLICATIONS AND LIMB FUNCTION IN PATIENTS WITH SOFT TISSUE SARCOMA OF THE THIGH

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Objective: The risk factors for developing a complication after soft tissue sarcoma resection have been previously described and include location in the lower extremity. Also, soft tissue sarcomas can occur in any compartment of the thigh, but little is known about the correlation of postoperative results on each compartment. This study aimed to analyze the relationship of various factors particularly tumor location with clinical outcome in the patient with primary malignant soft tissue tumors of the thigh.

Methods: Patients who underwent wide excision for soft tissue sarcomas of the thigh without metastasis at the time of initial visit from January 2006 to December 2017 were identified. Those with a follow-up period of less than 2 years were excluded. 40 patients (22 men and 18 women) were included. The average age was 56.3 years (10-85 years) and the average observation period was 76.7 months (24-156 months). The stage classification of UICC/AJCC (8^{th} edition) was stage I in 14, stage II in 4, and stage III in 22 cases. The mean tumor size was 10.9 cm (3.2-24 cm). The tumors were histologically classified as 19 cases of liposarcoma, 7 cases of malignant fibrous histiocytoma/ undifferentiated pleomorphic sarcoma, 5 cases of myxofibrosarcoma, 3cases of leiomyosarcoma, 2cases of fibrosarcoma, and 4 other types of sarcoma. 17 tumors located in the anterior, 13 in the medial, and 10 in the posterior. The relationships between sex, age, body mass index (BMI), tumor grade, tumor size, stage of UICC/AJCC, tumor localization, operation time, amount of muscle removed, with or without neoadjuvant chemotherapy, surgical margin and seroma, complications, MSTS score (without emotion score), and prognosis were statistically analyzed.

Results: *Seroma developed in 8 (20%) patients (Figure 1) and complications in 10 (25%). Mean MSTS score was 21.3 (12-25). On multivariate analysis, positive surgical margin (p=0.014) was significantly associated with lower 5-year recurrence-free survival rate (Figure 2). The longer surgical time > 120 min (p=0.018) was also significantly associated with lower 5-year metastasis-free survival rate (Figure 3). Tumor location, sex, age, BMI were not significantly related to any variables.*

Conclusion: Although seroma developed higher for medial-compartment tumors, in our case the location of tumor showed weak impact for clinical results.

Soren et al reported surgical margin influences local recurrence in 152 patients with soft-tissue sarcoma of the thigh. The wide excision with histologically negative margin could prevent the local recurrence, however the excision of the tumors which involved neurovascular bundles might consume time and increase the recurrence and metastasis rates.

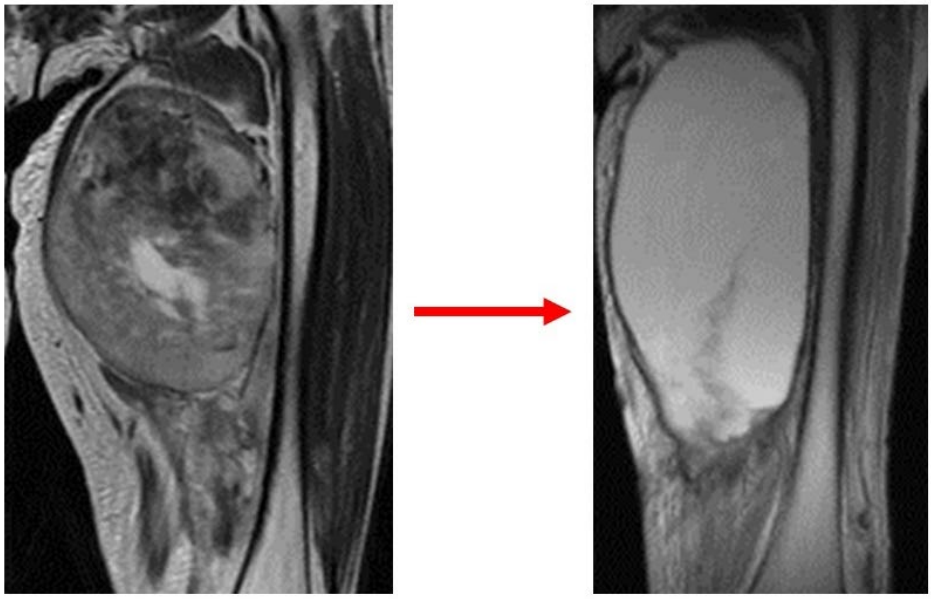

Figure 1. Post-operative seroma

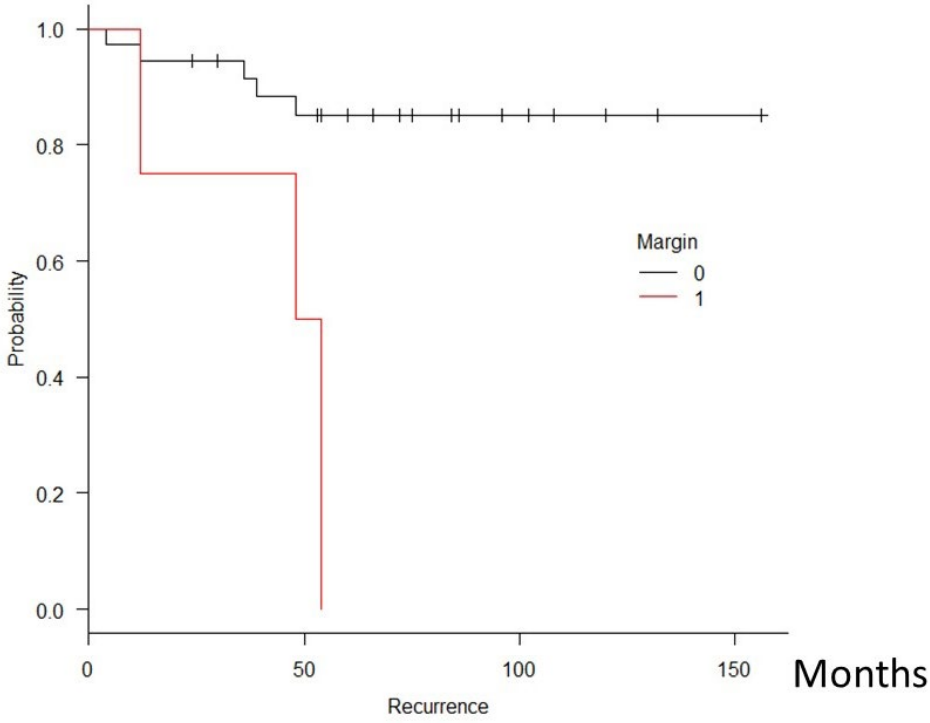

Figure 2. Recurrence-free survival

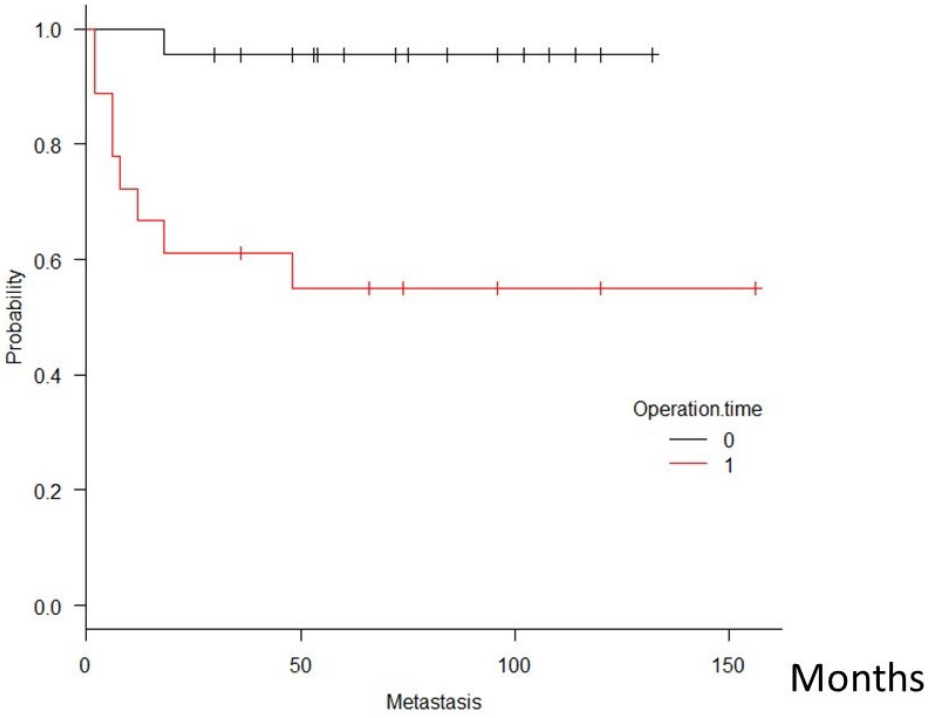

Figure 3. Metastasis-free survival

Poster #234 3256118

POOR TREATMENT OUTCOMES WITH SECOND-LINE CHEMOTHERAPY IN ADULT ADVANCED AND METASTATIC SYNOVIAL SARCOMA

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Objective: Synovial sarcoma arises in younger age groups than other sarcomas, predominantly in adolescent and young adults. In cases of unresectable or metastatic synovial sarcoma, doxorubicin with or without ifosfamide therapy is the standard option as first-line treatment. However, there is no standard chemotherapy for second-line therapy. The purpose of the current study is to evaluate the outcome of second-line chemotherapy for patients with synovial sarcoma.

Methods: We retrospectively evaluated the outcome of 50 patients with unresectable or metastatic synovial sarcoma, who had received first-line chemotherapy at our institution between 1997 and 2017.

Results: Among the 50 patients treated first-line chemotherapy, we identified 33 patients received second-line chemotherapy. The median age was 37.5 (range, 17-71). As chemotherapeutic regimens, 4 (12.1%) patients were with doxorubicin with / without ifosfamide, 10 (30.3%) with ifosfamide with / without etoposide, 7 (21.2%) with pazopanib, 2 (6.1%) with docetaxel and gemcitabine, 1 (3.0%) with trabectedin, 1 (3.0%) with eribulin and 7 (21.2%) with others. The overall response rate according to RECIST for all patients was 6.1%. The median progression-free survival and overall survival were 5.1 months and 12 months, respectively.

Conclusion: Our exploratory study revealed that a response rate of second-line chemotherapy regimens for patients with synovial sarcoma was 6.1%. There is an urgent need to develop more active therapeutic regimens for synovial sarcoma.

Poster #235 3256204

A CLINICAL RANDOMIZED CONTROLLED TRIAL OF TOTAL (IPSILATERAL) RETROPERITONEAL LIPECTOMY WITH HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY FOR RETROPERITONEAL LIPOSARCOMA

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Objective: To optimize local control and overall survival for patients with retroperitoneal liposarcoma (RPLS), different treatment modalities, including conventional complete resection (CR), total (ipsilateral) retroperitoneal lipectomy (TRL) and hyperthermic intraperitoneal chemotherapy (HIPEC), have been compared in this randomized trial.

Methods: 150 primary/first recurrence patients undergoing tumor resection between 2015 and 2019 were identified using a prospectively maintained database at Peking University International hospital and randomly assigned to three different groups. Patients who underwent CR, TRL and TRL with HIPEC were assigned to group A, B and C, respectively. Scatter plots were used in all three groups to assess the relationship between tumor size and amount of bleeding. Disease specific survival (DSS) rate was evaluated using Kaplan Meier analysis.

Results: Seventy-eight patients underwent CR (group A), twenty-three underwent TRL (group B) and thirty-two underwent TRL with HIPEC (group C). Group B patients were more likely to present with larger tumors (≥20cm), whereas group A and C patients were more likely to present with moderate size tumors (10 to <20 cm). In all three groups, the larger the tumor size, the more it bled. Local recurrence (LR) rate was 20%, 9% and 40% as well as mortality rate was 20%, 13% and 6% in group A, B and C, respectively. Although group C was associated with a higher LR rate (40%), tumor related death rate was the lowest (6%) in this group.

Conclusion: TRL plus HIPEC reduces mortality in patients with RPLS. Thus, this treatment strategy is recommended for patients with RPLS.

Table 1. Clinical Characteristics of Patients with Retroperitoneal Liposarcoma

	Group A	Group B	Group C
No. of patients	78	23	32
Median age (range)	52（24~78）	53（30~78）	54（28~68）
Male/Female	49/29	10/13	15/17
Tumor Size (cm)			
Median <10cm 10~<20cm ≥20cm	20 2 39 29	25 1 7 15	16 6 16 10

Table 2. Prognosis of the Three Groups

Outcome	Group A	Group B	Group C
Alive without disease	40	16	14
Alive with disease	16	2	13
Tumor death	16	3	2

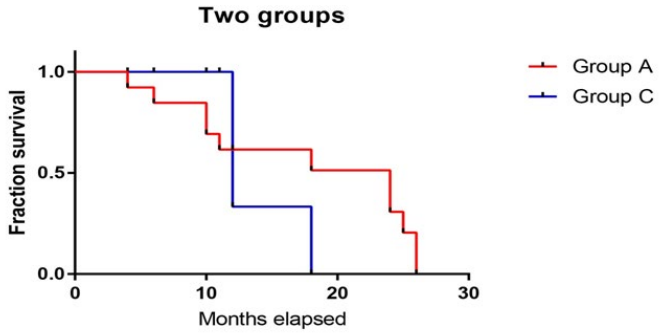

Fig. 4 Survival curves for group A and group C

Poster #236 3256260

DOES RADIOTHERAPY BENEFIT PATIENTS WITH SUPERFICIAL SOFT TISSUE SARCOMAS?

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Objective: The role of adjuvant radiotherapy (RT) for superficial soft tissue sarcomas (STSs) has been rarely discussed and the existing clinical guidelines does not describe clear indication. The purpose of this study was to determine the efficacy of adjuvant RT for superficial STSs.

Methods: A total of 307 patients with superficial STSs who underwent surgical resection at a tertiary sarcoma centre were analysed. The efficacy of RT was investigated according to the tumour size and grade. Four groups of patients were defined and studied including: group 1, ≤ 5 cm, low-grade; group 2, ≤ 5 cm, high-grade; group 3, > 5 cm, low-grade; group 4, > 5cm, high-grade.

Results: The 5- and 10-year local recurrence-free survival (LRFS) for all patients was 88% and 81%, respectively. While the efficacy of adjuvant radiotherapy was not proven in local control of all patients (5-year LRFS; RT+, 90% versus RT-, 83%; p=0.074), the LRFS was significantly improved by adjuvant radiotherapy in group 2 (5-year LRFS; RT+, 96% versus RT-, 83%; p=0.023) and group 4 (5-year LRFS; RT+, 87% versus RT-, 73%; p=0.027). In group 2 and group 4, the adjuvant RT significantly reduced the LR risk if the resection margin was clear and less than 5 mm; the LR rate was 7% by the use of adjuvant RT and 26% by surgery alone (p=0.005). In group 1 and group 3, patients treated with adjuvant RT had no LR, but the efficacy of it does not reach statistical significance. At a median follow-up of 53 months (range, 1 to 181 months), the 5- and 10-year disease-specific survival for all patients was 75% and 66%, respectively. There was no statistical correlation with the use of adjuvant radiotherapy and survival outcome in every group.

Conclusion: Adjuvant radiotherapy reduces the risk of local failure in patients with superficial high-grade STSs regardless of tumour size, especially when resection margin is clear but less than 5 mm.

Poster #237 3256278

PROGNOSTIC ROLE OF INITIAL ELEVATED NEUTROPHIL-LYMPHOCYTE RATIO AND POOR PERFORMANCE STATUS IN SOFT TISSUE SARCOMA

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Objective: A lot of initial prognostic factors such as performance status (PS), serum albumin (Alb), serum lactate dehydrogenase (LDH), C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR) have been reported to possess significant prognostic value in multiple types of cancer. We conducted a retrospective analysis to evaluate the prognostic value of pretreatment NLR in soft tissue sarcoma (STS).

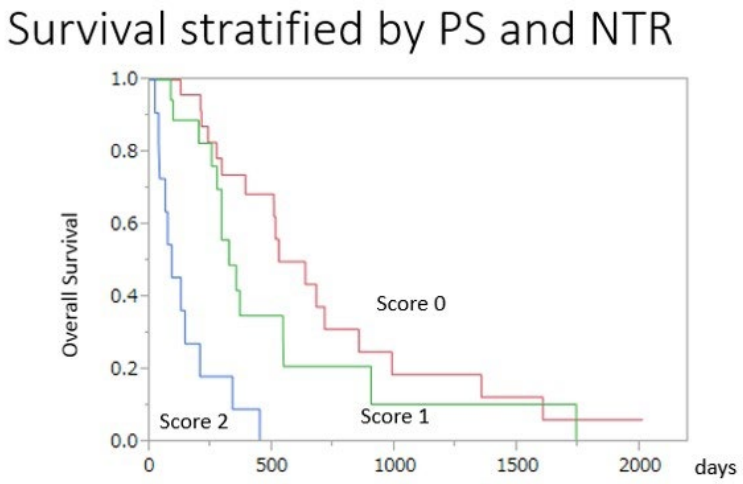
Methods: Fifty-two patients who presented with unresectable or metastatic soft tissue sarcoma treated with doxorubicin monotherapy for first-line therapy were retrospectively reviewed. The study period was from February 2010 to June 2019. Prechemotherapy PS, LDH, Alb, CRP, NLR, and overall survival were analyzed. The survival was analyzed with the Wilcoxon test. Multivariate analysis was performed with the Cox Hazard model.

Results: The median age was 56 years old. The median survival time was 350 days. In univariate analysis, prechemotherapy PS 1-2 ($p=0.0037$), Alb 3.7g/dl or under ($p=0.0037$), CRP 0.2mg/dl or more ($p<0.0001$), NLR 5 or more ($p<0.0001$) were significantly associated with a worse OS. In multivariate analysis, PS 1-2 ($p=0.033$), Age 56 or more ($p=0.025$), NLR 5 or more ($p=0.041$) was an only poor prognostic factor for OS. With the number of prognostic factors (PS, NLR), the prognosis was stratified by 3 (score 0 to 2). The median OS of score 0, 1, 2 were 88 days, 321 days, 525 days, respectively.

Conclusion: Prechemotherapy performance status and NLR were poor prognostic factors. Because the median OS of patients with a score of 2 was less than three months, doxorubicin induction may be considered more carefully than in patients with a score of 0-1.

Univariate Analyssi (p value) of each Prognostic Factors

Factors	p-value
Gender	0.45
Age over 54	0.85
ECOG performance status ≥1	0.0037
LDH ≥ 225 IU/L	0.050
Alb ≤ 3.7 mg/dl	0.0037
CRP ≥ 0.2 mg/dl	＜0.0001
Neutrophil-Lymphocyte ratio ≥ 5	＜0.0001
Lung metastasis	0.35
Liver metastasis	0.52
Bone metastasis	0.59



Poster #238 3256317

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

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Objective: Doxorubicin (dox) alone or with ifosfamide (dox-ifos) are standard first-line regimens for the treatment of soft tissue sarcoma (STS), with dox-ifos used commonly in patients (pts) with symptomatic disease and in neoadjuvant/adjuvant settings. Olaratumab (olara) is a recombinant, fully human monoclonal antibody that binds PDGFRα. After a phase 2 study of dox plus olara in pts with STS demonstrated a survival benefit over dox alone, the present phase 1b study (JGDR; NCT03283696) was designed to evaluate the safety of adding olara to dox-ifos. Here we report the final study results.

Methods: Adults with advanced/metastatic STS, no prior lines of systemic therapy, and ECOG PS 0-1 were enrolled into 1 of 2 olara dosing cohorts. Pts received olara on Days 1 and 8 at either 15 mg/kg (Cohort 1) or 20 mg/kg (Cohort 2) in Cycle 1, followed by olara 15 mg/kg in subsequent cycles, in combination with dox (75 mg/m2; D1-3) and ifos (10 g/m2; D1-4) in Cycles 1-6 of a 21-day cycle. G-CSF therapy was mandatory. Dox was allowed to be administered by continuous infusion or bolus and with cardiac protection at investigator discretion, per institutional standard. Mesna dosing was at least 60% of the ifos dose, per local standard. The primary objective was to characterize the safety of olara plus dox-ifos and to determine a phase 2 dose. Secondary objectives included pharmacokinetics (PK) and antitumor activity. Considering the known toxicities of dox-ifos, a pre-specified dose limiting toxicity (DLT) rate of <60% (ie, ≤8 of 15 pts) during Cycle 1 was deemed acceptable for olara plus dox-ifos. Enrollment was discontinued when the negative results of the phase 3 trial of olara plus dox in STS became available.

Results: All enrolled pts in Cohort 1 (N=16) and Cohort 2 (N=8) received olara plus dox-ifos and completed the DLT period as of data cutoff (29-Apr-2019). Three (18.8%) pts in Cohort 1 had DLTs (one with Grade 4 febrile neutropenia, one with both Grade 3 febrile neutropenia and Grade 3 mucositis, and one with Grade 3 febrile neutropenia). Two (25%) pts in Cohort 2 had DLTs (one with Grade 3 febrile neutropenia and one with Grade 4 thrombocytopenia, Grade 4 neutropenia, and Grade 3 febrile neutropenia). Adverse events occurring in >25% of pts are presented (Table). Reasons for discontinuation of study treatment as of data cutoff were physician decision (n=11), progressive disease (n=10), pt decision (n=2), and death (n=1). Among the 23 pts evaluated for tumor response according to RECIST, 6 pts in Cohort 1 and 1 pt in Cohort 2 had a partial response, 7 pts in Cohort 1 and 6 pts in Cohort 2 had stable disease, and 3 pts in Cohort 1 had progressive disease as their confirmed best response. One pt in Cohort 2 was not evaluable as study treatment was discontinued for an adverse event prior to first response assessment. In Cohorts 1 (N=16) and 2 (N=8), respectively, best objective response rate (ORR: CR/PR) was 37.5% (n=6) and 12.5% (n=1), with a disease control rate (CR/PR/SD) of 81.3% (n=13) and 87.5% (n=7). Four pts had an infusion-related reaction (IRR). Of these pts, 3 had a Grade 2 IRR, one of whom had a Grade 1 IRR on rechallenge, and one had a Grade 1 rash starting on the day of infusion, consistent with an IRR. Median progression-free survival was 9.5 months and 6.9 months for Cohorts 1 and 2, respectively, with about 7.9 months between the start of accrual of Cohort 1 and subsequent start of accrual of Cohort 2. PK data will be presented.

Conclusion: Toxicities of the triplet were common, consistent with the known toxicity profile of dox-ifos in pts with STS. Most Grade ≥3 toxicities were hematologic in nature. There were 6 partial responses in Cohort 1 for an ORR of 37.5%, consistent with that reported in the literature for dox-ifos. The duration of follow-up in Cohort 2 was too short to understand the ORR of 12.5% (1 partial response) relative to historical data. In summary, it is feasible and tolerable to add olara to dox-ifos in pts with STS.

	Cohort 1 (N=16)		Cohort 2 (N=8)	
MedDRA Preferred Term, n (%) *Consolidated Category*[a]	Any Grade	Grade ≥3	Any Grade	Grade ≥3
≥1 TEAE	16 (100.0)	14 (87.5)	8 (100.0)	8 (100.0)
Nausea	14 (87.5)	1 (6.3)	6 (75.0)	0
Fatigue	15 (93.8)	2 (12.5)	7 (87.5)	0
Anemia	11 (68.8)	8 (50.0)	8 (100.0)	5 (62.5)
Constipation	11 (68.8)	1 (6.3)	3 (37.5)	0
Neutropenia	10 (62.5)	9 (56.3)	5 (62.5)	4 (50.0)
Mucositis	8 (50.0)	3 (18.8)	4 (50.0)	0
Musculoskeletal pain	8 (50.0)	1 (6.3)	2 (25.0)	0
Febrile neutropenia	7 (43.8)	7 (43.8)	5 (62.5)	4 (50.0)
Thrombocytopenia	7 (43.8)	5 (31.3)	6 (75.0)	4 (50.0)
ALT increased	5 (31.3)	0	3 (37.5)	0
Hypokalemia	5 (31.3)	2 (12.5)	1 (12.5)	0
Vomiting	5 (31.3)	0	3 (37.5)	0
Leukopenia	6 (37.5)	5 (31.3)	5 (62.5)	5 (62.5)
Hyperglycemia	0	0	4 (50.0)	0

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event. [a]Consolidated categories (italicized) included the following preferred terms (in parentheses): fatigue (fatigue, asthenia); anemia (anemia); neutropenia (neutropenia, neutrophil count decreased); mucositis (mucosal inflammation, stomatitis, oropharyngeal pain); musculoskeletal pain (myalgia, arthralgia, back pain, bone pain, neck pain, pain in extremity, muscle spasms, musculoskeletal pain); thrombocytopenia (thrombocytopenia, platelet count decreased); hypokalemia (hypokalemia); and leukopenia (leukopenia, white blood cell count decreased).

Poster #239 3256398

CLINICOPATHOLOGIC PROFILE OF EXTREMITY SOFT TISSUE SARCOMAS TREATED AT NATIONAL CANCER INSTITUTE (MEXICO) FROM 1990-2017

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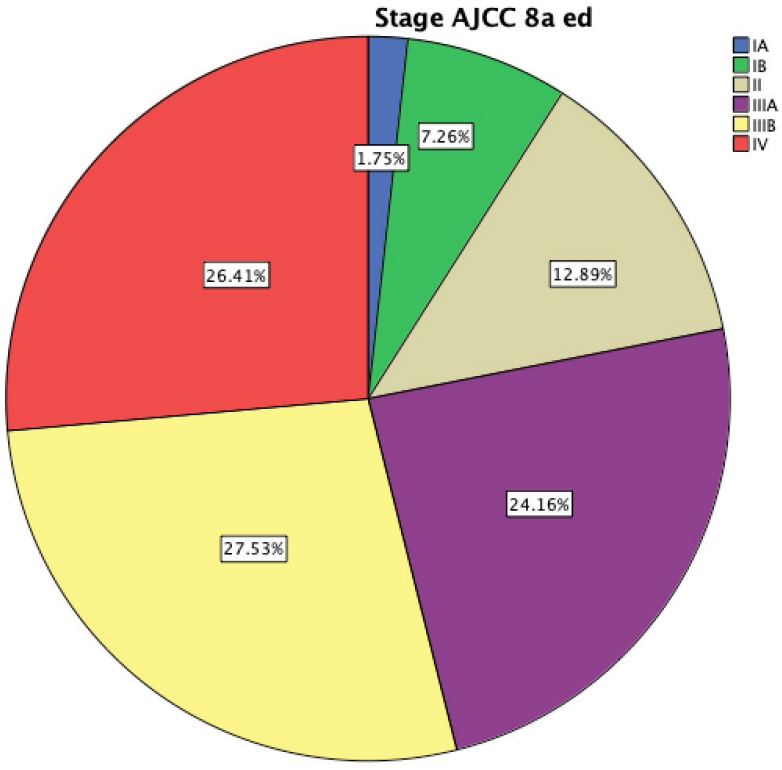
Objective: Soft tissue sarcomas are problematic tumors: they are rare, comprise 1% of malignancies, there are more than 50 histologic types with different prognosis and clinical behavior and can arise in any anatomic location. Most STS develop in the extremities, specifically the thigh (60%). And most frequent histologies are liposarcomas, undifferentiated pleomorphic sarcoma. Literature regarding epidemiology and pathologic characteristics in Mexico and Latin America is scarce and cases are usually more advanced at diagnosis. Complexity of treatment and lack of awareness leads to unadequate treatment in low volume centers. The aim of this study is to analyze the characteristics of a cohort treated at NCI's Sarcoma department during 1990-2017.

Methods: We analized a retrospective data base of patients treated for extremity STS from Jan 1st 1990 to Dec 31st 2017. 813 patients were analized. Histologic type was confirmed by two high volume pathologist. A descriptive analysis is presented, using central tendency and dispersion measures.

Results: 813 patients were analyzed; 417 (51.3%) females and 396 (48.3%) males. Mean age was 45y (18-91). Median tumor size 12.4cm (1.8-78 cm). Lower limb and specifically the thigh was the most common location (49.2%), followed by the leg(15.8 %) and the forearm (8%). Synovial Sarcoma was the most frequent histology (26.2%), 24.6% cases were liposarcoma and 12.4% were UPS. Using the 8th Ed of the AJCC Staging System, 27.1% cases were stage IIIB; 26% Stage IV and 23.7% stage IIIA. 44 (5.4%) cases had node positive disease at presentation. Pulmonary metastasis were most common. Amputation was performed in 22.4%. Genetic syndromes were identified in 2.2% of cases, being NF the most common and associated to MPNST.

Conclusion: To our knowledge this is the largest extremity STS cohort reported in Latin America. SS was the most common, unlike most reports. Treatment has evolved during the 30yr span included in this report. Strategies for limb salvage such has ILP have been implemented. Preoperative or adjuvant systemic and local therapies have also improved, but surgery remains the most important treatment. Still, most cases are diagnosed in advanced stages, making sarcoma awareness for both patients and physicians a potential strategy to early diagnosis. Our group strongly advocates for early referral to a sarcoma center.



Poster #240 3256405

IVCSARC STUDY: INFERIOR VENA CAVA SARCOMA EXPERIENCE AT A TERTIARY CARE CENTER IN SOUTH INDIA

Beulah R. Samuel, MS[1]*; Coelho Victor*[1]*; Titus DK*[1]*; Abinaya Nadarajan*[1]*; Suchita Chase*[1]*; Sukria Nayak*[1]*; Vimalin Samuel*[2]*; Philip Joseph*[3]*; Sitaram V*[3]*; Anne J. Prabhu*[4]*; Patricia Solomon*[5]*; Ashish Singh*[6]

[1]General Surgery, Christian Medical College Vellore, Vellore, Tamil Nadu, India; [2]Vascular Surgery, Christian Medical College Vellore, Vellore, Tamil Nadu, India; [3]HPB Surgery, Christian Medical College Vellore, Vellore, Tamil Nadu, India; [4]Pathology, Christian Medical College Vellore, Vellore, Tamil Nadu, India; [5]Radiation Therapy, Christian Medical College Vellore, Vellore, Tamil Nadu, India; [6]Medical Oncology, Christian Medical College Vellore, Vellore, Tamil Nadu, India

Objective: To collate the existing Institutional data on Inferior vena cava leiomyosarcoma, IVC LMS with the purpose of looking at disease presentation, Complexity of Operations performed and their outcomes, role of neo-adjuvant and adjuvant therapy employed and recurrence patterns and their management.
To identify areas that need standardization of practice in the future.
To identify the group of patients with high risk biology of disease and to study potential role of other modalities of therapy in these patients.

Methods: Prospectively stored electronic database of all patients operated for inferior vena cava leiomyosarcoma, IVC LMS, between October 2002 and May 2019 was compiled in an Epidata form and analysed.

Results: IVCSARC cohort at our center had 14 patients. There were 10 female and 4 male patients with a mean age at diagnosis of 55 years. Pre-operative Contrast enhanced CT of abdomen was done in all patients. CT of the chest was done in 6, was negative for metastasis. Image guided pre-operative biopsy was done in 13 patients, with no discordance as compared to surgical biopsy. One patient had 3 cycles of anthracycline based neo-adjuvant chemotherapy. One patient had a diagnosed double pathology of Intra-abdominal lymphoma and IVC LMS, had R-CHOP chemotherapy for lymphoma prior to surgery for IVC LMS. All 14 patients had operation. One patient had IVC tumor enbloc excision with auto-transplantation of liver, 1 patient had concomitant iliac artery resection and graft reconstruction. IVC was ligated in 4, reconstructed with prosthetic graft in 9 and primary closure done in 1 patient. Right nephrectomy done in 3, Caudate lobe excision in 1, Right iliac artery en-bloc excision with reconstructtion in 1 patient. Post-operative complications with Clavien Dindo grade >/= 3 was seen in 4 patients. Acute renal failure in 2 patients, Pulmonary embolism in 1 patient, Ventilator acquired pneumonia in 1 patient, Re-operation in 1 patient for arterial graft thrombectomy, Mortality 1 patient, who underwent auto-transplantation of liver. Average size of surgical specimen was 100 x 75 x 54 mms. Surgical margin was negative in 9 patients, positive in 1 patient, unknown in 4 patients. Immunohistochemical analysis for desmin was positive in 4 of 4, smooth muscle actin SMA positive in 11 of 11, H-caldesmon positive in 6 of 7 patients and CD 117 was negative in 7 of 8 patients in whom the test was done. There was no microinvasion in 3 renal specimens, 1 caudate lobe liver specimen. Iliac artery specimen showed microinvasion. The mean hospital stay of patients was 17 days. The mean follow-up period was 3years and 3 months. Local recurrence was documented in 2 patients, 1 who had bulky local recurrence refused chemotherapy, other who had rapid progression of disease and was unfit for re-operation or chemotherapy refused radiotherapy. Metastatic disease was seen in 5 patients. Metastasis in liver in 3, lung in 2, bone in 1, tail of pancreas in 1. Chemotherapy with sunitinib was offered for 1 patient, Topotecan then changed to gemcitabine with docetaxel regimen in 1 patient. Patient with liver metastasis who had primary operation in 2003 was re-operated thrice for recurrence, requiring non- anatomical resection of liver, central hepatectomy, right hepatectomy in 2008, 2010 and 2012 respectively. Earliest recurrence recorded in our cohort was at 10 months. Two patients in this cohort have succumbed to the disease.

Conclusion: Aggressive approach to operative resection of primary IVC LMS appears to provide good local control of disease with acceptable morbidity. Operative management of local and distant recurrence could be offered to a carefully selected patient cohort. The role of chemotherapy and radiotherapy will need to be prospectively studied and analysed.

Poster #241 3256503

PHASE 2 STUDY OF ALODOXORUBICIN WITH IFOSFAMIDE/MESNA IN TREATMENT SUBJECTS WITH METASTATIC, LOCALLY ADVANCED, OR UNRESECTABLE SOFT TISSUE SARCOMA

Sant Chawla, MD[1]*; Victoria Chua-Alcala*[1]*; Doris V. Quon*[1]*; Steven G. Wong*[1]*; Neal Chawla*[1]*; Ania Moradkhani*[1]*; John Lee*[2]*; Katherine M. Kim*[1]*; Rekha Baby*[1]*; Erlinda Gordon*[1]

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Objective: Patients with metastatic, locally advanced, or unresectable soft tissue sarcomas have a poor prognosis. Aldoxorubicin is doxorubicin with a linker which rapidly binds in vivo to albumin after intravenous administration. Aldoxorubicin has demonstrated superior anti-tumor efficacy and lack of cumulative cardiac toxicity in multiple studies.

Methods: This was a phase 2, open-label, single-arm, single-center study (NCT02235701). The objectives of this study were to evaluate the safety and efficacy of Aldoxorubicin in combination with ifosfamide/mesna in subjects with metastatic, locally advanced, or unresectable STS as assessed by overall response rate, PFS, survival and tumor necrosis in patients who underwent resection of the residual primary or metastatic disease.

Aldoxorubicin was administered on day 1 at a dose of 250 mg/m^2 every 28 days. Ifosfamide/mesna (1 gm/m^2/day) was given by continuous infusion for 10-14 days via a portable/ambulatory infusion pump using a central line. Combination chemotherapy cycles were repeated at 28-day for 4-6 cycles if patients continued to respond were then treated with Aldoxorubicin alone every 21 days until disease progression or unacceptable toxicity. Hematopoetic growth factors were routinely administered. Echocardiogram was performed after every 2 cycles of Aldoxorubicin.

Results: Sixty-four subjects were enrolled in this study (37 males and 27 females; age range 18 to 78 years). The primary tumor locations were breast (1.4%), head and neck (4.3%), musculoskeletal (54.3%), lung (1.4%), or other location (38.6%).

The most common treatment-related AEs (> 50% subjects) were anemia, neutropenia, nausea, and fatigue. 25% of the patients had SAE. One SAE (grade 3 mucositis) was considered to be related only to aldoxorubicin. The most common SAEs were neutropenic fever and worsening of anemia. None of the patients developed clinical congestive cardiac failure or an ejection fraction of less than 50%.

The median PFS was 10.3 months (95% CI= 7.3-12.8). The Investigator-assessed best overall response revealed CR of 3%, PR of 22% and SD of 72%. Because of prolonged control or response to therapy, 15 patients underwent tumor resection of primary and/or metastatic disease. Tumor necrosis of >90% was observed in 7 patients., 80% in 2 patients, 70% in 2 patients and <50% in 4 patients. Median survival was 21 months (range: 2 to 52+ months)

Conclusion: Administration of 250 mg/m^2 of Aldoxorubicin with Ifosfamide/Mesna for treating advanced soft tissue sarcoma was well tolerated without any evidence of cardiac toxicity. The overall response rate of 25% and stable disease of 72% along with a median PFS of 10.3 months and overall survival of 21 months is very promising and warrants additional studies.

Poster #242 3256549

WHAT CAN YOU EXPECT FROM LYMPH NODE METASTASES IN SOFT TISSUE SARCOMAS?

***Georges Basile**; Jean-Camille Mattei; Ibrahim S. Alshaygy; Anthony Griffin; Peter Ferguson; Jay Wunder*
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Objective: Lymph node metastasis are a rare occurrence in extremity soft tissue sarcomas, arising in less than 5% of patients. The purpose of this study was to evaluate the impact of lymph node metastasis on patient survival.

Methods: A retrospective review was done of the prospectively collected soft tissue sarcoma database at our institution. Two thousand forty-five patients had surgery for soft tissue sarcoma of an extremity between January 1986 and August 2017. Demographic, treatment, and outcome data for patients with lymph node involvement were obtained from the clinical and radiographic records.

Results: One hundred eighteen patients with a mean age of 55.7 (SD=18.9) were included in our study. Seventy-two (61.3%) out of 119 patients were male. Thirty six patients (57.1%) had lymph node involvement at diagnosis. The mean follow-up from the date of the first surgery was 56.3 months. Eighty nine patients (89%) underwent surgical treatment of the lymph node metastasis while 21 (17.6%) were treated with chemotherapy and/or radiation therapy. The mean survival was 52.6 months (range 1-307).

Conclusion: Our results suggest that patients with a lymph node metastasis have a better prognosis than previously described. Their overall survival is superior to patients diagnosed with lung metastasis.

Poster #243 3257932

PRELIMINARY DATA ON A PHASE 2 STUDY ON TRABECTEDIN (T) IN ADVANCED RETROPERITONEAL LEIOMYOSARCOMA AND WELL DIFFERENTIATED/DEDIFFERENTIATED LIPOSARCOMA (TRAVELL)

Roberta Sanfilippo, MD[1]; *Giovanni Grignani*[2]; *Bruno Vincenzi*[3]; *Tommaso De Pas*[4]; *Toni Ibrahim*[5]; *Maria Abbondanza Pantaleo*[6]; *Antonella Brunello*[7]; *Giacomo G. Baldi*[8]; *Alessandro Comandone*[9]; *Sonia Fatigoni*[10]; *Andrea Marrari*[11]; *Alfredo Berruti*[12]; *Monica Giordano*[13]; *Michele Guida*[14]; *Giuseppe Badalamenti*[15]; *Angela Buonadonna*[16]; *Marcella Occelli*[17]; *Elena Fumagalli*[1]; *Matilde De Luca*[18]; *Luciano Carlucci*[18]; *Piero Picci*[19]; *Emanuela Marchesi*[21]; *Angelo Paolo Dei Tos*[20]; *Paolo Casali*[1]

[1]Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [2]Department of Medical Oncology Sarcoma Unit, Candiolo Institute IRCCS, Candiolo, Turin, Italy; [3]Department of Medical Oncology, Campus Bio-medico University, Rome, Italy; [4]Oncology Unit of Thymic Cancer, Rare Tumors and Sarcomas, European Institute of Oncology IRCCS, Milan, Italy; [5]Osteo-oncology and rare Tumours Unit, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori IRCCS, Meldola-Forlì, Italy; [6]Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Bologna, Italy; [7]Department of Medical Oncology, Istituto Oncologico Veneto IRCCS, Padua, Italy; [8]Department of Medical Oncology, "Stanto Stefano" Hospital, Prato, Italy; [9]Department of Cancer Medicine, Presidio Sanitario Gradenigo, Turin, Italy; [10]Department of Medical Oncology, Azienda Ospedaliera Santa Maria, Terni, Italy; [11]Department of Medical Oncology and Hematology, Humanitas Cancer Center and Research Hospital IRCCS, Rozzano-Milan, Italy; [12]Medical Oncology Unit, Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University of Brescia, ASST Spedali Civili, Brescia, Italy; [13]Department of Medical Oncology, Azienda Ospedaliera S. Anna, Como, Italy; [14]Department of Medical Oncology, Ospedale Oncologico "Giovanni Paolo II" IRCCS, Bari, Italy; [15]Department of Medical Oncology, Policlinico Universitario P. Giaccone, Palermo, Italy; [16]Department of Medical Oncology, Centro di Riferimento Oncologico CRO IRCCS, Aviano-Udine, Italy; [17]Department of Medical Oncology, Azienda Ospedaliera Santa Croce E Carle, Cuneo, Italy; [18]Istituto Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy; [19]Laboratory of Experimental Oncology, Institute of Orthopedics Rizzoli, Bologna, Italy; [20]Department of Pathology, Civil Hospital of Treviso, Treviso, Italy; [21]Italian Sarcoma Group Clinical Trial Unit, IRCCS Istituto Ortopedico Rizzoli, Bologna, Italy

Objective: To further explore the activity of T as second/further line treatment in retroperitoneal leiomyosarcoma and well differentiated/dedifferentiated liposarcoma. The primary end-point of the study was the proportion of responders to T based on the ratio between the time to progression under T (TTP1) and the time to progression during previous chemotherapy treatment (TTP2). The secondary end-point were objective response rate as per RECIST and PFS.

Methods: This was a multicentre, single-arm Phase 2 study. This study was conducted in 20 Italian centres. Patients with locally relapsed or metastatic disease, already treated with one or more previous systemic treatments with anthracycline and/or ifosfamide, were enrolled. T was administered at a dose of 1.3-1.5 mg/mq with a top dose of 2.6 mg per cycle. T was administered as a 24h continuous infusion until progressive disease, major toxicity, patient's intolerance or medical decision. For each patient, TTP1 under T was compared to TTP2 of the previous line of chemotherapy, giving rise to a TTP1/TTP2 ratio. When TTP1/TTP2 $\geq$1.33, a patient was considered to be responsive, if $\leq$0.75 non responsive and if 0.76-1.32 as neither. Patients enrolment was completed in February 2019.

Results: Overall, 104 patients were enrolled. At the time of this analysis, patients evaluable for the secondary end point (PFS and RR) were 83, with an ORR (CR +PR) of 12% and a SD of 58%. Median PFS was 6.4 months. A longer follow-up is needed with regard to the primary end-point.

Conclusion: In this Phase 2 study, RR and PFS are consistent with the previous studies on T in liposarcoma and leiomyosarcoma.

Poster #244 3206529

DOXORUBICIN VS DOXORUBICIN+IFOSFAMIDE VS OBSERVATION FOR THE ADJUVANT TREATMENT OF PATIENTS WITH SOFT-TISSUE SARCOMA: AN UPDATED META-ANALYSIS

***Lisa M. Hess, PhD**; Alan J. Brnabic; Zbigniew Kadziola; Patrick Peterson; Volker Wacheck*
Eli Lilly and Company, Indianapolis, IN, USA

Objective: There is no universally accepted standard of care for treatment of patients with localized, high-risk STS. While individual randomized studies have not demonstrated clinical benefit for adjuvant systemic treatment, there are 3 known published meta-analyses (the most recent analysis was >10 years ago) and 4 pooled analyses of selected randomized clinical trial (RCT) data show inconsistent outcomes for the use of adjuvant therapy for the care of patients with soft tissue sarcoma. For example, the Pervaiz and Tierney meta-analysis found significant improvements in overall survival (OS) for adjuvant therapy, but the Sarcoma Collaboration did not. One of challenges in interpreting these studies is the combination of diverse trials with varying regimens into single groups (e.g. 'treated' versus 'untreated' were compared, regardless of the drugs used). The objective of this study was to build on prior analyses by conducting a meta-analysis specifically limited to studies of doxorubicin monotherapy or doxorubicin plus ifosfamide doublet therapy versus observation.

Methods: Eligible studies from published meta-analyses compared doxorubicin versus observation or doxorubicin plus ifosfamide versus observation in the setting of adjuvant or neoadjuvant treatment of patients with soft tissue sarcoma. Studies were excluded that included other anti-cancer drugs. The inverse-variance method and DerSimonian-Laird estimator for Tau squared was used to pool RCT data. Hazard ratios were calculated using the log-rank-expected number of events and variance, consistent with the methods used in the included prior meta-analyses. No limitation was placed on the use of concurrent radiation therapy or by disease stage or grade. Sensitivity analyses were conducted to test the stability of findings by grade, tumor location and inclusion of neoadjuvant courses of therapy. All analyses were conducted using R (Vienna, Austria) and CMA (Biostat Inc, Englewood, NJ).

Results: Seven RCTs of doxorubicin versus observation and three RCTs of doxorubicin plus ifosfamide versus observation were eligible. Across all analyses, disease-free survival (as well as distant but not local disease-free survival) was statistically significantly improved with doxorubicin monotherapy. Overall survival was reported in three studies (ranging from 38 months (observation) to 74 months (doxorubicin) and 75 months (doxorubicin plus ifosfamide); these data are limited due to the short duration of follow up (16-46 months) across eligible studies. The available data are summarized below for doxorubicin versus observation and doxorubicin plus ifosfamide versus observation (see Figure).

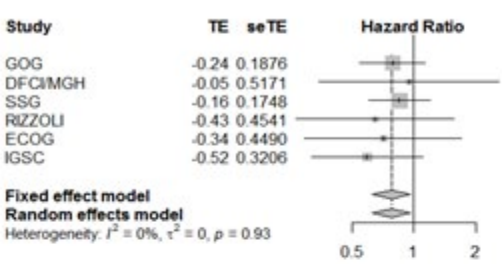
Figure Legend: HR=hazard ratio; OR=odds ratio; left favors doxorubicin or doxorubicin + ifosfamide; right favors observation

Conclusion: This refined analysis was conducted including RCTs of doxorubicin monotherapy versus observation or doxorubicin plus ifosfamide doublet therapy versus observation. The results of this analysis show a statistically significant benefit of adjuvant doxorubicin therapy for distant but not local disease-free survival. Few studies could be analyzed comparing doxorubicin plus ifosfamide to observation. There remains a gap in evidence with regard to overall survival for either doxorubicin monotherapy or in combination with ifosfamide, in part due to the short duration of participant follow up in each included study. The observed statistical significance must be considered in the context of magnitude of benefit, any potential survival benefits, and treatment toxicity. The next steps in this line of research will be to expand the included studies to those reported beyond the prior meta-analyses. This is necessary to obtain sufficient data regarding overall survival and to incorporate adverse event rates, as the selection of an appropriate adjuvant therapy must include an appropriate risk to benefit ratio.

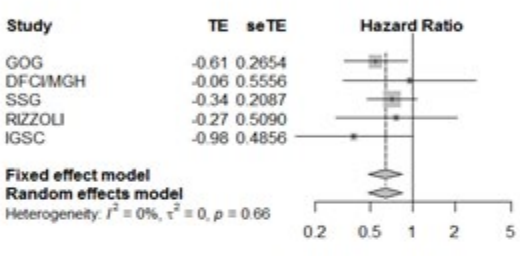
DOXORUBICIN VS OBSERVATION

Sarcoma Collaboration

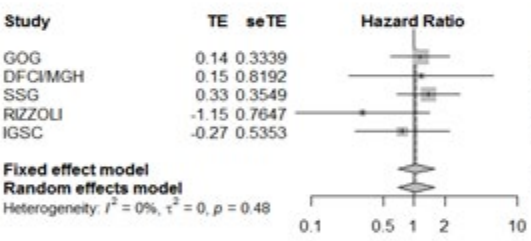
Disease-free survival (DFS)



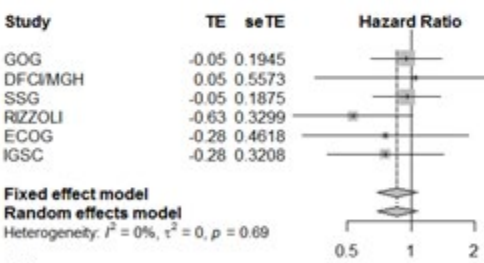
Distant disease-free survival (dDFS)



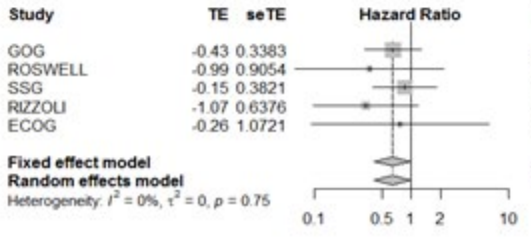
Local disease-free survival (lDFS)



Overall survival (OS)

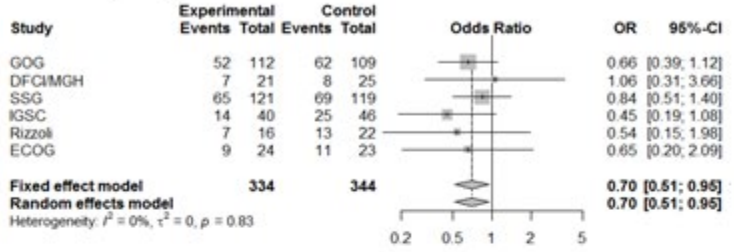


Tierney

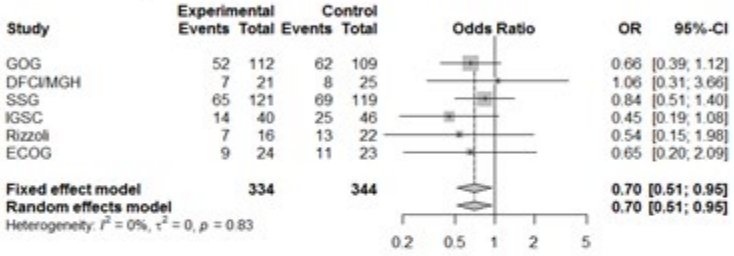


Pervaiz

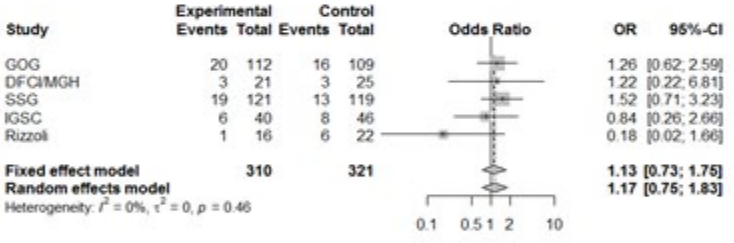
Disease-free survival (DFS)



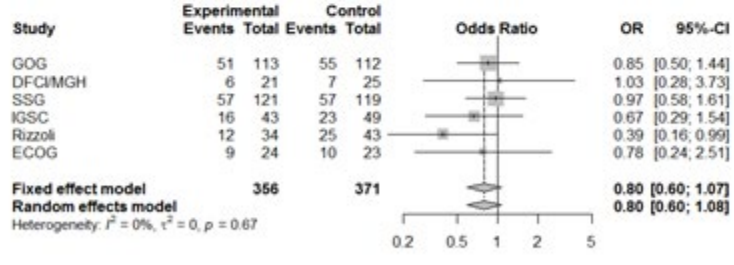
Distant disease-free survival (dDFS)



Local disease-free survival (lDFS)

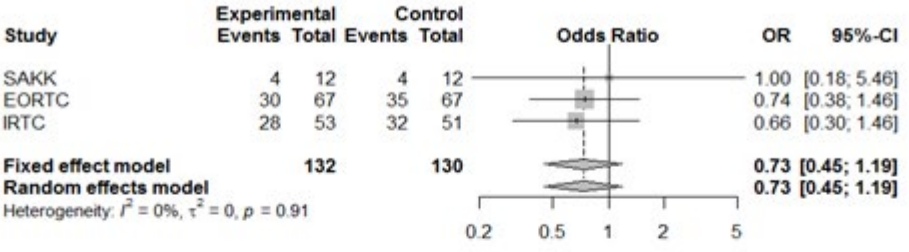


Overall survival (OS)

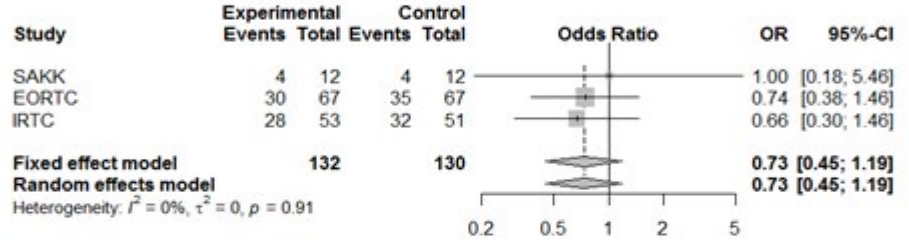


DOXORUBICIN+IFOSFAMIDE VS OBSERVATION

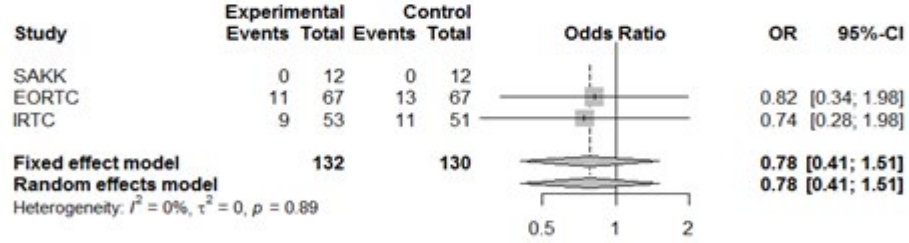
Pervaiz - DFS



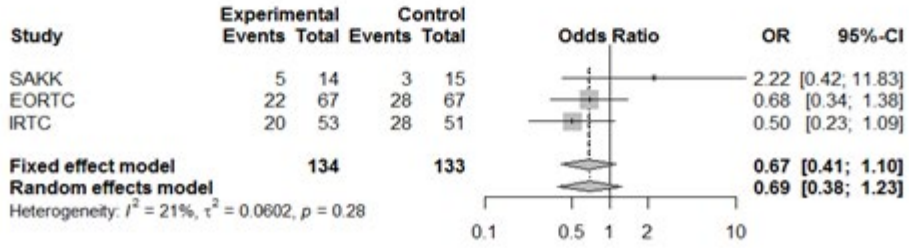
Pervaiz - dDFS



Pervaiz - lDFS



Pervaiz - OS



Poster #245 3208650

PEXIDARTINIB FOR LOCALLY ADVANCED TENOSYNOVIAL GIANT CELL TUMOR (TGCT): OVERALL LONG-TERM POOLED EFFICACY AND SAFETY WITH CHARACTERIZATION OF HEPATIC ADVERSE REACTIONS FROM ENLIVEN AND OTHER STUDIES

John H. Healey[1]*; Hans Gelderblom*[2]*; Andrew Wagner*[3]*; Silvia Stacchiotti*[4]*; William D. Tap*[1]*; Nicholas M. Bernthal*[5]*; Sebastian Bauer*[6]*; Chia-Chi Lin*[7]*; Laurie D. DeLeve*[8]*; Emanuela Palmerini*[9]*; Jayesh Desai*[10]*; Antonio López Pousa*[11]*; Arun Singh*[5]*; Mihaela Druta*[12]*; Henry H. Hsu*[13]*; Dale E. Shuster*[14]*; Joseph McGill*[14]*; Qiang Wang*[14]*; James H. Lewis*[15]*; Michiel van de Sande*[2]

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Objective: TGCT is a rare, locally aggressive neoplasm of the joint/tendon sheath related to colony-stimulating factor 1 (CSF1) overexpression with no approved systemic therapy. Pexidartinib (PEX), a selective CSF1 receptor inhibitor, had compelling activity in the phase 1 TGCT cohort: PLX108-01 (NCT01004861). In phase 3 ENLIVEN (NCT02371369), PEX had a robust tumor response rate vs placebo at wk 25 by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (39% vs 0%; *P*<0.0001) and by tumor volume score (TVS) (56% vs 0%; *P*<0.0001), and PEX caused serious hepatic adverse reactions (ARs). The present analysis assessed long-term overall efficacy and safety from pooled ENLIVEN and PLX108-01, and hepatic safety including results from 2 other studies with TGCT: NCT02734433 and NCT03291288.

Methods: ENLIVEN, a randomized, placebo-controlled study, and the TGCT extension of PLX108-01 enrolled patients (pts) ≥18 y with histologically confirmed locally advanced TGCT that was inoperable or for which surgery was associated with worsening functional limitation or severe morbidity. Objective response rates at wk 25 by RECIST v1.1 and TVS were based upon central review. In the ENLIVEN double-blind phase, secondary endpoints included range of motion, patient-reported outcomes, and duration of response (DOR). Pts were centrally randomized 1:1 to PEX (1000 mg/d × 2 wk, then 800 mg/d × 22 wk) or matching placebo (24 wk). In the open-label phase, pts on placebo could cross over to PEX (800 mg/d). In PLX108-01, pts received PEX 1000 mg/d. Pooled overall efficacy and safety analysis included ENLIVEN and PLX108-01. Additional safety data (hepatic ARs) are from NCT02734433 (600 mg/d PEX; n=1) and NCT03291288 (800 mg/d PEX; n=9).

Results: For long-term pooled efficacy and safety, 130 pts in ENLIVEN and PLX108-01 received PEX; 61 (47%) remained on treatment at data cutoff. Median follow-up from first dose to data cutoff was 23 mo (range, 16, 67); median treatment duration was 17 mo (range, 1, 60+). Five pts (4%) discontinued PEX due to progressive disease. Pooled RECIST v1.1-based best overall response (BOR) was 54%, with increased BOR from longer treatment; DOR results are shown in **Table 1**. The most common adverse events (AEs), occurring in >20% of the pooled TGCT population, are summarized in **Table 1**.

In 130 pts assessed for hepatic ARs from ENLIVEN and PLX108-01, mean PEX duration was 75 wk; 10 additional PEX-treated pts from 2 other phase 1 studies are included in **Table 2**. Hepatic ARs comprised aminotransferase elevations (in the absence of significant alkaline phosphatase or bilirubin elevation; frequent, dose-dependent, generally low-grade) and mixed or cholestatic hepatotoxicity (increase in alkaline phosphatase with or without aminotransferase elevations; uncommon and idiosyncratic, rarely serious, but can be life-threatening). All serious hepatic ARs occurred in the first 8 wk of treatment. Four serious mixed or cholestatic cases with increased bilirubin (1 biopsy-confirmed ductopenia) resolved in 1-7 mo. In clinical studies that included non-TGCT pts (N=658), 2 severe cases (0.3%) of liver toxicity (1 leading to liver transplant, 1 death with ongoing cholestasis and tumor progression) were observed with PEX.

Conclusion: Long-term follow-up showed increased tumor response with continued PEX. The safety profile was consistent with earlier reports, with no new safety signals. With liver test monitoring and benefit/risk assessment on an individual pt basis, PEX may benefit pts with symptomatic TGCT that is associated with severe morbidity or functional limitations and is not amenable to improvement with surgery.

Table 1. Long-Term Pooled Overall Efficacy and Safety (ENLIVEN and PLX108-01)				
Endpoint	**Phase 3 ENLIVEN Randomized (1000 mg/d)*** n=61	**Phase 3 ENLIVEN Crossover (800 mg/d)*** n=30	**Phase 1 PLX108-01 (TGCT Cohort) (1000 mg/d)*** n=39	**Pooled TGCT Population** N=130
First dose to data cutoff (follow-up)				
Median (range), mo	22 (16, 31)	18 (16, 27)	49 (32, 67)	23 (16, 67)
Mean (SD), mo	22 (4)	19 (3)	49 (10)	29 (14)
Treatment duration				
Median (range), mo	16 (1, 30)	17 (2, 27)	17 (1, 60+)	17 (1, 60+)
RECIST v1.1-based BOR				
CR/PR, n (%) [95% CI]	32 (53) [40, 65]	16 (53) [36, 70]	22 (56) [41, 71]	70 (54) [45, 62]
RECIST v1.1-based DOR				
Median (range), mo	NR (3+, 25+)	NR (3+, 23+)	34 (2, 53+)	NR (2, 53+)
TVS-based BOR				
CR/PR, n (%) [95% CI]	39 (64) [51, 75]	20 (67) [49, 81]	24 (62) [46, 75]	83 (64) [55, 72]
TVS-based DOR				
Median (range), mo	NR (0+, 28+)	NR (6+, 23+)	37 (2, 53+)	NR (0+, 53+)
Most common AEs (>20%), n (%)				
Hair color change	45 (74)	25 (83)	28 (72)	98 (75)
Fatigue	34 (56)	8 (27)	36 (92)	78 (60)
Nausea	27 (44)	6 (20)	26 (67)	59 (45)
Arthralgia	17 (28)	9 (30)	24 (62)	50 (38)
AST increased	27 (44)	5 (17)	7 (18)	39 (30)
Diarrhea	16 (26)	9 (30)	14 (36)	39 (30)
Dysgeusia	17 (28)	7 (23)	14 (36)	38 (29)
Rash	17 (28)	7 (23)	12 (31)	36 (28)
Periorbital edema	15 (25)	4 (13)	15 (39)	34 (26)
ALT increased	19 (31)	7 (23)	7 (18)	33 (25)
Headache	14 (23)	6 (20)	13 (33)	33 (25)
Pruritus	10 (16)	6 (20)	14 (33)	30 (23)
Edema peripheral	10 (16)	6 (20)	14 (36)	30 (23)
Hypertension	12 (20)	9 (30)	8 (21)	29 (22)
Vomiting	13 (21)	2 (7)	12 (31)	27 (21)

*PEX starting dose.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; CR, complete response; NR, not reached; PR, partial response; SD, standard deviation.

Table 2. Frequency of Liver Test Abnormalities					
Clinical Parameter	**Phase 3 ENLIVEN Randomized (1000 mg/d)*** n=61	**Phase 3 ENLIVEN Crossover (800 mg/d)*** n=30	**Phase 1 PLX108-01 TGCT Cohort (1000 mg/d)*** n=39	**Other Phase 1[†] (600 or 800 mg/d)*** n=10	**Total[‡]** N=140
Aminotransferase elevations, n (%)					
ALT or AST					
≥1 to ≥3 to ≥5 to ≥10 to ≥20 × ULN	48 (79) 8 (13) 7 (11) 3 (5) 2 (3)	21 (70) 3 (10) 2 (7) 1 (3) 0	27 (69) 4 (10) 2 (5) 2 (5) 0	6 (60) 2 (20) 0 0 0	102 (73) 17 (12) 11 (8) 6 (4) 2 (1)
Mixed or cholestatic hepatotoxicity, n (%)					
ALT or AST ≥3 ×, TBIL ≥2 ×, and ALP	0	0	0	0	0
ALT or AST ≥3 ×, TBIL ≥2 ×, and ALP ≥2 × ULN	3 (5)	0	1 (3)[§]	1 (10)	5 (4)[§]
TBIL ≥2 × ULN (in absence of ALT ≥3 × or ALP >2 × ULN)	0	0	1 (3)	0	1 (1)

*PEX starting dose.
[†]Includes 1 TGCT pt receiving 600 mg/d in NCT02734433 and 9 TGCT pts receiving 800 mg/d in NCT03291288.
[‡]Mean PEX duration of all studies was 71 wk (range, 2, 259).
[§]Includes 1 TGCT pt with a single timepoint elevation of TBIL considered unrelated to treatment.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; ULN, upper limit of normal.

Poster #246 3217271

LONG-TERM OUTCOMES FOR EXTRASKELETAL MYXOID CHONDROSARCOMA (EMC): A POPULATION-BASED ANALYSIS

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Objective: EMC is a rare mesenchymal tumor characterized by NR4A3 chromosomal translocations. Although EMC typically has an indolent course, there is a relatively high rate of local and distant recurrence. When metastatic, it is generally unresponsive to cytotoxic chemotherapy, with no observed responses in the largest series of 21 patients treated with chemotherapy. We queried the Surveillance Epidemiology and End Results (SEER) database to assess factors associated with metastasis and survival in patients with EMC.

Methods: We searched the 1973 to 2016 SEER custom database (with additional treatment fields) for patients with primary tumors diagnosed as myxoid chondrosarcoma (ICD-O-3: 9231/3). Cases with primary tumor location "Bones and Joints", cases with survival months equal to zero, and cases without SEER historical stage information were excluded. Kaplan-Meier analyses and Cox proportional hazard models were used to assess the effects on overall survival (OS) of patient demographics, tumor grade, extent of disease at presentation, primary tumor location, and treatment modality (surgery, radiation, and chemotherapy). Logistic regression models were used to assess the association between primary tumor location and either distant disease at initial diagnosis or receipt of surgical treatment. Statistical significance was reported at the 0.05 level.

Results: 423 cases met our inclusion criteria. Median OS for cases presenting with local disease was 262 months (m) (95% CI: 174-208 m), regional disease was 127 m (95% CI: 82-218 m), and distant disease was 43 m (95% CI: 18-61 m). Primary tumors located in the abdomen/trunk (OR: 12.40, 95% CI: 1.63 – 94.62, p=0.015) and lower extremity (OR: 7.74, 95% CI: 1.03 -57.89, p=0.046) were associated with increased likelihood of metastases at diagnosis, versus upper extremity primary tumors. For patients with locoregional disease (LRD), head and neck primary site was associated with a lower likelihood of surgical treatment versus other primary sites (OR: 0.12, 95% CI:0.021 – 0.66, p=0.015), but for patients with LRD who had surgery there was no difference in OS regardless of primary site (p=0.2779, log-rank test). Surgical treatment of LRD was associated with improved OS (HR 0.28; 95% CI: 0.15-0.51). Chemotherapy and radiotherapy in LRD were both associated with inferior OS (HR: 1.96, 95% CI: 1.14-3.37 and HR: 1.5, 95% CI 1.06-2.13, respectively). Chemotherapy was not associated with OS in those with metastatic disease (HR: 1.23, 95% CI 0.67-2.27).

Conclusion: These data represent the largest report of EMC patients with long-term follow up. Surgery strongly correlates with long-term survival in LRD and should be considered initial management whenever technically feasible. Although there was no benefit seen with chemotherapy or radiotherapy, limitations of the SEER database preclude our drawing conclusions on potential benefits of these modalities. Primary tumors of the upper extremity are less likely to be associated with metastatic disease than those at other sites. Despite the reputedly indolent nature of EMC, outcomes for patients who develop metastatic disease are poor and improved therapies for this population are needed.

5-, 10-, and 15- Year Survival by Extent of Disease

	5-year survival rate, (95% CI)	10-year survival rate, (95% CI)	15-year survival rate, (95% CI)
Local	83% (78% - 88%)	70% (62% - 76%)	59% (50% - 67%)
Regional	71% (61% - 78%)	51% (40% - 61%)	41% (30% - 52%)
Distant	38% (25% - 51%)	10% (2 % - 25%)	---

Factors associated with OS and extent of disease

	Locoregional disease (LRD)		Distant Metastasis	
	Hazard Ratio (95% CI) [1]	N=360 (%)	N=63 (%)	P-value[2]
Sex				
Male Female	Referent 0.96 (0.67-1.36)	220 (61) 140 (39)	48 (76) 15 (24)	0.023
Primary Tumor Location				
Abdomen/Trunk Upper Extremity Lower Extremity Head and Neck Unknown	Referent 0.66 (0.35-1.22) 0.85 (0.57-1.27) 1.45 (0.45 – 4.74) 2.20 (0.68-7.18)	89 (25) 46 (13) 214 (59) 7 (2) 4 (1)	24 (38) 1 (2) 36 (57) 0 (0) 2 (3)	0.007
Tumor Grade				
I II III IV Unknown	Referent 2.16 (1.05 – 4.45) 3.33 (1.42 - 7.79) 5.17 (2.23 – 11.99) 2.05 (1.01- 4.15)	45 (12) 101 (28) 27 (8) 22 (6) 165 (46)	3 (5) 12 (19) 4 (6) 5 (8) 39 (62)	0.385
Tumor Size				
≤ 5cm > 5cm Missing	Referent 2.13 (1.39-3.27) -	113 (32) 206 (57) 41(11)	7 (11) 40 (63) 16 (25)	0.004
Chemotherapy				
No Yes	Referent 1.96 (1.14-3.37)	333 (92.5) 27 (7.5)	41 (65) 22 (35)	<0.000
Surgery				
No Yes Missing	Referent 0.28 (0.15-0.51) -	18 (5) 341 (94.7) 1 (0.3)	n/a	n/a
Radiation				
No/Unknown Yes	Referent 1.50 (1.06-2.13)	224 (62) 136 (38)	n/a	n/a

[1] Hazard ratio for LRD cases only [2] Fisher's exact test assessing proportion between locoregional and distant disease in each characteristic excluding unknowns

Poster #247 3222026

LUNG SURVEILLANCE STRATEGY FOR HIGH-GRADE SOFT TISSUE SARCOMAS: CT SCAN OR CHEST X-RAY?

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Objective: Given the propensity for lung metastases, NCCN guidelines recommend lung surveillance with either computed tomography (CT) or chest x-ray (CXR) in patients with high-grade soft tissue sarcoma (STS). Considering survival, diagnostic sensitivity and cost, the optimal modality is unknown.

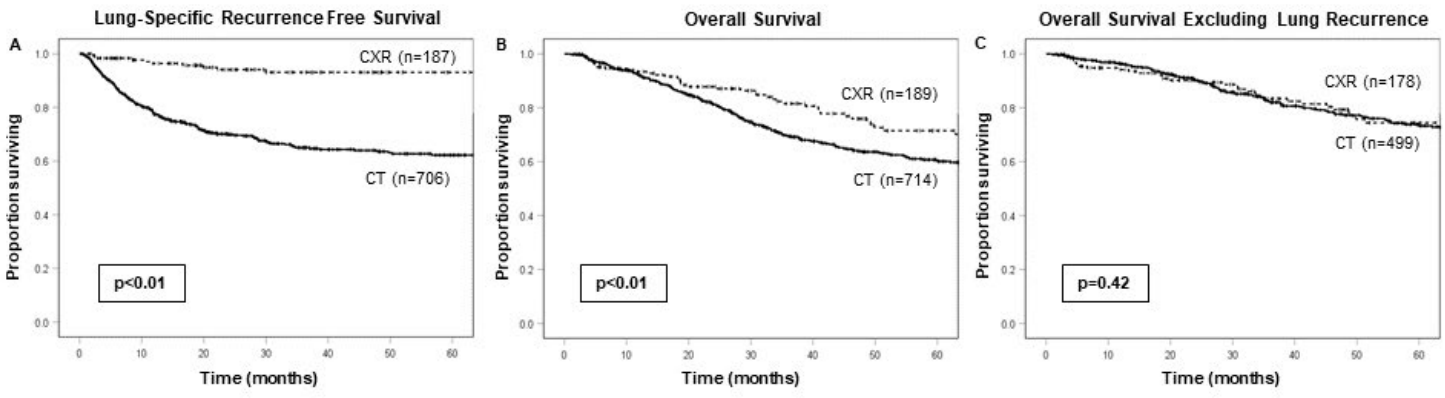
Methods: The US Sarcoma Collaborative database (2000-2016) was reviewed for patients who underwent resection of a primary high-grade STS. Primary outcomes were lung recurrence-free survival (L-RFS) and overall survival (OS). Estimated annual incidence of non-metastatic, high-grade STS was extracted from the literature, and cost of each imaging modality was derived from the 2018 Medicare Physician Fee Schedule to create a probabilistic cost model and determine the cost difference between a CXR and CT-based protocol.

Results: Among 909 patients identified, 83% had truncal/extremity and 17% had retroperitoneal (RPS) tumors. Recurrence at any site occurred in 48% of which 52% were in the lung. Lung surveillance was performed with CT in 80% and CXR in 20%. Both groups were similar for baseline demographics although patients surveyed with CT had more RPS tumors and recurrences. Regardless of imaging modality, 85-90% of lung metastases were detected within the first 2 years of surveillance, and both groups had a similar reintervention rate (p=0.77). Lung metastasis was associated with decreased OS (HR: 3.91; 95% CI 3.11-4.92; p<0.01).

Patients surveyed with CT had a decreased 5-year L-RFS (62 vs 93%, p<0.01; Fig1A) and 5-year OS (60 vs 71%, p<0.01; Fig1B). However, when considering age, tumor size, location, margin status, receipt of radiation, and presence of lung metastases, CXR was not associated with worse OS (HR: 1.01; 95% CI 0.71-1.4; p=0.97). Furthermore, when analyzing patients in whom no lung metastasis was detected, both imaging cohorts had a similar OS (73 vs 74%, p=0.42; Fig1C), suggesting equivalent diagnostic sensitivity.

When simulating surveillance imaging at NCCN-specified intervals for a projected 4,406 cases in 2018 while taking into account the sensitivity and specificity of each modality, lung surveillance for the initial 5 years would cost $677/patient in a CXR protocol versus $2,460/patient in a CT protocol, with a potential savings of $5-8 million/year to the US healthcare system when using a CXR-based protocol alone.

Conclusion: In this large multicenter study, when considering adverse clinicopathologic factors, utilizing CXR for lung surveillance of high-grade STS was not associated with decreased OS. Considering a potential cost savings of up to $8 million/year to the US healthcare system, a CXR-based protocol may optimize resource utilization for lung surveillance in patients with high-grade STS.



Poster #248 3229069

DISEASE RESPONSE WITH PD-1 IMMUNE CHECKPOINT INHIBITOR PEMBROLIZUMAB IN ADVANCED SARCOMA

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Objective: Bone and soft tissue sarcomas (STS) are rare malignancies derived from mesenchymal tissue with over 50 histopathological subtypes that collectively account for only 1% of all cancers. Systemic therapies for sarcoma have been relatively unchanged since the 2000s, and are largely palliative rather than curative given the poor disease prognosis. The oncologic emergence of immune-checkpoint inhibitors has prompted investigations into the clinical benefit of immunotherapy for sarcoma. Pembrolizumab, in particular, is a humanized monoclonal antibody against programmed cell death protein 1 (PD-1), a checkpoint molecule whose expression in sarcomas has been shown to be as high as that in other malignancies where anti-PD1 therapies demonstrated clinical benefit. In the phase II SARC028 trial, 18% of soft tissue sarcoma patients and 5% of bone sarcoma patients showed objective clinical responses. Our report highlights a substantially increased objective response rate in the soft tissue cohort treated with pembrolizumab.

Methods: A retrospective chart review was performed on 196 patients treated with pembrolizumab in a nonprofit teaching hospital or its affiliated outpatient infusion centers between May 2014 and April 2019. Patients that met inclusion criteria for analysis included those >18 years of age with a biopsy proven diagnosis of metastatic or surgically unresectable locally advanced sarcoma with at least one measurable lesion who had previously been offered or received at least one line of systemic anticancer therapy. Those who did not receive at least one dose of pembrolizumab or who were treated with the drug for a non-sarcoma diagnosis were excluded from this study. The objective response rate and progression free survival were the primary and secondary end points of this review, respectively. Using the National Cancer Institute's Dictionary of Cancer Terms, we define response rate as the percentage of tumor that shrinks or disappears after treatment and progression free survival as the length of time during and after treatment that a patient lives with the disease but it does not get worse.

Results: We identified 13 patients that were treated with pembrolizumab as sarcoma-directed therapy. Of these, 12 had a soft tissue sarcoma (comprised of 6 different histological subtypes) and 1 had a bone sarcoma (Ewing's). An objective response was noted in 5 of 12 (41.7%) patients from the soft tissue group: 3 of 5 (60%) with undifferentiated pleomorphic sarcoma, 1 of 2 (50%) with epithelioid sarcoma, and 1 of 1 (100%) with extraskeletal myxoid chondrosarcoma. Among those with an objective response, 3 ultimately developed disease progression and transitioned to alternative therapy while the other 2 continue to receive pembrolizumab without evidence of progression to date. None of the patients with liposarcoma, fibrosarcoma, or leiomyosarcoma demonstrated an objective response. In the soft tissue cohort, 6 of 12 (50%) had >12 weeks of progression free survival. The one patient with Ewing's sarcoma had neither an objective response nor >12 weeks of progression free survival.

Conclusion: Patients treated with conventional sarcoma-directed therapies (surgery, chemotherapy, and radiation) often develop metastatic and resistant disease, which fuels the need to foster new treatment strategies. Developing immune therapy for sarcoma is limited by the challenges of the rarity and heterogeneity of the disease. Several observations made from trials with immune checkpoint blockade in other malignancies suggest that this immunotherapeutic approach may prove useful in STS. Though the currently available human data to support the efficacy of checkpoint inhibition in STS is limited, the promising response rate of pembrolizumab in our patient population supports the need for additional clinical trials with this PD-1 inhibitor, either alone or in combination with other drugs.

Poster #249 3239155

CHARACTERISING THE IMMUNE MICROENVIRONMENT IN LIPOSARCOMA, ITS IMPACT ON PROGNOSIS AND THE EFFECT OF RADIOTHERAPY

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Objective: The tumour immune microenvironment is increasingly recognised as a key factor in cancer development and progression, with the presence of tumour-infiltrating lymphocytes (TILs) and other cell types reflecting immune engagement. TILs have been correlated with prognosis in a variety of cancers, with different TIL scoring systems created for different tumour types. There is no recommended method for grading TILs in sarcoma and the prognostic impact of alterations in TILs caused by radiotherapy is unclear.

The aims of this study were to characterise the immune microenvironment in liposarcomas, to analyse for changes in immune signature before and after radiotherapy and to assess for a prognostic significance of these signatures. By comparing two established TIL scoring methods, it also aims to identify the optimal TIL scoring system for sarcoma.

Methods: A retrospective analysis was performed of paired tissue samples pre- and post-radiotherapy from 44 patients with liposarcoma undergoing curative-intent surgery following neoadjuvant radiotherapy. Routine H&E samples were scored for TILs using scoring systems developed for breast cancer and melanoma. Then immune cell subsets were quantified with immunohistochemistry for immune markers: CD4+, CD8+, CD68, CD163, FoxP3 and PD-L1. All scoring was performed by two expert sarcoma pathologists.

Results: All patients had variants of liposarcoma: 16 well-differentiated/atypical lipomatous tumour, 14 dedifferentiated, 13 myxoid and 1 pleomorphic. 13 patients developed recurrent disease (6 local, 7 distant). Median tumour size was 15cm (range 5-39cm).

Testing for interobserver variability with Cohen's kappa coefficient, TIL scoring using the Salgado (2015) breast cancer TIL score yielded perfect agreement (k = 1.000) for the biopsy and moderate agreement for the resection specimen (k = 0.601), while the Azimi (2012) melanoma TIL score had weak agreement for both biopsy (k = 0.455) and resection (k = 0.394). The Salgado score was used for all subsequent analyses.

Radiotherapy increased TIL scores in 20.5% and had no effect in 79.5%. Almost all of this was in the dedifferentiated liposarcoma group, with 54.5% of patients having increased TIL scores. No well-differentiated liposarcoma had increased TILs.

CD68 and CD4 expression increased in 59.4% and 34.4% respectively after radiotherapy, while CD163, CD8, FoxP3 and PD-L1 did not increase or decrease. The CD8/FoxP3 ratio increased in 62.5% of patients and was more often seen in patients without recurrence (66.7%) compared with those who recurred (50%).

Disease recurred in 50% of patients with increased TILs post-radiotherapy, compared to 19.4% of patients without increased TILs. More patients with disease recurrence showed increased CD163 and CD4 infiltrates than those without recurrence (37.5% vs 12.5% and 62.5% vs 25%). Decreased numbers of FoxP3 regulatory T-cells were seen in 33.3% of patients without recurrence, while numbers were maintained or increased in patients with disease recurrence.

Conclusion: The Salgado TIL scoring system is readily reproducible when applied to soft tissue sarcoma and a similar system would be preferable to the Azimi system given the higher interobserver reliability.

Radiotherapy causes a clear alteration in immune infiltrates in a substantial number of patients. TIL infiltrates in liposarcoma may not be associated with improved prognosis, in contrast to other tumour types. In addition to the overall TIL increase, the balance of tumour-promoting to tumour-suppressing immune cells also seems to be affected by radiotherapy. These data suggest that patients who recur after radiotherapy may have an immune infiltrate that is more anti-inflammatory and tumour-promoting. But the significance in this exploratory cohort is unclear. This should inform future studies to investigate not only the tumour-suppressive effects of radiotherapy, but the tumour-promoting effects also.

Poster #250 3239422

SOFT TISSUE SARCOMA SURVIVAL RATES CORRELATE TO T-CELL RECEPTOR AND MUTANT AMINO ACID CHEMICAL COMPLEMENTARITIES

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Objective: The importance of T-Cell Receptor α (TCR-α) and the chemical properties of its complementarity determining region-3 (CDR3) domain have recently been indicated for distinguishing high and low survival patients in bladder cancer. We now apply a similar approach to soft tissue sarcoma (STS). Finding a connection between STS survival and the electrostatic complementarity of a patient's tumor antigens and their TCR-α CDR3 domain chemistry would provide support for the use of individualized neoepitope vaccines in STS patients.

Methods: Immune receptor V(D)J recombination reads were recovered from the whole exome sequence files, from the genomic data commons (GDC), representing 156 STS patients. The CDR3 domains of these V(D)J recombination reads were identified and translated. The net charge per residue (NCPR) was calculated for each CDR3. Mutect files (mutation data) were obtained from the GDC. The difference in the electrostatic charge caused by mutant amino acids (AA) was determined for each sample. The average product of the TCR-α CDR3 NCPR and mutant AA charge difference was calculated for each patient and represented the patient's complementarity score. Survival, clinical, and RNASeq data for 261 STS patients were obtained from cBioPortal (TCGA, Provisional). Kaplan-Meier curves were used for survival analysis. Pearson's correlation analysis and independent T tests were performed between complementarity scores and clinical characteristics, as well as for assessing RNASeq values.

Results: Improved OS was significantly correlated with complementarity between TCR-α CDR3 domains and electrostatic charge changes due to mutant AA (n=19). In contrast, lower OS was observed for patients lacking this complementarity (n=34, p=0.051); for all other patients (n=242, p=0.014); and for all patients without immune receptor recoveries in their tumor (n=185, p=0.013). When comparing pro-apoptotic gene expression using RNASeq values, patients with CDR3-mutant AA electrostatic charge complementarity had significantly increased GZMB expression in their tumors compared to patients who did not have complementarity (p=0.026). Survival analyses of the TCGA database showed that age at diagnosis, primary pathologic length, multifocal disease, fraction of genome altered, and surgical margin all correlated with OS in a univariate analysis. No correlation was found between these clinical characteristics and complementarity score. Patients with complementarity were distributed across STS subtypes. In other words, CDR3-mutant AA complementarity was an independent survival marker.

Conclusion: STS patients with complementarity between TCR-α CDR3 domains and tumor antigens show improved OS, as well as increased expression of pro-apoptotic genes in their tumors, compared to patients who did not have this complementarity. The independent survival advantage found in this study could be due to tumor infiltrating lymphocytes having increased ability to recognize tumors by the physiochemical properties of their TCR-α polypeptides and provides support for the presence of immunogenic potential in STS setting. These findings are clinically relevant, as achieving electrostatic complementarity to tumor antigens may be an important parameter for developing individualized neoepitope vaccines for patients with STS.

Figure 1: Stratification of STS Patients by TCR-α CDR3 and Tumor Antigen Complementarity

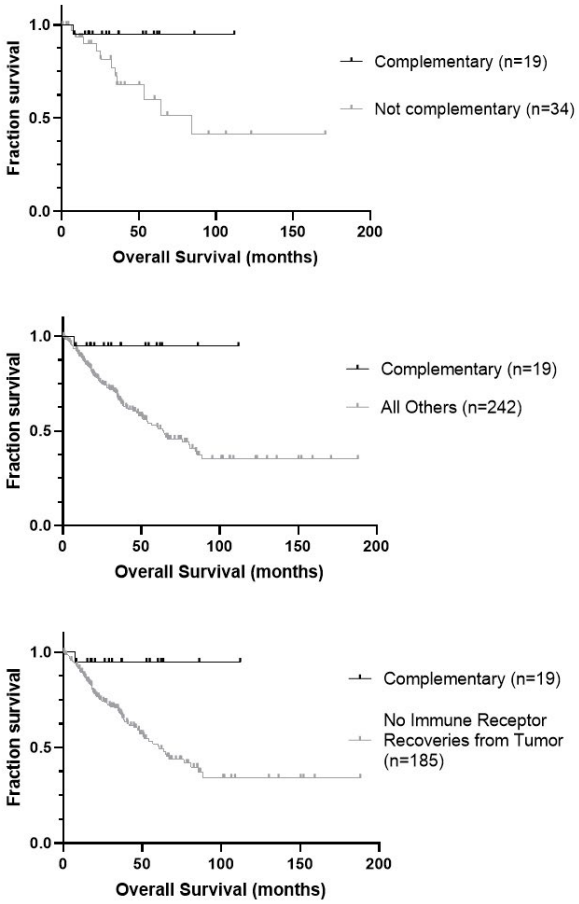
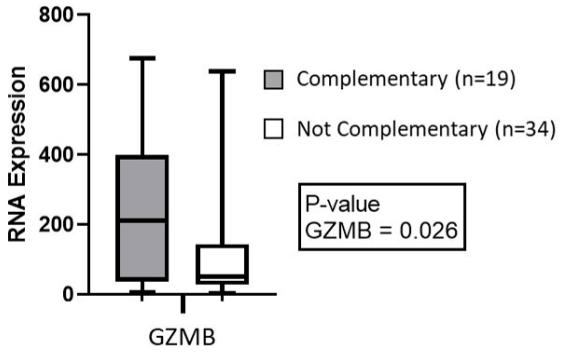


Figure 2: Pro-apoptosis Gene Expression Increased in STS Patients with TCR-α CDR3 and Tumor Antigen Complementarity



Poster #251 3240770

COMBINATION THERAPY WITH TETRAHYDROPYRANYL-ADRYAMICIN (PIRARUBICIN) + IFOSFAMIDE + ETOPOSIDE FOR ADVANCED SOFT TISSUE SARCOMA

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Objective: Pirarubicin is an analogue of adriamycin; it intercalates into DNA and interacts with topoisomerase II. The benefit of pirarubicin is that it has a 170-fold higher uptake potential and lesser cardiotoxicity than adriamycin. Our institution utilized this agent with etoposide and ifosfamide as the first- and second-line treatment for advanced soft-tissue sarcoma patients. In this study, we analyzed the oncological outcome and side effects in patients that received this combination therapy.

Methods: A total of 21 advanced soft-tissue sarcoma patients (with distant metastasis or unresectable lesions) from 2008–2017 [A1] were included in this study. The following cycles of chemotherapy were administered to the patients: pirarubicin (30 mg/m^2) on day 1 and 2, ifosfamide (1 g/m^2) on day 1 to 5, and etoposide (100 mg/m^2) on day 1 to 3. The best overall responses were assessed based on the RECIST criteria, and the rate of progression-free survival three months after the treatment (PFS3m) was analyzed. Furthermore, the side effects were evaluated based on the CTCAE ver 4.0.

Results: The mean age of the patients was 49.6 years. The average number of chemotherapy cycles was 3.3. All patients, except two, underwent this therapy as the first-line regimen. The subtypes of these patients were undifferentiated pleomorphic sarcoma (six patients), myxoid liposarcoma (two patients), epithelioid sarcoma (two patients), synovial sarcoma (two patients), alveolar soft part sarcoma (two patients), and others (five patients). The best overall responses were as follows: PD in five cases (24%), SD in ten cases (48%), PR in five cases (24%), and CR [A1] in one case (5%). Additionally, the rate of PFS3m was 70%. With regards to side effects, no heart failure was observed. However, hematotoxicity was a common problem; anemia (>Grade 3) was observed in 11 cases, the platelet count was decreased (>Grade 3) in 6 cases, and white blood cell count was decreased (>Grade 3) in 21 cases.

Conclusion: The first treatment choice for advanced soft-tissue sarcoma is adriamycin monotherapy, the response rate (PR and CR) for which was reported to be 10–20%. From the results of this study, the efficacy of the combination therapy seems to surpass that of the monotherapy. However, due to the stronger hematotoxicity of the combination therapy, the performance status and age of the patient should be considered prior to the administration of the combination treatment.

Poster #252 3241734

PHASE 1 STUDY OF DCC-3014 TO ASSESS THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND PHARMACODYNAMICS IN PATIENTS WITH MALIGNANT SOLID AND DIFFUSE-TYPE TENOSYNOVIAL GIANT CELL TUMOR

Breelyn Wilky, MD[1]*; Matthew Taylor*[2]*; Todd Bauer*[3]*; Steven Leong*[1]*; Ying Su*[4]*; Cynthia Leary*[5]*; Xiaoyan Li*[4]*; Keisuke Kuida*[4]*; Rodrigo Ruiz Soto*[4]*; Lara E. Davis*[6]

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Objective: DCC-3014 is a potent, orally administered, investigational kinase switch control inhibitor of colony-stimulating factor 1 receptor (CSF1R). DCC-3014 has exhibited greater than 100-fold selectivity from a family of kinases homologous to CSF1R including KIT proto-oncogene receptor tyrosine kinase and vascular endothelial growth factor receptor 2, and even greater selectivity against a panel of 300 other human kinases. DCC 3014 potently inhibits CSF1R signaling in cellular assays, as well as functionally inhibits macrophage-mediated tumor cell migration, osteoclast differentiation, and proliferation of a CSF1R dependent cell line. Tenosynovial giant cell tumor (TGCT) is a rare, monoarticular disease known to be caused by the translocation in the CSF1 gene leading to overexpression of CSF1. Most TGCT tumors consist of CSF1R signaling-dependent inflammatory macrophage infiltrates that migrate and grow in the joints and surrounding tissue. A subset of TGCT patients develop diffuse TGCT (DTGCT) with extensive involvement in the surrounding tissue and joint destruction requiring systemic treatment. Anti-CSF1R therapies have shown clinical activity in DTGCT. Thus, evaluation of DCC-3014 in DTGCT patients is warranted given the potency, selectivity and biological activity of DCC-3014 and the underlying pathophysiology of DTGCT.

Methods: This study is a multicenter, first-in-human study of DCC-3014 to determine a recommended Phase 2 dose (RP2D) or maximally tolerated dose (MTD) and evaluate the safety, efficacy, pharmacokinetics (PK) and pharmacodynamics (PD) of DCC-3014 in solid tumors including DTGCT with two parts [NCT03069469]. The first part is an ongoing 3+3 dose escalation and the second part is to further evaluate the safety of the RP2D or MTD in malignant solid tumor patients and the safety and efficacy in DTGCT patients in two separate cohorts. DCC-3014 is given orally in a 28-day cycle.

Results: As of 02 June 2019, the study is ongoing in the dose escalation phase and has enrolled 34 patients, including DTGCT patients, in 7 cohorts. The first cohort was initiated at 10 mg daily (QD) and loading and maintenance dosing schedules have been used from the second cohort to achieve steady-state exposures more quickly. DCC-3014 was generally well tolerated and most of reported adverse events (AEs) were Grade 1 or 2. Periorbital edema (Grade 1/2) was reported in 4 patients. Asymptomatic CPK and AST elevations have been observed, consistent with CSF1R inhibition and decreased clearance of these enzymes by liver macrophages. No bilirubin elevations and/or other laboratory abnormalities typically associated with liver damage have been observed. Exposure was approximately dose-proportional and induction of CSF-1 and IL-34 was seen in all cohorts. Preliminary data from this study with DTGCT patients, including case studies, will be provided.

Conclusion: DCC-3014 is being explored in an ongoing study including DTGCT patients. DCC-3014 was generally well tolerated with approximately dose-proportional exposure and PD effects. These results could support further exploration of DCC-3014 in this rare, debilitating disease.

Poster #253 3253165

EXPANSION COHORT OF ADVANCED SARCOMA PATIENTS IN THE PHASE I TRIAL OF PEMBROLIZUMAB COMBINED WITH ZIV-AFLIBERCEPT

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Objective: High PD-L1 expression is associated with worse overall survival (OS) in patients (pts) with various soft-tissue sarcomas. Angiogenesis is crucial to sarcoma growth and dissemination, and anti-vascular endothelial growth factor (VEGF) therapies such as pazopanib and regorafenib are US FDA–approved for certain sarcomas. Ziv-aflibercept is a fusion protein with high affinity for VEGF-A/B that reduces neovascularization and vascular permeability. Angiogenic factors also influence immune cell regulation and effector cell trafficking into tumors. In prior studies, the anti-PD-1 antibody nivolumab alone or combined with pazopanib yielded clinical benefit (partial response [PR] or stable disease [SD]) in 50% of evaluable pts, and anti-PD-1 antibody pembrolizumab combined with VEGF inhibitor axitinib yielded 8 PRs in 30 evaluable advanced sarcoma pts—7 of 8 PRs occurred in pts with alveolar soft-part sarcoma (ASPS). The combination of pembrolizumab with ziv-aflibercept has the potential to enhance immune activation and antitumor T cell responses, resulting in antitumor activity. Our phase 1 trial (NCT02298959) identified a recommended phase 2 dose (RP2D) of 2 mg/kg of pembrolizumab with 4 mg/kg of ziv-aflibercept in advanced solid tumors. Here, we report the activity of this RP2D in a sarcoma expansion cohort.

Methods: This sarcoma cohort is part of an international, multi-center phase 1 trial of pembrolizumab and ziv-aflibercept in adult pts with advanced soft tissue and bone sarcomas. The primary objective of this expansion cohort is to determine response rate. Secondary objectives are time to progression, progression-free survival at 6 months, and OS at 1 year. Exploratory objectives are to evaluate effects on immune cell components of the tumor and microenvironment. Pembrolizumab and ziv-aflibercept are given intravenously on day 1 of a 14-day cycle, on an outpatient basis. CT or MRI for re-staging is done every 12 weeks. The trial sample size is 18, with 85% power to detect a response rate of 35% from the null 10%. Tumor biopsies are collected pre- and 12 weeks post–treatment to assess drug effect, including immune status (PD-1/PD-L1, T-cell activation, regulatory immune cell subsets) and epithelial-mesenchymal transition, which may indicate metastasis. Phenotypic changes of peripheral blood mononuclear cells subsets are studied by flow cytometry. Humoral and cellular immune responses are investigated by ELISA, ELISPOT, and cytotoxic T cell chromium release assays. Tumor vasculature effects are assessed by circulating angiogenic factor (e.g., VEGF) measurements.

Results: Eleven pts were enrolled as of 6/18/19: 9 women and 2 men, median age 51 (23-62). Histologies (1 each) were desmoplastic small round cell tumor, malignant spindle cell tumor, perivascular epithelioid cell neoplasm, leiomyosarcoma, chordoma, Ewing's sarcoma, angiosarcoma, sarcoma of peritoneum (not otherwise specified), liposarcoma, gastrointestinal stromal tumor, and a high-grade pleomorphic sarcoma (HGPS). Pts had up to 9 known prior lines of therapy. The most common adverse effects (AE) possibly related to drugs were grade 1 fatigue, hoarseness and headache (n=5 per AE). Grade 3 toxicities were seen in 5 pts: hypertension (n=3), proteinuria (2), amylase/lipase increase (1), anemia/ovarian hemorrhage (1). There were no grade 4/5 toxicities. Three pts are awaiting re-staging evaluation. Among the remaining 8 pts, median cycles on treatment is 7 (range 2-10) with two minor responses (HGPS, leiomyosarcoma) and two SD at up to 20 weeks. The median lines of prior treatment in this latter group is 4.

Conclusion: These early results for the pembrolizumab and ziv-aflibercept combination in pts with advanced sarcomas are promising given that the study population is both heavily pre-treated and lacks any ASPS pts. Safety and efficacy endpoints are continuing to be assessed, with ongoing biomarker studies pending.

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Poster #254 3253225

RARE MULTINUCLEATED GIANT CELLS IN HUMAN ANGIOSARCOMA CONFER WORSE CLINICAL OUTCOMES

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Objective: Multinucleated giant cells (MGCs) have been recognised as a rare subpopulation of malignant cells across many cancer types, though their clinical significance remains poorly understood. We aim to examine the clinical impact of MGCs in human angiosarcoma, as well as provide further phenotypic and molecular characterization.

Methods: Archival H&E stained slides from primary angiosarcoma tissue (n=58) were examined for MGCs, defined as atypical large cells (≥3x size of surrounding cells) harboring multiple bizarre hyperchromatic nuclei. Survival analysis was performed using the Kaplan-Meier method and multivariate Cox proportional models. The angiosarcoma samples were further analysed using the NanoString PanCancer IO 360 Gene Expression Panel. *In vitro* experiments were conducted using angiosarcoma cell lines ISO-HAS-B and MO-LAS-B.

Results: MGCs were present in 24/58 (41.4%) of angiosarcomas. Presence of MGCs was independently associated with poorer overall survival (OS, median 9.8 vs 20.6 months , HR 2.38, 95% CI 1.29-4.43, p=0.0059) and progression-free survival (PFS, median 3.4 vs 7.0 months, HR 2.01, 95% CI 1.13-3.58 p=0.0190) in a Cox regression model accounting for clinical and demographic attributes. Metastatic disease at diagnosis also conferred poorer OS (median 6.9 vs 12.2 months, HR 1.95 95% CI 1.01-3.73, p=0.0463). MGC-positive tumours were enriched for interferon signaling, matrix remodeling/ metastasis and cytotoxicity gene expression pathways in comparison to MGC-negative tumours, as well as a tumour microenvironment containing a higher proportion of leukocytes, macrophages and cytotoxic cells. In both angiosarcoma cell lines, MGCs were identified as a non-senescent subpopulation (<5%), which persist in culture despite treatment with doxorubicin or paclitaxel.

Conclusion: Presence of MGCs in angiosarcoma is independently associated with poorer OS and PFS, and is characterized by a chemoresistant and immune-evasive phenotype.

Poster #255 3253280

MULTIDISCIPLINARY INTERVENTION IN RADIATION-ASSOCIATED ANGIOSARCOMA OF THE BREAST: PATTERNS OF RECURRENCE AND RESPONSE TO TREATMENT

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Objective: Radiation-associated angiosarcoma (RAAS) of the breast is a highly aggressive malignancy whose incidence is rising and is thought to affect ~1:1000 breast cancer (BC) patients treated with radiation therapy (RT). While RAAS has a poor prognosis, it is sensitive to chemotherapy and radiation. There is limited knowledge about sarcoma multidisciplinary team (SMDT) management of this disease and patient outcomes. The objective of our study was to determine differences in treatment and outcome for those who had initial management by SMDT versus other centers (OC).

Methods: Patients with RAAS of the breast diagnosed between 2004 and 2019 were identified from our sarcoma database (Mount Sinai/Princess Margaret) following ethics approval. DSS, RFS, clinicopathologic characteristics, recurrence patterns and factors predictive of survival were assessed. Kaplan Meier survival analysis and log rank test of significance was performed using SPSS. Clinicopathological features were compared using chi-square, Fisher's exact and one-way ANOVA statistical tests. Alpha was set at $p<0.05$ for all analyses.

Results: 51 patients with RAAS were identified. The median latency period for RAAS after radiation therapy was 8 years (range 3-27). The median age at RAAS diagnosis was 74 years (range 41-89). 28 patients had primary management by SMDT, vs 23 by OC. 49 patient had a surgical resection; 2 were not surgical candidates and were excluded from further analysis (Table 1). Paclitaxel-based neoadjuvant chemotherapy (NC) was administered to 10/26 (38%) patients in the SMDT cohort vs 0/23 (0%) in the OC cohort ($p=0.0008$). The number of cycles administered was determined by toxicity and response to therapy (median 3, 1-5 cycles). 25/26 (96%) patients underwent radical mastectomy with immediate reconstruction in the SMDT group vs 4/23 (17%) in the OC group ($p=0.00001$). The remaining 19 patients in the OC group and 1 in SMDT underwent a simple mastectomy or lumpectomy (limited). R1 margins occurred in 4% of the SMDT and 9% in OC cohort. LN were not involved in any cases. No patients received radiotherapy (neoadjuvant or adjuvant) nor adjuvant chemotherapy. At a median follow-up of 26 months, recurrence occurred in 10/26 (38%) patients treated by SMDT and 19/23 (83%) by OC ($p=0.002$). Radical mastectomy was associated with improved 3 year DSS (83% vs. 63%, $p=0.041$), but not 3 year RFS. Of the 29 patients with a first recurrence, 25 (86%) had a local recurrence (LR) alone, 1 (3.4%) patient had distant recurrence (DR) and 3 (10.3%) had both LR and DR. Median time to recurrence was 6 months in the SMDT group (range 1-11 m) and 9 months (2-92 m) in the OC group. Development of first recurrence was statistically different between groups ($p=0.0017$). Treatment and outcomes of first relapse are listed in Table 1. 10 patients experienced a second recurrence and 4 patients experienced a third recurrence (Table 1), of which no survivors were identified. Importantly, 3 patients experienced a recurrence of their initial BC following treatment and complete response of their angiosarcoma. At last follow up, 26/49 (53%) patients were NED from RAAS, 18/26 (69%) were SMDT and 8/26 (35%) were OC ($p=0.016$).

Conclusion: RAAS is a rare and aggressive sarcoma with a high rate of relapse. Radicality of surgery was associated with improved DSS. Neo-adjuvant chemotherapy may have a role to play in preventing recurrence but warrants further investigation. Early referral of patients with RAAS of the breast is recommended as they likely benefit from treatment by a sarcoma multi-disciplinary team.

Treatment and Outcome in RAAS of the Breast

	SMDT n=26	OC n=23	p value
Initial treatment of RAAS			
Surgery			
Radical resection (%) Limited resection (%)	25 (96.2) 1 (3.8)	4 (17.4) 19 (82.6)	0.00001
Neo-adjuvant chemotherapy (%)	10 (38.5)	0 (0)	0.0008
Outcome			
NED AWD DOD DOC	18 5 3 0	8 4 10 1	0.035
First Recurrence of RAAS			
Total (%) Local recurrence (%) Distant recurrence (%) Local +Distant recurrence (%)	10 (38.4) 8 (30.8) 1 (3.8) 1(3.8)	19 (82.6) 17 (73.9) 0 (0) 2 (8.7)	0.0017
Treatment			
Surgery alone Surgery/adjuvant RT Surgery/neo-adjuvant chemo Chemotherapy RT Chemo/RT No treatment	1 1 0 2 2 3 1	6 0 2 8 1 1 1	
Outcome			
NED AWD DOD DOC	2 5 3 0	5 4 10 0	0.27
Second Recurrence of RAAS			
Total Local Recurrence Distant Recurrence Local + Distant Recurrence	2 2 0 0	8 6 1 1	0.019
Treatment			
Surgery alone Chemotherapy/Radiotherapy Chemotherapy alone Radiotherapy alone No treatment	1 1 0 0 0	3 1 1 1 2	
Outcome			
NED AWD DOD DOC	1 1 0 0	0 3 5 0	
Third Recurrence of RAAS			
Total Local Recurrence Distant Recurrence Local + Distant Recurrence	0 - - -	4 2 2 0	
Treatment			
Surgery Surgery/Radiotherapy	- -	3 1	
Outcome			
NED AWD DOD DOC	- - - -	0 2 2 0	
3 year RFS (n=49)	47.8% [95% CI 25.3-70.3]	26.8% [95% CI 0.6-53]	0.114
3 year DSS (n=49)	79.8% [95% CI 55.8 – 103.8]	67.7% [95% 32.2 – 103.2]	0.25

Poster #256 3254044

POST-NEPHRECTOMY OUTCOMES FOLLOWING EN BLOC RESECTION OF PRIMARY RETROPERITONEAL SARCOMA: A MULTICENTER ANALYSIS

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Objective: Resection of the tumor with en bloc resection of involved adjacent structures is the standard of care for patients with primary retroperitoneal sarcomas (RPS). The long-term outcomes of nephrectomy and risk of developing postoperative chronic kidney disease (CKD) in patients with primary RPS remain unclear. We report postoperative renal function data in the largest series of patients with primary RPS undergoing nephrectomy at two high-volume centers.

Methods: We identified all patients with primary RPS who underwent surgery between 2008-2018 at our institutions. Serum creatinine values were used to calculate the estimated glomerular filtration rate (eGFR, mL/min per 1.73m2) in patients undergoing en bloc nephrectomy using the CKD-Epidemiology Collaboration formula. Patients were classified in stages of CKD based on eGFR (stage I: ≥90, II: 60-89, III: 30-59, IV: 15-29, V: <15) and dichotomized based on the accepted definition of CKD (eGFR <60) for analysis. Impact of nephrectomy on cumulative incidence (CI) of postoperative eGFR (post-eGFR) recovery to preoperative eGFR (pre-eGFR; within 5% margin or above) and predictors of eGFR recovery were analyzed. Locally weighted scatterplot smoothing (LOWESS) was used to analyze temporal trends of post-eGFR at multiple timepoints during follow-up.

Results: Nephrectomy was performed in 385 (70%) of 551 patients undergoing resection of primary RPS. Analysis was limited to 315 of the 385 patients with adequately documented pre- and post-eGFR values. The median pre-eGFR was 88 (interquartile range (IQR) 73-100). Stage I, II, and III CKD was presented in 146 (46.3%), 133 (42.2%), and 36 (11.4%) patients, respectively. No patients had preoperative stage IV or V disease. Clinicopathologic details are in Table 1. Preoperatively, 279 (88.6%) patients had a pre-eGFR ≥60 and 36 (11.4%) patients had a pre-eGFR <60. Follow-up pre- and post-eGFR values are presented in Table 2 at defined timepoints. LOWESS plot demonstrates an initial decline in post-eGFR followed by a gradual upward trend over time (Figure 1A) with those patients with pre-eGFR <60 approaching pre-eGFR at earlier timepoints (Figure 1B). At 1-year postoperatively, 58 (20.8%) patients developed new postoperative CKD stage ≥3 disease. With a median follow-up of 35 mos (IQR 18-62 mos), the 1- and 3-year CI of post-eGFR recovery to pre-eGFR was significantly higher for patients with pre-eGFR <60 (18% and 54%) than ≥60 (5% and 9%, P<0.001, Figure 2). The median time to recovery to pre-eGFR was 36 mos for patients with pre-eGFR <60 (pre-eGFR ≥60 median not reached). Renal replacement therapy was initiated in 9 (2.9%) patients postoperatively and death due to renal disease was documented in 4 (1.3%) patients. While an infrequent event, these occurred significantly more often in patients with pre-eGFR <60 (P<0.001). Postoperative renal dysfunction significantly altered the use of adjuvant systemic therapy in 4 (1.3%) patients. On univariate analysis, when including pre-eGFR, age, gender, length of stay, and local and distant recurrence, only pre-eGFR <60 was a significant predictor of pre-eGFR recovery (P=0.002) while age was the only significant predictor of new postoperative CKD stage ≥3 disease (P<0.001). No significant predictors were identified on multivariate analysis for pre-eGFR recovery or new postoperative CKD stage ≥3 disease.

Conclusion: While the majority of patients will not recover to pre-eGFR, rarely do patients develop clinically significant postoperative renal dysfunction; nonetheless, patients should be informed of the risks preoperatively. Pre-eGFR <60 should not be considered a contraindication to nephrectomy or exclusion from clinical trials as these patients demonstrate a significantly higher rate of pre-eGFR recovery. In our series, pre-eGFR was not an independent predictor of pre-eGFR recovery. Future studies are needed to investigate predictive factors further in this complex patient population.

TABLE 1. Clinicopathologic characteristics for patients (n=315) undergoing en bloc nephrectomy for primary retroperitoneal sarcoma according to preoperative estimated glomerular filtration rates (eGFR, mL/min per 1.73m2) ≥60 (n=279) and eGFR

Clinicopathologic characteristics	eGFR ≥60	eGFR <60	*P*-value
	n	n	
Age, median (range)	62 (26-85)	71.5 (52-83)	**<0.001**
Gender Male Female	142 (50.9%) 137 (49.1%)	20 (55.5%) 16 (44.4%)	0.7
Neoadjuvant therapy Radiation Chemotherapy	44 (15.8%) 17 (6.1%)	7 (19.4%) 1 (2.8%)	0.7
Rationale for nephrectomy Encasement/abutment alone Involvement of renal vessels alone Involvement of ureter alone Encasement/abutment and involvement of renal vessels Encasement/abutment and involvement of ureter Involvement of renal vessels and ureter Encasement/abutment and involvement of renal vessels and ureter	208 (74.5%) 17 (6.1%) 2 (0.7%) 12 (4.3%) 4 (1.4%) 4 (1.4%) 32 (11.5%)	25 (69.4%) 2 (5.6%) 1 (2.8%) 4 (11.1%) 0 1 (2.8%) 3 (8.3%)	0.5
Histology Well-differentiated liposarcoma Dedifferentiated liposarcoma Leiomyosarcoma Undifferentiated pleomorphic sarcoma Solitary fibrous tumor Malignant peripheral nerve sheath tumor	78 (28.0%) 132 (47.3%) 39 (14.0%) 3 (1.1%) 3 (1.1%) 4 (1.4%)	7 (19.4%) 16 (44.4%) 10 (27.8%) 0 1 (2.8%) 1 (2.8%)	0.4
Median tumor size, cm (range)	12.8 (3.4-30)	12 (8.1-25)	0.9
Number of organs resected (median)	5	5	0.7
Major postoperative complications (Grade ≥ 3)	84 (30.1%)	13 (36.1%)	0.5
Local recurrence	66 (23.7%)	9 (25%)	1
Distant recurrence	47 (16.8%)	11 (30.6%)	0.8

eGFR, estimated glomerular filtration rate

TABLE 2. Renal outcomes for patients (n=315) undergoing en bloc nephrectomy for primary retroperitoneal sarcoma according to preoperative estimated glomerular filtration rates (eGFR, mL/min per 1.73m2) ≥60 (n=279) and eGFR

Renal-specific outcomes	eGFR ≥60	eGFR <60	*P*-value
	n	n	
Median eGFR (IQR)			
Preoperative (within 30 days)	91 (79.1-101)	47.2 (43.3-56)	<0.001
Post-neoadjuvant therapy/preoperative	89 (83-99)	47 (40-55.5)	0.002
Peak hospital course eGFR	51.5 (41.4-62.8)	32.5 (23.7-41.0)	<0.001
At discharge from initial hospital course	63.4 (53.4-77.7)	35.7 (28.1-51.7)	<0.001
Within 30 days of surgery	65.9 (50.4-78.9)	39.1 (18.7-44.3)	<0.001
31-120 days	58.3 (48.1-71)	44.5 (38.8-57.8)	0.03
121-180 days	59 (49-71.5)	39.2 (29.6-50.9)	<0.001
181-365 days	57 (47-71.4)	34.2 (26.8-49.4)	<0.001
At date of last follow-up	59 (46.4-70.7)	35.2 (28.6-47.3)	<0.001
Initiation of renal replacement therapy postoperatively	4 (1.4%)	5 (13.9%)	<0.001
Death due to renal disease	1 (0.4%)	3 (8.3%)	<0.001
Recovery to preoperative eGFR (within 5% or above)	28 (10%)	8 (22.2%)	0.002

eGFR, estimated glomerular filtration rate; IQR, interquartile range

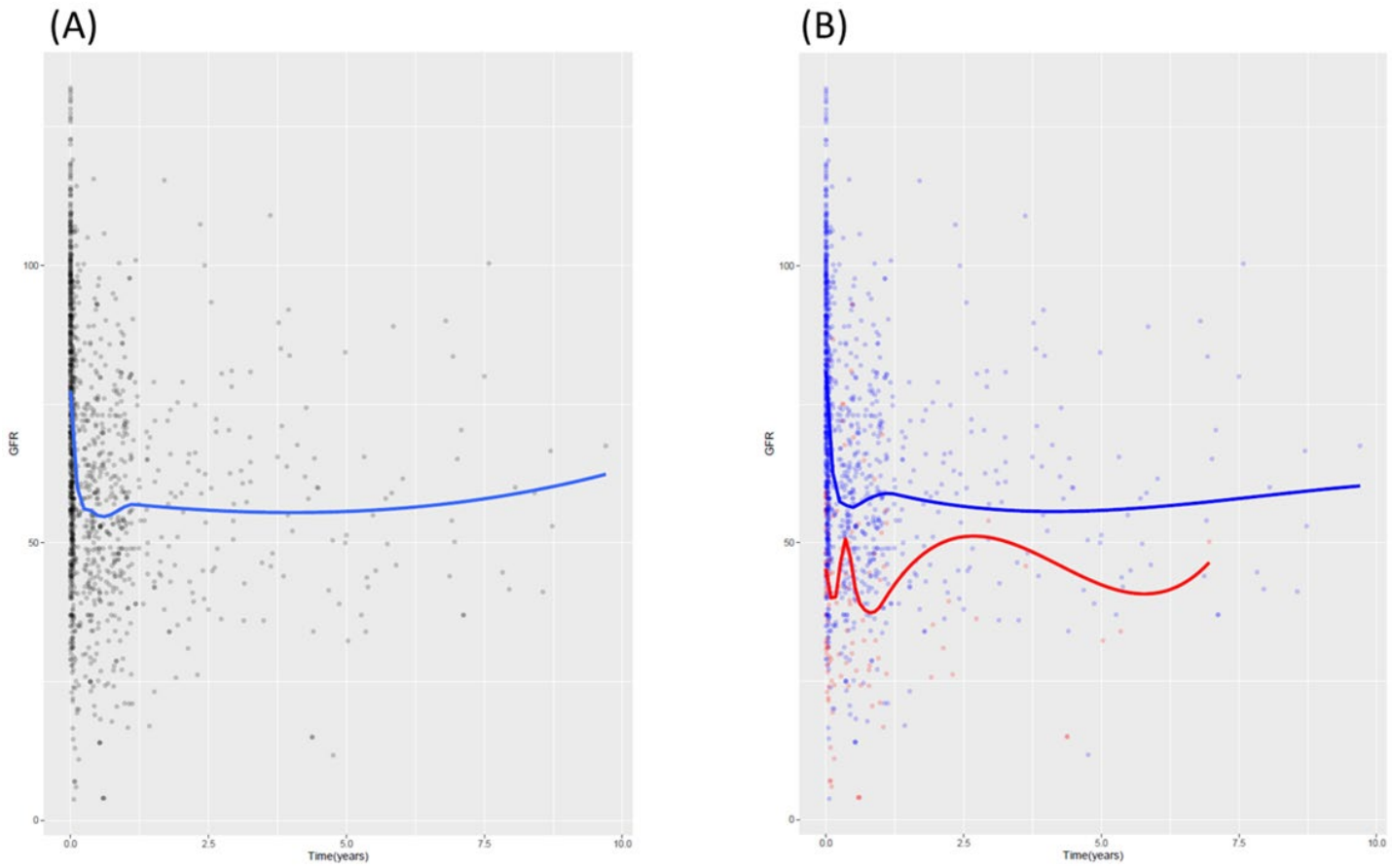

Figure 1. Locally weighted scatterplot smoothing (LOWESS) demonstrating trend of postoperative estimated glomerular filtration rate (eGFR, mL/min per 1.73m2) for (A) entire cohort and (B) patients according to preoperative eGFR (blue line eGFR ≥60, red line eGFR

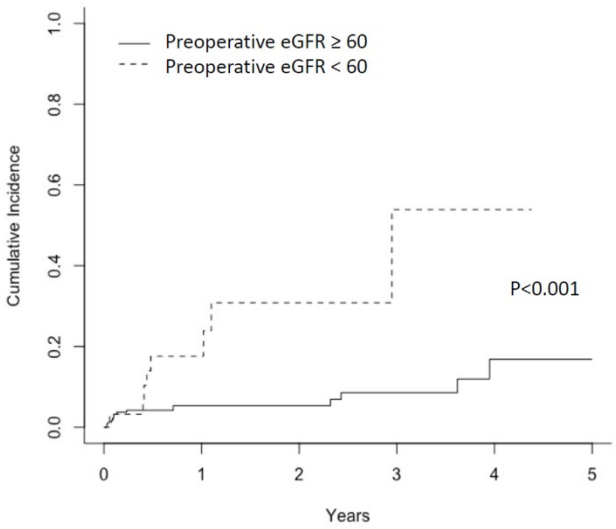

Figure 2. Crude cumulative incidence of postoperative estimated glomerular filtration rate (eGFR, mL/min per 1.73m2) recovery to preoperative eGFR according to preoperative eGFR.

Poster #257 3220630

IMPACT OF SMOKING ON LUNG METASTASIS-FREE SURVIVAL IN SOFT TISSUE SARCOMA PATIENTS

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Objective: Pulmonary metastases are common manifestation of soft tissue sarcoma (STS) that requires special attention. Although smoking history has been known to be predictive of poor lung metastasis-free survival in several epithelial tumors, the impact of smoking on pulmonary metastasis in STS patients has not been revealed yet. The purpose of the current study was to investigate the impact of smoking history on pulmonary metastasis in STS patients.

Methods: Institutional review board approval was obtained prior to initiation of this study. All patients with STS of the extremity and trunk who presented to our institution between 2008 and 2017 were retrospectively reviewed. Exclusion criteria included metastatic lesion on first presentation, age < 20 years old, histopathologic types demonstrating "so-called" small round cell sarcoma such as rhabdomyosarcoma, extraosseous primitive neuroectodermal tumor and Ewing's sarcoma. Patients who did not have complete medical records including treatment information, a pathology report and smoking history were excluded. Information on date of diagnosis, age at diagnosis, tumor size, tumor depth, French Federation Nationale des Centers de Lutte Contre le Cancer (FNCLCC) grading and smoking status were recorded on a standardized data collection instrument. Patients who had at least 5 pack years history of smoking (20 cigarettes/day/year × 5 years) were deemed as smokers. Pulmonary metastasis free survival (PMFS) and overall survival (OS) were estimated using the Kaplan–Meier estimate of the survival function. The impact of smoking history, comorbid conditions (diabetes mellitus, hyperlipidemia, hypertension and cardiovascular disease), histological grade (grade 1: low grade, grade 2 and 3: high grade), tumor depth (deep-seated) and tumor diameter (≥ 10cm) on PMFS, OS and survival rate after pulmonary metastasis was examined by multivariate analysis (MVA) using Cox proportional hazards model. Hazard ratios (HR) and 95% confidence intervals (CIs) were used to estimate the impact on pulmonary metastasis. All statistical tests were two-sided, and statistical significance was set at $P < 0.05$.

Results: Following exclusion criteria, the sample size for this analysis included 250 patients with available smoking history, defined as a binary variable (Fig. 1). Patients with smoking history and high-grade sarcoma had worse PMFS on MVA (smoking; HR = 2.00, 95% CI 1.12 – 3.60, P = 0.019, high grade sarcoma; HR = 6.78, 95% CI 2.88 – 19.88, P < 0.01, tumor size; HR = 1.52, 95% CI 0.83 – 2.81, P = 0.18, tumor depth; HR = 1.61, 95% CI 0.826 – 2.81, P = 0.36, diabetes mellitus; HR = 0.423, 95% CI 0.127 – 1.40, P = 0.12, hyperlipidemia; HR = 1.00, 95% CI 0.390 – 2.57, P = 1.00, hypertension; HR = 1.45, 95% CI 0.786 – 2.66, P = 0.24, cardiovascular disease; HR = 1.49, 95% CI 0.731 – 3.03, P = 0.29, Fig. 2A). On the other hand, smoking history did not have impact on OS (smoking; HR = 1.26, 95% CI 0.611 – 2.58, P = 0.52, high grade sarcoma; HR = 3.76, 95% CI 1.52 – 11.4, P < 0.01, tumor size; HR = 1.34, 95% CI 0.624 – 2.94, P = 0.46, tumor depth; HR = 1.71, 95% CI 0.563 – 7.43, P = 0.37, diabetes mellitus; HR = 0.183, 95% CI 0.0101 – 0.906, P = 0.034, hyperlipidemia; HR = 2.52, 95% CI 0.920 – 5.98, P = 0.071, hypertension; HR = 2.12, 95% CI 1.01 – 4.38, P = 0.047, cardiovascular disease; HR = 3.52, 95% CI 1.58 – 7.46, P < 0.01, Fig. 2B). Two years survival rates after pulmonary metastasis for the smoking and non-smoking groups was 55% and 62% respectively (P = 0.37).

Conclusion: This study clearly demonstrated that smoking history was poor predictive factor for pulmonary metastasis in STS patients. Our data also found that smoking did not appear to influence OS, perhaps a product of our modest cohort size, lessened statistical power, or short follow-up period. Although further investigation, including prospective study, are needed, STS patients should be followed by frequent clinical evaluation if they have a smoking history.

	Smoker	Non-smoker
Number of patients	109	141
Median age	67	68
Follow-up period (month)	36	36
Tumor location		
Head and Neck	3 (3 %)	2 (1 %)
Trunk	28 (26 %)	41 (29 %)
Upper extrimity	14 (13 %)	25 (18 %)
Lower extrimity	64 (59 %)	73 (52 %)
Complications		
Hypertension	36 (33 %)	47 (33 %)
Cardiovasular disease	23 (21 %)	17 (12 %)
Diabetes mellitus	17 (16 %)	12 (9 %)
Hyperlipidemia	13 (12 %)	14 (10 %)
Histological grade		
Low	41 (38 %)	50 (36%)
High	68 (62 %)	91 (65 %)
Size		
< 10cm	53 (49 %)	68 (48 %)
10cm ≧	56 (51 %)	73 (52 %)
Location		
Superficial	9 (8 %)	20 (14 %)
Deep	100 (92 %)	121 (86 %)
Chemotherapy	14 (13 %)	17 (12 %)
Radiation	22 (20 %)	31 (22 %)
Pulmonary metastasis	25 (23 %)	21 (15 %)

Fig. 1 Patient, tumor, and treatment characteristics.

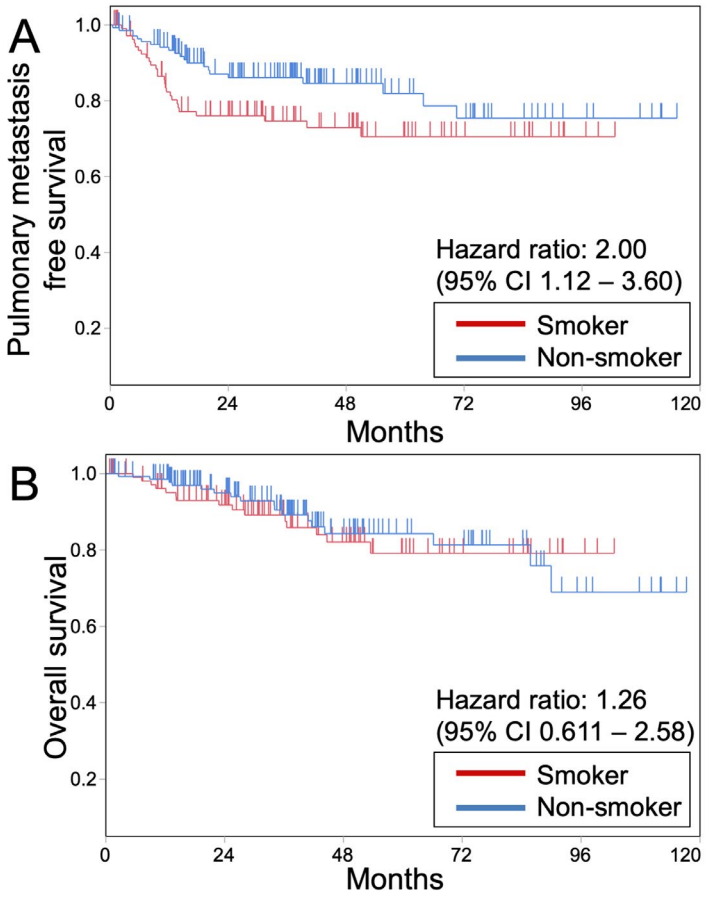

Fig. 2 Smoking and pulmonary metastasis free survival (A) and overall survival (B).

Poster #258 3225003

EFFICACY AND SAFETY OF TRABECTEDIN FOR PATIENTS WITH UNRESECTABLE AND RELAPSED SOFT TISSUE SARCOMA IN JAPAN: A JAPANESE MUSCULOSKELETAL ONCOLOGY GROUP (JMOG) STUDY

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Objective: Although the efficacy and safety of trabectedin were revealed in patients with translocation related sarcoma (TRS) at an initial dose of 1.2mg/m^{2}in Japan, the efficacy of trabectedin in other types of soft tissue sarcoma (STS) had not been evaluated. This retrospective study investigated the efficacy and safety of trabectedin in 140 patients with unresectable and relapsed STS by using the data of real-life clinical practice, postmarketing surveillance data.

Methods: Patients received trabectedin with the objective of treating local recurrence or unresectable local lesion (n =17), metastasis (n=106), and both (n=17). The patient median age was 49 years. The primary endpoint was progression-free survival (PFS). The secondary endpoints included overall survival (OS), the growth modulation index (GMI), overall survival, and an adverse events and risk factors of adverse events.

Results: The median treatment cycle was 3 cycles. All adverse events and Grade ≥3 adverse events occurred in 135 patients (96%) and 100 patients (71%). Grade ≥3 adverse events included liver dysfunction (37.8%), neutropenia (32.8%), febrile neutropenia (3.6%), rhabdomyolysis (3.6%). High risk group of Grade ≥3 rhabdomyolysis (36%) was classified by body height ≥170.2 and age ≤32 by classification and regression trees model (AUC=0.9). Eleven patients (7.9%) require dose reduction at the timing of average 3.2 cycles, mainly because of liver dysfunction. Dosing delay related to toxicities was needed in 49 patients (35%), because of liver dysfunction and neutropenia.

Median PFS was 15.7 weeks, and PFS of each histologic type was as follows; myxoid liposarcoma (MLS) 74.6 weeks, leiomyosarcoma (LMS) 21.1 weeks, synovial sarcoma (SS) 24.1 weeks, dedifferentiated liposarcoma (DDLS) 15.7 weeks, solitary fibrous tumor (SFT) 9.9 weeks, and undifferentiated pleomorphic sarcoma (UPS) 5.7 weeks. Significant better PFS was observed in younger Age (≤65), histologic type (L-sarcoma, TRS) and Grade ≥3 neutropenia after the treatment with trabectedin. Median growth modulation index (GMI) was 0.91, and 37patients (36.7%) experienced a GMI >1.33, and the rates of GMI >1.33 in SS, MLS, DDLS, UPS, LMS, and SFT were including 43.8%, 31.8%, 36.4%, 42.9%, 31.3%, and 60%, respectively.

The median OS was 16.4 months. The median OS depending on their histologic subtypes as follows; MLS 27.6 months, LMS 18.0 months, SS 19.3 months, DDLS 11.8 months, and UPS 8.4 months. Poor prognostic factors in patients received treatment with trabectedin were Alb<4, PS≥2, BMI≤18.Similar to the result of PFS, histologic types (L-sarcoma, TRS) were correlated with better OS. Furthermore, GMI ≥1.33 was associated with a significant improvement of OS.

Conclusion: In the setting of an initial dose of 1.2mg/m^2, trabectedin has clinically meaningful benefits to patients with L-sarcoma and TRS as previous clinical trials. SS, MLS, and SFT out of TRS are relatively responsive to trabectedin. Furthermore, trabectedin is a good option for other histologic types, including DDLS and UPS. Safety profile is comparable and dose reduction was less common compared to previous clinical trials and P4 studies.

Poster #259 3229371

DETECTION OF *CSF1* REARRANGEMENTS DELETING THE 3′ UTR IN TENOSYNOVIAL GIANT CELL TUMOURS

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Objective: Tenosynovial giant cell tumors (TGCT) are a group of benign but sometimes locally-aggressive tumours that affect the synovium, bursae, and tendon sheath. Individuals with TGCT suffer from reduced quality of life due to impaired mobility, swelling, stiffness and pain in their affected joints. In 2006, microarray profiling work identified CSF1 (monocyte/macrophage colony stimulating factor) overexpression, sometimes associated with *COL6A3-CSF1* translocations, as the underlying oncogenic mechanism in TGCT. Specifically, a small minority of tumor cells bearing *CSF1* gene rearrangements drive overexpression of secreted CSF1, promoting recruitment of non-neoplastic mononuclear and multinucleated inflammatory cells and consequent tumor growth. Subsequent work has demonstrated major therapeutic benefits in TGCT from targeted therapies using CSF1/CSF1R inhibitors, a finding selected as an ASCO 2019 Advance of the Year. Nevertheless, the mechanism by which *CSF1* rearrangement leads to overexpression is not clear in many cases, as fusions to collagen promoters are not always detectable.

Methods: We investigated two cohorts, totalling 39 diffuse and localized TGCTs, for *CSF1* rearrangements using massive parallel sequencing technologies. Cohort A included TGCT that had RNA sequencing performed using the TruSight RNA Fusion Panel as part of the diagnostic workup. Cohort B were samples from a Novartis clinical trial where DNA sequencing was performed using a custom Agilent capture panel providing full *CSF1*, *COL6A3*, *NOTCH2*, *PTGFRN* and *S100A10* genomic coverage. Potential DNA breakpoints were confirmed using Sanger sequencing.

Fluorescent in-situ hybridization (FISH) was performed on both cohorts using BAC probes flanking *CSF1*. For each case, at least 100 nuclei were scored for positive *CSF1* translocated cases and 1000 nuclei were scored for negative cases. The percent of nuclei with *CSF1* translocated (i.e. separation of red and green-labeled probes) or 3′ deleted (loss of one green signal) was determined and positive translocation or deletion was defined as ≥2% of cells with *CSF1* split signal or a deleted green signal, respectively.

Results: The study comprised 13 TGCTs of localized type, 21 diffuse and five unspecified. *CSF1* rearrangements were identified by FISH in 30 cases (13 with translocations and 17 with 3′ deletions). The fraction of tumor cells bearing a *CSF1* event ranged from 2-29%. Targeted sequencing identified *CSF1* breakpoints in 28 cases, with ten confirmed by Sanger sequencing. In all 28 cases, the breakpoint was found to be downstream of exon 5, replacing or deleting a long 3′UTR containing known miRNA and AU-rich element negative regulatory sequences. Among cases where both FISH and sequencing were informative, nine of ten cases where FISH showed a *CSF1* split signal had a translocation to a partner gene on a different chromosome, whereas nine of 13 cases where FISH showed a loss of one green signal corresponded to a 7-10Mb deletion of the 3′ end of *CSF1* by sequencing. This latter intrachromosomal event results in *CSF1* fused to a variable partner gene, such as *NOTCH2* or *CD101* on 1p12-13.3. Six of 21 cases showed mutations in the linker/RING domain of *CBL*, including 2 cases where *CSF1* alterations were undetectable.

Conclusion: We present herein the largest tenosynovial giant cell tumor cohort genetic analysis performed so far, confirming and extending a recent report that beyond the *COL6A3-CSF1* fusions previously reported in TGCTs, variable alterations leading to truncation of the 3′ end of *CSF1* are the dominant tumorigenic mechanism, with a subset of cases showing alterations in *CBL*. The diversity of fusion partners but consistent integrity of *CSF1* functional domains encoded by exons 1-5 support a mechanism whereby CSF1 overexpression results from transcription of a truncated form of *CSF1* that lacks 3′ negative regulatory sequences. This mechanism may be relevant in other diseases. CSF1/CSF1R signaling may be further augmented by *CBL* mutations.

Poster #260 3230868

COMPETING RISKS ANALYSIS OF THE INFERIORITY OF PATIENTS AGED 80 YEARS OR OLDER WITH SOFT TISSUE SARCOMAS

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Objective: An increasing number of elderly patients with soft-tissue sarcoma are being seen at cancer centers in many countries in the era of advances in cancer treatment. The unique therapeutic and prognostic implications of treating soft-tissue sarcoma in geriatric patients warrant further consideration in order to optimize outcomes. The aims of this study were to examine differencies in the clinical features and oncological outcomes between elderly patients and a younger population, and to assess possible factors that could account for the differences in outcomes between the age groups.

Methods: This is a single-institution retrospective study of consecutive non-metastatic primary extremity and trunk high-grade sarcomas surgically treated in 1996-2012, with at least 2 years of follow-up for survivors. Patient characteristics and oncological outcomes were compared between age groups, (≥80 vs. <80 years), using Chi-square or Fisher-exact test and Log-Rank or Wilcoxon test, respectively. Deaths from other causes were censored for disease-specific survival estimation. In addition, a competing risks analysis and regression modeling of competing risk, using R, were also conducted to examine the adverse impact of increasing age. A $p < 0.05$ was regarded as statistically significant.

Results: A total of 333 cases were eligible. Thirty-six patients (11%) were aged ≥80 years. Unplanned surgery incidence and surgical margin status were comparable between the age groups (33% (≥80 years) vs. 35% (<80 years), and 11% vs. 6%, respectively). Five-year local-recurrence-free, metastasis-free and disease-specific survivals were 72% (≥80 years) vs. 90% (<80 years) ($p = 0.004$), 59 vs. 70% ($p = 0.07$) and 55 vs. 80% ($p < 0.001$), respectively. A significantly earlier first metastasis after surgery (8.3 months vs. 20.5 months, mean) and poorer survival after first metastasis ($p = 0.03$) were observed. A competing risks analysis also showed that "age ≥80 years" was significantly associated with the disease-specific mortality. Competing risk regression model revealed the age 80 years and the higher AJCC stage as significant factors affecting "died of disease" (DOD), and the sub-distribution hazard ration, considering "died of other disease" (DOOD) as a competing risk factor, was 1.99 (95% CI: 1.09–3.61) for "age ≥80 years" and 2.68 (95% CI: 1.66–4.34) for AJCC stage III.

Conclusion: Oncological outcomes were significantly worse in high-grade sarcoma patients aged ≥80 years. The findings of more frequent local failure regardless of a consistent primary treatment strategy, an earlier time to first metastasis after surgery, and poorer prognosis after first metastasis suggest that more aggressive tumor biology, in addition to multiple co-morbidity, may explain the inferiority.

Poster #261 3232627

ABDOMINAL METASTASES OF SOFT TISSUE SARCOMA. INCIDENCE AND OUTCOME IN 769 PATIENTS

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Objective: About 30% of patients with primary localised soft tissue sarcoma (STS) will develop metastatic disease, most commonly to the lungs, whilst abdominal metastases (AM) are rare.

The aim of the present study was to analyse risk factors for development of AM and compare outcome between patients with AM and those with metastases to other sites.

Methods: In the present multicentre study, 769 patients with primary localised STS were retrospectively included (mean age 55.6 years; 47% female; 4.1 years median follow-up). Descriptive statistics as well as uni- and multivariate Cox-regression models were calculated to discover potential risk factors for AM.

Results: Secondary metastases were detected in 202 patients (26.3%) after a median of 15 months (IQR: 10-29 months). Pulmonary metastases were most common (n=114), followed by metastases to bone (n=32). AM developed in 10 patients as primary lesions and in 14 patients as secondary lesions, after being diagnosed with metastases to other sites (total incidence: 3.1%). Median time to development of primary and secondary AM was 2.4 and 2.0 years, respectively. Irrespective of age or grading, patients with liposarcoma had a higher risk of developing AM (HR: 6.915; 95%CI: 1.727-27.683; p=0.006). There was no difference in post-metastasis-survival (PMS) between patients with AM at any time point and those with metastases to other sites (p=0.585). Neither there was a difference between patients with primary and secondary AM regarding PMS, suggesting that development of AM at any time point has a similar influence on survival (p=0.884).

Conclusion: Irrespective of whether AM develop secondarily to other metastases or not, survival is poor. Regular abdominal surveillance with sonography/CT-scan of the abdomen is recommended in patients with liposarcoma, as risk for AM is significantly increased.

Poster #262 3236442

PRIMARY RETROPERITONEAL ILIOCAVAL LEIOMYOSARCOMAS: OUTCOME FOLLOWING SURGICAL RESECTION AND THE CALL FOR NOVEL THERAPEUTICS

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Objective: Iliocaval leiomyosarcomas (ICLM) present a surgical challenge given their origin from major retroperitoneal veins, and their involvement of surrounding structures and viscera. The propensity for metastatic spread dictates oncological outcome. A recent integrative genomic and transciptomic analysis of leiomyosarcomas identified the presence of the BRCA molecular phenotype in these tumours. We review the results of 32 patients who underwent surgical resection with the aim to identify prognostic factors and propose future therapeutic directions.

Methods: A prospective database was used to identify patient demographics, clinicopathological variables and oncological outcomes in 32 patients who underwent surgical resection for ICLM between 2003 – 2018. Univariate and multivariate cox regression analyses were used to determine clinically relevant prognostic factors. Gene set enrichment analysis was performed on a separate cohort of leiomyosarcomas (The Cancer Genome Atlas (TCGA); LMS, n=107) to assess dysregulation of the BRCA network genes, specifically comparing ICLM to leiomyosarcomas arising from other sites.

Results: In this study, 15 patients (46.9%) were female and 17 patients (53.1%) were male. 13 patients (40.6%) presented with abdominal pain, 10 patients (31.3%) were diagnosed after incidental finding while the rest of the patients had miscellaneous symptoms. Two patients underwent neoadjuvant chemotherapy or radiotherapy. Median duration of surgery was 185 min and median hospital stay was 11 days. Venous reconstruction was performed in 7/32 patients – reconstruction of the IVC in 4 patients and both venous and arterial reconstruction in 3 patients. Arterial reconstruction only was required in 3 patients. Nephrectomy was performed in 18/32 cases (56.3%). 65.6% of the tumours were grade 2 while 21.9% were grade 3. Microscopic clear margins (R0) were obtained in 84.4% of our patients. Five patients developed Clavien-Dindo grade 3 complications and there was no 90-day surgical mortality. With a median follow-up time of 67.0 months (95% CI 49.3–84.7), 3/32 patients (9.4%) recurred locally while 17/32 (53.1%) developed distant metastasis. The median survival of our cohort was 41.0 months (95% CI 17.9 – 64.2) and five-year overall survival rate was 34.1%. Multivariate survival analysis using the Cox proportional hazard model identified clinical presentations, tumour grade and blood loss of more than 2 litres as key prognostic factors in our model. The bioinformatics analysis of the TCGA cohort demonstrated that ICLM had significant lower enrichment scores for the BRCA network genes compared to extremity LMS ($p=0.012$) and uterine LMS ($p<0.01$).

Conclusion: Surgical resection of ICLM can be safely performed with low morbidity and mortality in a specialist sarcoma centre. Reconstruction of the IVC is not routinely required. Overall survival for ICLM is poor and distant metastasis is the significant pattern of failure which dictates oncological outcome. Recent publications focusing on the molecular biology of leiomyosarcomas have identified frequent deletions targeting genes involved in homologous recombination of DNA double-strand breaks including BRCA2. Consistent with this data, our transcriptomic analysis suggests decreased expression of BRCA network genes in ICLM compared to extremity and uterine LMS. This may imply that ICLM harbours genetic differences compared to other leiomyosarcoma subtypes. Further studies into the possible benefit of neoadjuvant treatment and targeted therapies are awaited.

Table 1. Demographic and clinical characteristics of patients with iliocaval leiomyosarcomas (ICLM) (n=32)

Characterisrics	No.	%
Age [mean (s.d.)]	60.3 (11.8)	
Male	17	53.1
Presenting symptoms		
Incidental	10	31.3
Pain	13	40.6
Others	6	18.8
Neoadjuvant therapy	2	6.2
Grade of surgical sample		
Low	4	12.5
Intermediate	21	65.6
High	7	21.9
Blood loss, mL [median (range)]	950 (200 - 7000)	
Duration of surgery, min [median (range)]	185 (35 - 395)	
Resection status		
Iliac vein	3	9.4
IVC	22	68.8
Iliac vein and IVC	7	21.9
Iliac artery	5	15.6
Kidney	18	56.3
Reconstruction		
Venous	4	12.5
Arterial	3	9.4
Both	3	9.4
Margin status		
R0	27	84.4
R1	4	12.5
Length of hospital stay, days [median (range)]	11 (5 - 35)	
Clavien-Dindo grade 3 classification	5	15.6

Note: Sums of numbers may not add up to total number of patients in cohort due to missing data.

Poster #263 3239268

SOFT TISSUE SARCOMAS OF THE TRUNK: CLINICAL OUTCOME AND FACTORS AFFECTING LOCAL RECURRENCE

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Objective: Previous studies of soft tissue sarcoma (STS) of the trunk have identified a number of possible prognostic factors; however, the majority of these studies include retroperitoneal sarcomas, despite the fact that these sarcomas have clearly different clinical outcomes. Therefore, factors affecting local recurrence in STS occurring with the layers of the abdominal or chest wall is still uncertain. In this study, truncal STS was defined as originating from the soft tissue of the region include the entire circumference of the body bordered by the clavicle superiorly and the inguinal crease inferiorly. The main purpose of this study was to evaluate the clinical results of patients with truncal STS.

Methods: Clinicopathological data was collected on 97 patients between 2000 and 2017 presenting with primary or recurred truncal STS treated with surgical resection for curative intent. Patients with synchronous metastatic disease, palliative resections were excluded. Patients with inadequate surgical margins received postoperative radiotherapy. The Kaplan-Meier and log-rank methods were used to draw and identify the prognostic factors affecting local recurrence of the patients. Difference were considered statistically significant when the *p* value was less than 0.05.

Results: There were 66 men and 31 women ranging in age from 0 to 93 years (mean 57.4), and observation period was 1 to 180 months (mean 68). The site of origin was the back in 54 cases (55.7%), chest wall in 30 (30.1%), abdominal wall in 9 (9.3%), and lumbar region in four (4.1%). The maximum tumor diameter measured 2 to 20 cm (mean 7.4). The pathological diagnosis was undifferentiated pleomorphic sarcoma (UPS) in 36 cases, liposarcoma in 20, dermatofibrosarcoma protuberance in 11, malignant peripheral nerve sheath tumor in 6, leiomyosarcoma in 5, rhabdomyosarcoma in 2, synovial sarcoma in 2, and others in fifteen. UICC stage (8th edition) was IA in 7 cases, IB in 19, II in 28, IIIA in 31, and IIIB in twelve. Twenty-five tumors were superficial, and 72 were deep seated. Twenty-seven cases (27.8%) have undergone unplanned surgery before presentation to our institutions. Sixteen cases (16.5%) received adjuvant chemotherapy and 13 (13.4%) postoperative radiotherapy. Flap transfer was required in 22 cases (22.7%). Five-year overall survival rates were 100% in IA, 100% in IB, 100% in II, 78.5% in IIIA and, 72.2% in IIIB. Local recurrence was found in thirteen cases. Of thirteen cases, 8 were UPS cases (61.5%). Five-year and 10-year local recurrence-free survival rates were 84.5% and 82.0%, respectively. Factors significantly affecting local recurrence were age>65 years ($p < 0.05$), depth of tumor ($p < 0.05$) and histological diagnosis of UPS ($p < 0.05$). Other factors, such as gender, UICC stage, tumor location, tumor size, additional wide excision following unplanned excision, surgical margin status, chemotherapy, and radiotherapy were not significant for local recurrence.

Conclusion: Univariate analyses disclosed age>65, depth of tumor and histological diagnosis of USP as independent predictors of local recurrence. Surgical margin status is the most important predictor of local control in STS of the extremity. In our cases of high-grade truncal sarcoma, most of them were underwent surgery with wide margin, and the rest was given postoperative radiotherapy. This is the reason why surgical margin status was not identified as a significant prognostic factor for local recurrence in this study. Truncal STS frequently invades underlying organs, and thus necessitating complex reconstruction with a multidisciplinary approach. To avoid local recurrence after complex reconstruction, surgeons should recognize prognostic factors for local recurrence in detail.

Poster #264 3240025

OUTCOMES OF ELDERLY PATIENTS WITH SOFT TISSUE SARCOMA OF THE EXTREMITIES

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Objective: Current standard of care for management of localized soft tissue sarcoma (STS) of the extremity includes aggressive local therapy, including limb-salvage surgery with radiotherapy and/or chemotherapy. STS has a high incidence rate in the elderly. However, due to comorbidities associated with advanced aged, elderly patients with STS of the extremities may receive de-intensified therapy leading to adverse outcomes. We performed a single tertiary-care institution review of patients age 70 or above treated for STS to identify patient, disease, and treatment factors associated with outcomes, with a focus on the impact of treatment de-intensification in this population.

Methods: Patients age 70 or older at time of biopsy-proven STS were identified from a single institution electronic health record from 1991-2015. Local control was calculated from time of completion of upfront local therapy (surgery and/or radiotherapy) to recurrence or last follow up. Associations between patient, disease, and treatment factors with outcome were interrogated with Fisher exact and log-rank tests.

Results: We identified 126 patients with median age of 79 (Interquartile Range, IQR: 74-85) at diagnosis. The most common histologic subtypes included undifferentiated pleomorphic sarcoma (40%), liposarcoma (16%), and myxofibrosarcoma (14%). Grade distribution was 9%, 17%, and 74% for (Fédération Nationale des Centres de Lutte Contre Le Cancer) grade 1, 2, and 3, respectively. Stage distribution was 14%, 33%, and 52% for (American Joint Committee on Cancer 7th Edition) stage I, II, and III, respectively. Forty-seven percent had a documented significant cardiovascular, pulmonary, or cognitive comorbidity. Among patients with grade 3 STS (n=88), 93% underwent limb preservation (LP) surgery and 7% underwent amputation. In the LP subgroup, 38% had positive margins (< 1 mm). Seventy percent of LP patients received pre- or post-operative adjuvant radiotherapy. Nine percent received chemotherapy. Median follow up was 17.6 months (IQR 4.4-58.2 months). Actuarial local control at one and five years was 91.9% (95% CI 79.7-96.9%) and 66.3% (95% CI 45.8-80.6%), respectively. Thirty-five percent of patients developed distant recurrences. Twenty-six percent of patients had late complications following combined modality therapy, predominantly lymphedema. Median overall survival was 2.8 years. On multivariate analysis, only radiotherapy was associated with local control and chemotherapy with distant control ($p<0.05$).

Conclusion: While almost half of all patients had significant comorbidities, aggressive multimodal therapy, for appropriately selected patients was associated with improved survival outcomes. Our institutional series affirmed the association of radiotherapy with local control in elderly patients with grade 3 STS of the extremities treated with LP surgery. Moreover, a high rate of distant metastases was observed, potentially related to limited use of chemotherapy in patients at-risk for distant recurrences.

Poster #265 3240767

TYPES OF PNEUMOTHORAX DURING TRATMENT WITH PAZOPANIB FOR SOFT-TISSUE TUMOR

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Objective: Pazopanib (PZ) is an inhibitor of multi-channel kinase, including VEGF, PDGF, or c-kit, and has been approved for the treatment of soft-tissue tumor or renal cell carcinoma. According to the phase 3 clinical trial, pneumothorax was not reported as a common adverse event; the rate of incidence was 3.3%. However, according to subsequent studies, the incidence might exceed this and the range was 7-15%. The actual etiology of pneumothorax has not been elucidated but was considered the leak of air from the degenerated tumor by PZ treatment. In this study, we reviewed the experience of pneumothorax during PZ treatment and proposed two types of pneumothorax caused by PZ.

Methods: The pneumothorax patterns were defined as follows: 1. Peripheral type: The metastatic lesion is located around or attached to the visceral pleura. After the cavitation of the metastatic tumor, pneumothorax occurred at the connection to the chest cavity and the ruptured cavity. 2. Central type: The metastatic lesion is located at the central part of the lung. After the cavitation, the check valve or continuous air leakage to the cavity is generated (like a pneumatocele). In the end, the high-pressured thin cavity ruptures and pneumothorax occurs. From 2014 to 2018, patients with metastatic soft-tissue tumors in the lung and treated with PZ were retrospectively analyzed. Then, the pneumothorax patterns were classified.

Results: In this period, a total of 12 patients with advanced soft-tissue tumor were treated with PZ. Most of the histology was undifferentiated pleomorphic sarcoma and the mean age of the patients was 44.6 years. Of these, 13 incidences of pneumothorax (4 patients) occurred as a peripheral pattern and 2 incidences of pneumothorax (2 patients) occurred as a central pattern. Based on the ACCP guideline, the severity of pneumothorax was low in 11 incidences, high in 2 incidences of the peripheral type, and high in 2 incidences of the central type. Time to first pneumothorax was 6.6 months (2 weeks to 20 months). Cavitation of the tumor preceded in all the pneumothorax cases.

Conclusion: As a response to PZ, cavitation of lung lesion occurs. Depending on the patterns of cavitation, 2 types of pneumothorax patterns were observed. The peripheral type was more prevalent and milder than the central type. Once the pneumothorax occurred, it sometimes repeated and was intractable.

Poster #266 3241937

SOFT TISSUE LEIOMYOSARCOMA: RECURRENCE RATE BASED ON TUMOR DEPTH

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Objective: Non-uterine leiomyosarcomas (LMS) are a rare type of soft-tissue sarcoma. Several studies have looked at treatment strategies and outcomes for deep LMS, but few have evaluated the outcomes of superficial LMS. It is known that deep LMS has a higher recurrence rate than superficial LMS, but few have compared recurrence rates stratified by tumor depth (dermal, subcutaneous, deep). The purpose of the study is to characterize treatment outcomes based on depth of LMS with regards to (1) disease specific survival and (2) tumor recurrence.

Methods: 102 (51 males, 51 females) patients, mean age 58±17 years, with LMS of the trunk and extremities were identified between 1990 and 2016. 10 cases were classified as dermal (10%), 51 as subcutaneous (50%), and 41 as deep (40%). The tumors were located in the upper extremity (n=68, 67%), lower extremity (n= 23, 23%) and trunk (n=11, 10%). Mean tumor size was 4.6±4.5 cm. All patients were treated surgical with the goal of achieving a negative margin. Margins were reported as negative in 98 (96%), in 4 patients they were microscopically positive (R1). Mean follow up was 7±5 years. Depth was classified as dermal (confined to the skin not extending into subcutaneous tissue), subcutaneous (below the dermis, above the fascia), and deep (below fascia).

Results: Over the course of the study 20 patients died of disease. The 10-year disease specific survival was 71%. When comparing the disease specific survival based on depth, the 10-year survivals (P<0.001) were: dermal 100%; subcutaneous 84%, and deep 46%. Tumor recurrence occurred in 23 patients; classified as metastatic (n=22) and local (n=1). The 10-year metastatic disease free survival was 74%. When comparing the metastatic free survival based on depth, the 10-year survivals (P<0.001) were: dermal 100%; subcutaneous 84%, and deep 56%. In addition there was no difference in survival (P=0.12) or metastatic disease (P=0.23) based on tumor location. Tumor size ≥5 cm was also associated with disease specific mortality (HR 6.49, P<0.001) and metastatic disease (HR 3.85, P<0.001).

Conclusion: The results of this study indicate that patient survival is related to the depth of the tumor. Patients with dermal LMS can routinely be cured with appropriate surgical treatment; although considered a superficial sarcoma, patients with a subcutaneous LMS should be evaluated and treated by a multidisciplinary sarcoma team due to the risk of metastatic disease.

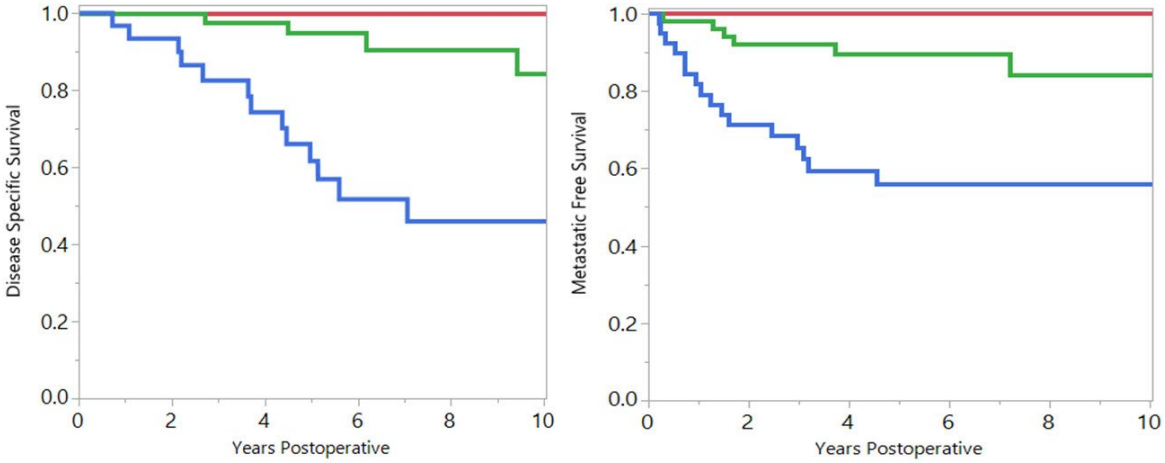

Figure 1: Following surgical resection, patients with dermal (red) leiomyosarcoma had a 100% disease specific and metastatic free survival. The 10- year disease specific and metastatic free survival for subcutaneous (green) and deep (blue) leiomyosarcoma were 84% and 84%, and 46% and 56%, respectively.

Table 1: Risk Factors for Disease Specific Survival and Metastatic Disease

Risk Factor	Hazard Ratio Disease Specific Survival (95% CI)	P Value	Hazard Ratio Metastatic Free Survival (95% CI)	P Value
Male Gender	0.69 (0.28-1.71)	0.43	0.70 (0.30-1.65)	0.42
Tumor Size ≥5cm	6.49 (2.24-18.78)	<0.001	3.85 (1.49-9.95)	<0.001
High Grade Tumor	1.55 (0.45-5.33)	0.47	2.13 (0.63-7.22)	0.22

Poster #267 3245414

ERIBULIN SUPPRESSES CLEAR CELL SARCOMA GROWTH BY INHIBITING CELL PROLIFERATION AND INDUCING MELANOCYTIC DIFFERENTIATION BOTH DIRECTLY AND VIA TUMOR VASCULAR REMODELING

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Objective: Clear cell sarcoma (CCS) is a rare but chemotherapy-resistant and often fatal high-grade soft-tissue sarcoma (STS) characterized by melanocytic differentiation under control of microphthalmia-associated transcription factor (MITF). Chemotherapy was reported to be largely ineffective in patients at advanced stages, resulting in poor prognosis. Therefore, novel therapeutic strategies including effective chemotherapy regimens are needed to improve patient prognosis. Eribulin mesilate (eribulin) is a mechanistically unique microtubule inhibitor commonly used for STS treatment, particularly liposarcoma and leiomyosarcoma. A Phase 3 clinical trials of liposarcoma and leiomyosarcoma patients reported that eribulin improved OS without corresponding effects on progression-free survival (PFS) compared to treatment of dacarbazine. In this study, we first report potent antitumor activity of eribulin against four CCS cell lines and a mouse xenograft model.

Methods: We first evaluated the potential antitumor effects of eribulin *in vitro* and *in vivo* by using cell proliferation assays, flow cytometric analysis, immunoblot analysis and a mouse xenograft model. Next, we explored the underlying molecular mechanisms of eribulin-induced melanocytic differentiation. Finally, we investigated the impact of eribulin-induced vascular remodeling on tumor differentiation and CCS cell growth.

Results: Eribulin dose-dependently reduced viable cell numbers of all four lines, with the highest potency against the Hewga-CCS line (IC_{50} = 1.29 nmol/L), followed by SU-CCS1 (2.12 nmol/L), MP-CCS-SY (3.37 nmol/L), and KAS (4.9 nmol/L). Flow cytometric analyses revealed that 100 nmol/L eribulin treatment induced G_2-M block in all four CCS lines beginning as early as 3 h after exposure and increasing with time thereafter. The cellular level of cleaved caspase-3, the major effector of apoptosis, was enhanced after 72 h exposure to 10 nmol/L eribulin by western blotting. In *in vivo* experiments, treatment with both 1 and 3 mg/kg eribulin shrunk Hewga-CCS xenograft tumors, increased tumor vessel density and mitigated intratumoral hypoxia.

Intriguingly, Eribulin upregulated melanin synthesis and tyrosinase activity in CCS cells. Additionally, eribulin enhanced the expression levels of melanocytic differentiation markers such as MITF, TYR, TRP1, and TRP2, but not of EWSR1–ATF1, in CCS cells. In cycloheximide chase assay performed to reveal the mechanisms underlying the augmentation of MITF protein levels, we found that eribulin stabilized MITF protein by prolonging its half-life. Furthermore, Phosphorylation of ERK1/2, which promotes degradation of MITF, was inhibited by eribulin treatment. Consistent with eribulin-induced melanocytic differentiation, the ERK1/2 selective inhibitor, SCH772984, blocked ERK1/2 phosphorylation and upregulated the melanocytic differentiation markers, MITF, TYR, TRP1, and TRP2, without any effect on EWSR1–ATF1 expression, in CCS cells. These findings suggest inhibition of ERK1/2 phosphorylation causes increased MITF expression, at least in part, by direct effect of eribulin on CCS cells, which evokes melanocytic differentiation.

Furthermore, we found that cell growth was increased and ERK1/2 signaling was activated in CCS cells under hypoxic conditions. Thus, our data suggest that tumor reoxygenation, possibly caused by eribulin-induced vascular remodeling, attenuated cell growth and inhibited ERK1/2 activity, leading to MITF upregulation and further melanocytic differentiation of CCS cells.

Conclusion: Taken together, eribulin suppresses CCS through inhibition of cell proliferation and promotion of tumor differentiation by acting both directly on tumor cells and indirectly through tumor reoxygenation.

Poster #268 3250619

RADIOGUIDED CORE NEEDLE BIOPSIES ARE ACCURATE FOR THE DIAGNOSIS OF DEEP ATYPICAL LIPOMATOUS TUMORS OF THE LIMBS: A RETROSPECTIVE STUDY OF 110 CASES FROM A CENTER OF THE FRENCH SARCOMA NETWORK NETSARC

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Objective: Percutaneous core needle biopsies performed by an expert radiologist is now considered to be the standard diagnostic biopsy for soft tissue tumors. Adipocytic tumors are the most frequent soft tissue tumors with Atypical Lipomatous Tumors (ALT) being the most frequent subtype of liposarcomas. We did a retrospective study to evaluate the accuracy of core needle biopsies for the diagnostic of deep ALT of the limbs in adults.

Methods: 110 patients with an adipocytic deep tumor of the limb were referred to our center from 2010 to 2018. For each patient at least 3 biopsies were done with 16 G core needle. MDM2 gene amplification was searched by FISH. Final diagnosis was done on surgically removed specimens.

Results: Median age was 61 years. The size of the tumors varied from 3 to 36 cm (median= 12.5). FISH was interpretable except in one case and showed MDM2 amplification for 24 cases. Additional diagnoses of liposarcomas were done on surgical specimens based on microscopic features and molecular data: 4 ALT/well differentiated liposarcomas and 1 myxoid liposarcoma with extensive "lipoma-like" component. Sensitivity and specificity of core needle biopsy including FISH analysis were respectively 86 and 100% with positive predictive value of 100 % and negative predictive value of 95%.

Conclusion: Core needle biopsies are accurate for the diagnosis of ALT of the limbs when done by an expert radiologist and combined with the search of MDM2 gene amplification by FISH. However if atypical microscopic features are observed on surgically removed specimens molecular study should be repeated.

Poster #269 3252202

SAFETY AND EFFICACY OF IMMUNE CHECKPOINT INHIBITORS IN PATIENTS WITH ANGIOSARCOMA

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Objective: Angiosarcoma (AS) is rare but one of the most aggressive soft-tissue sarcomas. After standard therapy with doxorubicin, taxane, and pazopanib based regimens there are no active therapeutic options. Recent evidence suggests that the genomic background of cutaneous angiosarcomas shares similarities with cutaneous melanoma. This has prompted the anecdotal use of immune checkpoint inhibitors (ICIs) in patients with angiosarcoma. We sought to determine the activity and safety in a series of patients treated with ICIs.

Methods: In order to better define the safety and activity of ICIs in patients with AS, we retrospectively reviewed all patients treated with these agents at our institution under an IRB-approved protocol. Descriptive statistics and Kaplan-Meier survival estimate were used for data analysis.

Results: We identified ten advanced, AS patients treated with ICIs on clinical trials or off label [Pembrolizumab + Axitinib (NCT02636725; n=1), a CTLA-4 inhibitor (NCT02694822; n=2), Pembrolizumab (n=6), Ipilimumab/Nivolumab (n=1)]. Seven (70%) patients had cutaneous AS, one primary breast AS, one radiation associated breast AS and one splenic AS. The average age was 67.4 years and 5 (50%) patients were female. All patients had received prior systemic therapy (range 1-7, median 3) and 6 (60%) patients had metastatic disease at the time of treatment. The median number of checkpoint inhibitor doses was 7 (Range, 2-14). At twelve weeks, partial response (PR) rate (by imaging and/or clinical exam) was 50% (n=5), stable disease (SD) rate was 10% (n=1) while 40% (n=4) had progressive disease (PD). Disease control rate (PR + SD) at 3 months was 60% (n=6). The progression-free survival (PFS) rate at 2-, 4- and 6- months was 90%, 70% and 60% respectively (Fig 1). The median overall survival (OS) was 7.3 months and 70% (n=7) of all patients are alive at a median follow-up of 8.5 months. Progressive patients had primary breast AS [n=1], cutaneous AS [n=2], or splenic AS [n=1]). One patient initially had PR on Pembrolizumab but later progressed and achieved PR again with Nivolumab/Ipilimumab. Two patients died of progressive AS, while 1 died of unrelated causes. The median duration of ICI therapy was 4.1 months and 30% (n=3) of patients remain on immunotherapy. One patient (10%) discontinued the treatment after 14 cycles (12 months) and continues to have no evidence of disease 24 months later, one (10%) patient discontinued ICI due to toxicity (grade 3 polyarthritis) and one (10%) due to personal preference. No other patient experienced any toxicity higher than grade 2. Grade 1 toxicities included hypothyroidism and fatigue.

Conclusion: ICIs show promising activity and acceptable safety in patients with AS. Robust, durable, responses were observed. Prospective clinical trials are warranted to systematically study this effect.

Table 1. Patient characteristics

Patient	Age, Gender	Pathology	Disease state	Line of therapy	ICI	Number of ICI doses	12th week response	Duration of response (months)	Status
1	62, female	Cutaneous AS	Multifocal	7th	Anti-CTLA-4 (NCT02694822)	14	PR	Ongoing	Off ICI
2	68, female	Cutaneous AS	Metastatic	4th ----- 5th	Pembrolizumab ---------- Ipilimumab/ Nivolumab	6 --- 8	PR ----- PR	3.4 ------ Ongoing	Off ICI -------- Off ICI
3	89, female	Cutaneous AS	Multifocal	4th	Pembrolizumab	5	PR	Ongoing	Off ICI
4	76, male	Cutaneous AS	Multifocal	4th	Pembrolizumab	12	PR	Ongoing	On ICI
5	65, male	Cutaneous AS	Locally Advanced	5th	Anti-CTLA-4 (NCT02694822)	7	PD	5.1	Off ICI
6	63, male	Cutaneous AS	Metastatic	2nd	Pembrolizumab	6	SD	Ongoing	On ICI
7	83, male	Cutaneous AS	Metastatic	2nd	Pembrolizumab	2	PR	2.1	Died of unrelated causes- OS 2.1 months
8	32, female	Breast AS	Metastatic	2nd	Axitinib + Pembrolizumab (NCT02636725)	4	PD	2.6	Died of progressive disease- OS 7.6 months
9	71, female	Breast Radiation Associated AS	Metastatic	4th	Pembrolizumab	11	PR	Ongoing	On ICI
10	65, male	Splenic AS	Metastatic	7th	Ipilimumab/ Nivolumab	2	PD	1.4	Died of progressive disease- OS 2.07 months

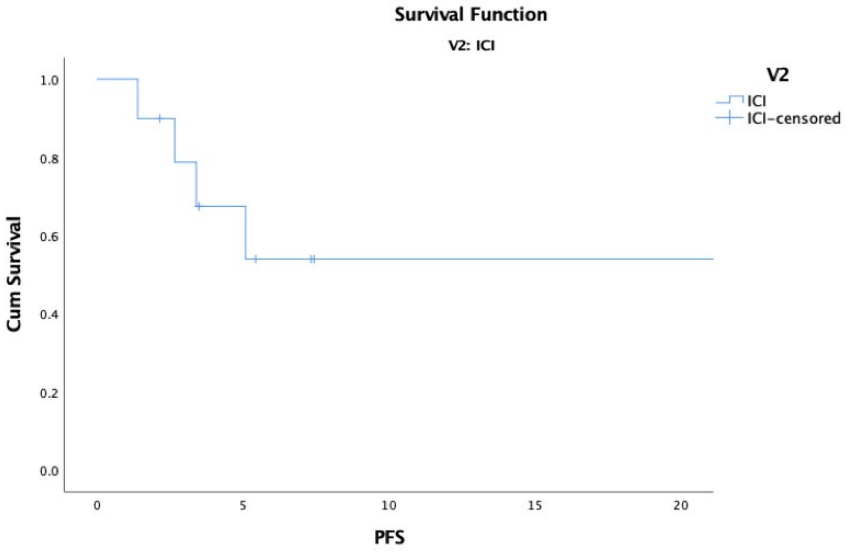

Fig 1. Progression Free Survival of all AS patients treated with ICI

Poster #270 3252942

OUTCOMES OF ELDERLY PATIENTS WITH SOFT TISSUE SARCOMA IN AN ASIAN TERTIARY CANCER CENTRE

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Objective: The optimal management and outcomes of elderly patients with soft tissue sarcomas (STS) remain poorly described, particularly in Asian populations. In this study, we aim to review the patterns of care and survival outcomes of this unique group of patients diagnosed at an Asian tertiary cancer centre.

Methods: A retrospective review of elderly patients (≥ 65 years old) diagnosed with STS from 2008 to 2018 at the National Cancer Centre Singapore was conducted. Clinicopathological characteristics, treatment data, and survival outcomes were examined.

Results: We identified 285 patients (132 females) with a median age of 73 years (range 65-104). The most common histological subtypes include liposarcoma (22.1%), angiosarcoma (20.0%) and undifferentiated pleomorphic sarcoma (15.8%). Most angiosarcomas were of scalp or facial origin (73.7%). A total of 165 patients had advanced disease either at presentation (n=97) or at relapse (n=68), out of which 81 (49.1%) received chemotherapy. 79.0% received single-agent chemotherapy, the most common being paclitaxel (42.2%) or doxorubicin (42.2%). Out of 58 cases with available treatment response data, 24 achieved objective responses, including 1 case of complete response. The median overall survival was 16.4 months, and was particularly dismal in patients with metastasis at diagnosis (3.7 vs 41.0 months, HR 7.45, 95%CI 5.2-10.5, $p < 0.001$). On multivariate analysis, metastasis at diagnosis, age > 80 years, and non-liposarcoma histology were independent predictors of overall survival.

Conclusion: Asian elderly patients with STS present with histological subtypes distinct from Western populations. Outcomes are dismal and more effort is required to improve the level of care in this group of patients.

Poster #271 3253088

OVERALL SURVIVAL OF PATIENTS WITH SOFT TISSUE SARCOMAS NOT INFLUENCED BY SOCIO-ECONOMIC FACTORS WHEN PATIENTS TREATED AT A LARGE RESEARCH INSTITUTION

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Objective: Treatments for soft tissue sarcoma (STS) can include extensive surgical resection, intensive radiation, and chemotherapy, and can necessitate specialized care and excellent social support. Previous studies have demonstrated that socioeconomic factors, such as income, marital status, urban/rural residence, and educational attainment may be associated with overall survival in STS and other cancers. We hypothesized that the impact of socioeconomic factors on patient outcomes may be diminished when patients are treated at a large tertiary referral center.

Methods: We performed a retrospective chart review of patients with new biopsy-confirmed STS treated at our institution. Patients younger than 18 years, with metastatic disease, who lived out-of-state, or received primary treatment at another institution were excluded. Clinical stage, pathological grade, treatment modality, permanent residence zip code, marital, employment, and insurance status were obtained from the electronic medical record. Average income and average educational attainment were obtained from the US Census bureau based on the patient's permanent residence ZIP code. Rural-Urban Code (RUC) classifications were obtained from the United States Department of Agriculture Electronic Research Service. State-specific Area Deprivation Index (ADI) deciles were obtained from the University of Wisconsin School of Medicine and Public Health and linked using ZIP code. Overall survival (OS) was defined as the time from pathologic diagnosis to death from any cause. OS was summarized using Kaplan-Meier curves. Relationships between clinical and socioeconomic variables and OS were evaluated using multivariate Cox regression models.

Results: 435 patients met the inclusion/exclusion criteria. The median follow-up was 3 years. 120 deaths (28%) were observed with median survival of 11 years after diagnosis. Average age of the population at diagnosis was 52 years with slightly higher male predominance (54%). 37% of the population had high grade tumors and 44% had disease larger that 5cm. Most patients were privately insured (38%), married (67%) and retired or unemployed (43%). Median distance from the treatment center was 42 miles and median ADI was 5 (10 represents most deprived communities). Overall 19% underwent resection only while 52% received neoadjuvant radiation therapy (RT) or chemotherapy, 24% adjuvant RT or chemotherapy, and 5% RT or chemotherapy without resection. Median time from pathologic diagnosis to first treatment was 34 days. From multivariate analysis, higher grade (hazard ratio [HR] of grade 3 vs. grade 1: 3.1, $p<0.001$), tumors >5cm (HR: 1.3, $p<0.001$), and involved nodes (HR: 3.2, $p<0.05$) were negatively associated with OS. Time to first treatment was not significantly associated with OS ($p=0.6$), nor were any demographic or socioeconomic factors, including sex ($p=0.12$), age at diagnosis ($p=0.3$), marital status ($p=0.8$), employment status ($p=0.7$), urban vs. rural location ($p=0.13$), income ($p=0.6$), education ($p=0.9$), distance to the treatment center ($p=0.2$) and ADI ($p=0.4$). The relative proportion of each treatment approach changed significantly over the study period. From prior to 2005 to 2011-2015, the use of neoadjuvant RT/chemotherapy increased from 41% to 68% of patients ($p<0.001$) and use of RT/chemotherapy without surgery increased from 1% to 8%. Use of resection only (31% to 14%, $p<0.001$) and adjuvant RT/chemotherapy (26% to 10%, $p=0.004$) significantly decreased over the same period.

Conclusion: Contrary to prior studies of STS, this study did not find any statistically significant associations between socioeconomic factors and OS of patients with STS treated in a multidisciplinary fashion at a large research institution. This suggests that access to specialty care may improve outcomes for patients with socioeconomic risk factors. These factors remain difficult to address, so improving access to specialized multidisciplinary STS care may negate some of their detrimental effects.

Poster #272 3253172

IMMUNOTHERAPY AND HYPERPROGRESSION IN SOFT TISSUE SARCOMA: A TWO INSTITUTION EXPERIENCE

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Objective: Immunotherapy induced hyperprogression (HP) is described as a surge in tumor growth, often coupled with clinical decline, at the initiation of treatment. The question remains whether this is natural history of tumor growth kinetics or induced by immunotherapy. Recent clinical trials with in soft tissue sarcoma (STS) have raised the concern of HP, with a subset of patients having an increase in target lesions of >50%. Potential risk factors identified include older age and MDM2 status. We investigated patients with STS who had received immune checkpoint inhibitors.

Methods: We retrospectively reviewed all patients with advanced STS who had received anti-PD-1 treatment at two institutions. HP was defined as time-to-treatment failure (TTF) of < 3 months, >50% increase in tumor burden in two diameters compared to pre-treatment imaging (obtained within 2 months prior to start of IO) and ≥2-fold increase in progression pace in one diameter. Survival was calculated using Kaplan-Meier. The remaining statistics were descriptive.

Results: A total of 81 patients had received immunotherapy, with or without a concurrent targeted or chemotherapy agent. Ten (12%) patients were identified with HP. Multiple histopathologic types were represented (Table 1). With the exception of one patient, who received immunotherapy plus axitinib on clinical trial, the remainder of patients received immunotherapy alone. This was either nivolumab or pembrolizumab. Mean age was 56. Mean line of treatment was four (range 2-6). Seven patients had next generation sequencing (NGS) available; one patient had in-house testing, while the remainder of testing was done with Foundation One (Table 2). Mean TTF was 1.7 mo (range 1-2.3 mo). Median number of doses received was 2.9 (range 2-4). Overall survival from first treatment was 3.5 mo (1.7-20.7 mo).

Conclusion: Hyperprogression remains a controversial topic in STS. In our group, RB1 and TP53 were the most common alterations in NGS. However, similar to MDM2 amplification identified in other literature, these are among the most common alterations in STS. Larger, multi-institution collaboration analysis and predictive biomarkers are needed.

Histopathologic type (table 1)

Leiomyosarcoma	4
Undifferentiated pleomorphic sarcoma	3
Dedifferentiated liposarcoma	1
Myxoid round cell liposarcoma	1
Fibrosarcoma	1

Next Generation Sequencing

Pt # (subtype)	
1 (UPS)	RB1 loss exons 18-25
2 (UPS)	KRAS G12R
3 (LPS)	FGFR3 A257V, NOTCH1 E1583K, RB1 R661W, TP53 I232Mfs*24 NM, TP53 W91*
4 (FS)	RB1 R787*, TP53 loss exons 2-9
5 (LMS)	EGFR amplification, CKDN2A/B loss, NOTCH2 loss exons 26-32, TP53 R156C , R273H
6 (UPS)	RB1 R251fs*17, TP53 R175H
7 (LMS)	PTEN loss exon 1, CKDN2A/B loss, TP53 E287D

Poster #273 3253322

DEMOGRAPHICS, DISEASE CHARACTERISTICS, TREATMENT PATTERNS, RESOURCE UTILIZATION, AND SURVIVAL OF PATIENTS WITH ADVANCED SOFT-TISSUE SARCOMA IN TAIWAN USING THE NATIONAL HEALTH INSURANCE DATABASE

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Objective: Soft tissue sarcoma (STS) is a type of cancer primarily found in the connective tissue with many subtypes. This study utilizes a claims-based database and cancer registry in Taiwan to understand the demographics, disease characteristics, treatment patterns, and survival of patients with STS in Taiwan.

Methods: Taiwan's National Health Insurance Research Database (NHIRD) and Taiwan's Cancer Registry (TCR) were utilized to identify patients with STS from 2007 through 2014. Patients with STS were indexed into the study if they had a primary site of soft tissues (ICD-O-3 C47 or C49) or other primary sites (ICD-O-3 C00-C80; excluding C40, and C41) during the index period. Patients must have fitted one of the following criteria to be classified as advanced: treatment or diagnostic codes indicating additional treatment associated with disease progression one year after surgery +/- adjuvant therapy, or one year after neoadjuvant therapy and surgery; no surgery but other treatments associated with disease progression for STS; a death within one year of STS diagnosis; or a classification of metastatic disease in the TCR at STS diagnosis. Patients with other cancers prior to STS diagnosis, less than 18 years of age at index, and insufficient pre-index or follow-up length were excluded. STS patients with a primary site in the soft tissue were excluded if they had a gastrointestinal stomal tumor (GIST) or utilized imatinib.

Results: A total of 3,529 patients with STS were included in the analysis. Of the patients with STS, 38.7% (n=1,366) had a primary site in the soft tissue, and 61.3% (n=2,163) had primary disease in another site. Patients had a mean (SD) age of 59.8 (17.3) years, and 56.8% (n=2,003) of patients were male. For patients with a primary site in the soft tissue, the most common subtype was liposarcoma (19.8%; n=271) or fibrosarcoma (12.1%; n=165). Patients with a primary site outside the soft tissue most commonly had subtypes of GIST (23.2%; n=502) or leiomyosarcoma (13.4%; n=290).

A total of 270 (7.7%) patients with STS received a first-line chemotherapy during the study period. STS patients with a primary site in the soft tissue receiving first-line chemotherapy (5.7%; n=78) were most commonly treated with ifosfamide (56.4%; n=44) followed by doxorubicin (43.6%; n=34), and epirubicin (23.1%; n=18) in the first-line. Patients with STS and a primary site outside the soft tissue treated with chemotherapy (8.9%; n=192) most frequently received first-line treatment with imatinib (86.5%; n=166). Regardless of primary site, patients receiving first-line chemotherapy went on to receive second- and third-line therapy 41.5% (n=112) and 20.0% (n=54) of the time during the follow-up period, respectively.

During the one-year follow-up period patients with STS were admitted to the hospital an average of 2.7 times with 30.8 mean total hospitalization days per patient. Patients also had an average of 1.28 and 28.12 emergency room (ER) and outpatient visits per year, respectively. Patients with a primary site in the soft tissue had an average of 2.66 hospital admissions, 24.93 hospital days, 0.89 ER visits, and 32.38 outpatient visits in the one-year follow-up.

Four-year survival for patients remaining in the database was 30.3% (881/2,911), 41.8% (443/1,059), and 23.7% (438/1,852) of all STS patients, soft tissue, and other site patients, respectively.

Conclusion: There are significant unmet needs for patients being treated for advanced STS in Taiwan. Patients initiating a first-line chemotherapy regimen only received a second-line regimen 41.5% of the time. Additionally, overall survival at four years was only 30.3% for advanced STS patients. As the NHRID is a claims-based database, this study relies on a claims-based algorithm to identify patients with advanced disease and may not have captured all advanced STS patients in the dataset.

Most Common First-Line Treatment Patterns of Advanced STS Patients

THERAPY	SOFT TISSUE PATIENTS (n = 78)			OTHER SITE PATIENTS (n = 192)	
	N	%		N	%
Imatinib	0	0.0		166	86.5
Ifosfamide	44	56.4		5	2.6
Doxorubicin	34	43.6		11	5.7
Vincristine	17	21.8		7	3.6
Epirubicin	18	23.1		1	0.5
Cisplatin	16	20.5		5	2.6
Dacarbazine	15	19.2		2	1.0
Cyclophosphamide	13	16.7		3	1.6
Etoposide	9	11.5		1	0.5
Methotrexate	2	2.6		1	0.5
Fluorouracil	2	2.6		1	0.5

Poster #274 3253673

THE OUTCOMES OF INTENSIVE COMBINED THERAPY OF ADULT PATIENTS WITH HIGH RISK STAGE III PRIMARY LOCALIZED SYNOVIAL SARCOMA

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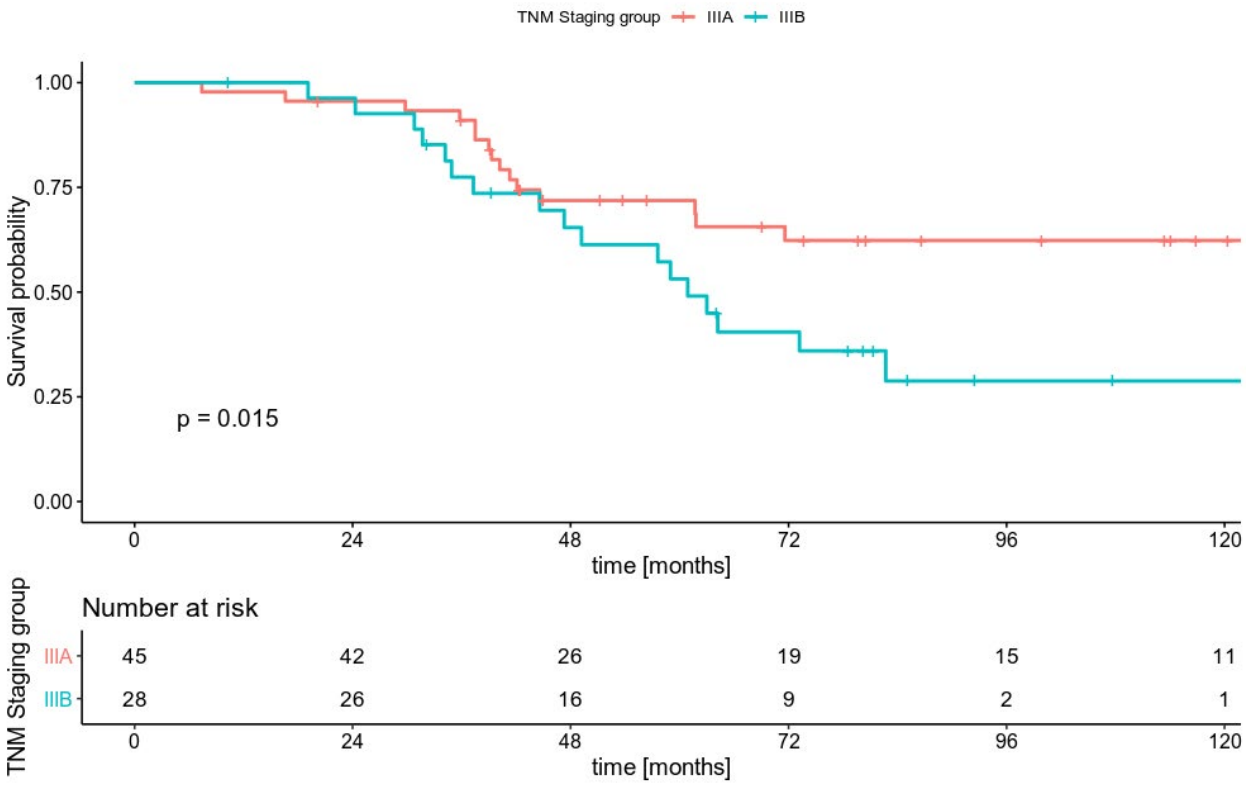
Objective: Synovial sarcoma is a high-grade, malignant soft tissue sarcoma (STS) accounting for 5%–10% of STS. This aggressive tumor is considered as relatively chemosensitive sarcoma subtype. The aim of the study was to analyze outcomes of patients (pts) with primary high risk stage III (according to AJCC version 8) synovial sarcoma treated in a single institution with uniform neo- and adjuvant combined therapy protocol.

Methods: Seventy three pts (47 women and 26 men) with localized stage III primary synovial sarcoma were treated at our institution between 1997 and 2016. Chemotherapy consisted of 4 cycles of ifosfamide 12 g/m^2 (2 cycles given preoperatively) and two cycles of doxorubicin-based regimen 75 mg/m^2. Most pts received neoadjuvant hypofractionated radiation therapy followed by immediate primary tumor resection. Thirty-five (48%) pts died at the time of analysis.

Results: Median age at diagnosis was 36 years (range 17-69). Extremity location (n=64) was the most common site, followed by trunk (n=7) and head and neck (n=2). Tumors ≥ 10 cm in size were found in 45% of pts (median 9 cm; range 6 – 30 cm). All patients underwent complete surgical resection of their primary tumor. With a median follow-up time of 93 months, the 5-year overall survival (OS), local recurrence-free survival (LRFS) and distant recurrence-free survival (DRFS) rates were 64%, 93% and 44%, respectively. In multivariable Cox's regression stage IIIB (p=0.01) (Fig. 1) and histology type other than monophasic (p=0.019) were associated with worse OS. The chemotherapy regimen was well tolerated, febrile neutropenia was seen in 1% of pts. There was no treatment-related mortality.

Conclusion: In adult patients with high-risk synovial sarcoma, a long-term survival can be achieved with intensive combined therapy. Our results demonstrated high local control rate despite large size of primary tumors if treated initially at reference center. New AJCC staging system can allow to differentiate the prognosis of stage IIIA and IIIB patients, and indicates that we need better and intensified therapy for synovial sarcoma stage IIIB disease.



Overall survival according to AJCC8 staging subgroup

Poster #275 3253904

REAL-WORLD OUTCOMES OF PATIENTS WITH LOCALLY ADVANCED OR METASTATIC EPITHELIOID SARCOMA

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Objective: Limited data are available on effectiveness and safety of systemic therapies for treatment of advanced (unresectable and/or metastatic) epithelioid sarcoma (ES). This natural history study collected real-world (rw) data on outcomes of ES patients receiving at least first-line (1L) or 2 or more lines (2L+) of systemic therapies.

Methods: Retrospective chart review was conducted in patients with advanced ES who initiated systemic therapy between 2000-2017 at 5 US cancer centers. Due to unavailability of RECIST assessment, rw overall response rate (rwORR) was assessed by review of radiology reports. rw disease control rate (rwDCR) was defined as percent of patients with response of any duration or stable disease ≥32 weeks. Median rw duration of response (rwDOR), rw progression-free survival (rwPFS) and overall survival (OS) were estimated from start of therapy by Kaplan-Meier method. The index date for time-to-event endpoints was the start of first line treatment. Adverse events (AEs) resulting in treatment modification, discontinuation, hospitalization, permanent sequelae or death, were abstracted.

Results: Of 74 eligible patients, 53 (71.6%) were male, and 63 (85.1%) had metastatic ES. INI1/BAF47 was not expressed in 90.2% of 41 tumors tested. Mean age at advanced ES diagnosis was 36.4 years. Anthracycline-based (54.1%) and gemcitabine-based (24.3%) regimens were most common in 1L. Median (range) number of lines of therapy received was 2 (1-7). 1L rwORR was 14.9%, rwDCR was 20.3%, rwDOR was 14.5 weeks, and median OS was 66.3 weeks. Table 1 shows 1L and 2L+ results. Over 50% of patients had an AE; most frequently febrile neutropenia (13.5%), pain (9.5%), anemia, dyspnea, fever, thrombocytopenia and transaminitis (5.4% each).

Conclusion: Currently available systemic therapies are not specific for advanced ES, have a limited response durability and low tolerability. This is the largest US-based rw study that provides benchmarking treatment efficacy and safety data for development of standard of care therapies for ES.

Table 1. Real-world outcomes by line of therapy

	1L N=74	2L+ N=46
rwORR (95% CI), %	14.9 (7.7-25.0)	9.4 (4.4-17.1)
Median rwDOR (95% CI), weeks	14.5 (9.1-22.6)	19.6 (3.1-24.3)
rwDCR (95% CI), %	20.3 (11.8-31.2)	19.8 (12.4-29.2)
Median rwPFS (95% CI), weeks	11.0 (7.3-29.9)	26.0 (13.9-32.0)
Median OS (95% CI), weeks	66.3 (49.6-94.1)	43.3 (33.6-78.3)

1L, first-line; 2L+, two or more lines; CI, confidence interval; DCR, disease control rate; DOR, duration of response; PFS, progression-free survival; ORR, overall response rate; OS, overall survival; rw, real-world

Poster #276 3254053

PALLIATIVE RESECTION FOR RETROPERITONEAL SARCOMA: EVALUATION OF POSTOPERATIVE SYMPTOMS AND SURVIVAL

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Objective: Retroperitoneal sarcomas (RPS) are frequently indolent tumors that often are only clinically evident when they have reached significant size with critical structure involvement, making R0/R1 surgical resection unachievable. We sought to investigate patient survival after palliative surgery for RPS and to evaluate symptom control after palliative surgery in this population.

Methods: Patient records from a single tertiary-care sarcoma referral center were queried from 2011 to 2018 to identify patients with RPS who underwent surgical resection. Patients were stratified by surgical intent (curative vs. palliative intent). Palliative intent was defined as surgeon preoperative indication and/or R2 resection. The Kaplan–Meier method and Log-Rank test was used to estimate overall survival (OS) between those who underwent curative and palliative surgery, from the time of initial diagnosis and from the time of index surgery. Symptom improvement was measured by patient reporting.

Results: There were 51 patients included in analysis (palliative: n=13, curative: n=38). In the palliative cohort, histopathologic subtypes included dedifferentiated liposarcoma (n=4), well-differentiated liposarcoma (n=4), mixed sarcoma (n=1), soft tissue (non-uterine) leiomyosarcoma (n=3), and undifferentiated pleomorphic sarcoma (n=1). Tumor size ranged from 3.7 to 44 cm; the most common presenting symptoms were abdominal pain (n=4) and bloating/fullness (n=4). Median OS from the time of sarcoma diagnosis was 180.2 months (95% confidence interval (CI): 145.7-214.6 months) for curative resection and 111.4 months for palliative resection (95% CI: 76.7-146.2 months) (p=0.025). Median OS from index resection was 59.9 months for curative resection (95% CI: 48.4-71.5 months) and 28.9 months for palliative resection (95% CI: 19.2-38.6 months) (p=0.064). A majority of patients (77%) in the palliative cohort reported postoperative symptom improvement for >2 months.

Conclusion: Palliative surgery may have a role in sustainable symptom improvement in patients with advanced RPS, particularly as median survival was >2 years, however the maintained difference in OS between patients who underwent curative resection vs. palliative resection must be emphasized when discussing the utilization of surgery in this patient cohort.

Poster #277 3254467

CLINICAL PRESENTATION, NATURAL HISTORY, THERAPEUTIC APPROACH AND TREATMENT OUTCOME IN PATIENTS WITH SOLITARY FIBROUS TUMOR

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Objective: Solitary fibrous tumor (SFT), a rare variant of soft tissue sarcoma (STS), is characterized by the presence of a NAB2-STAT6 fusion. Given the orphan character of SFT we performed a retrospective analysis of all cases treated in our tertiary care site.

Methods: We retrospectively reviewed all patients (pts) with SFT treated in our institution between 12/1990 - 09/2017

Results: We identified 94 SFT pts (incl. hemangiopericytoma) with a median follow-up for 4.7 yrs. Common anatomic sites were chest (33%), abdomen (21.3%), brain (12.8%) and extremities (9.6%). The symptomatology at diagnosis was variable. Only 6.4% of pts presented with synchronous metastasis. Hypoglycemia (Doege-Potter syndrome) was seen in 2.1% of cases. A resection of the primary SFT was done in 86 pts (91.5%), their disease-free survival was 35.5 months (mo) and 43% stayed SFT-free during follow-up. Local recurrence occurred in 26.7% of cases, associated with a median overall survival (OS) of 45.1 mo. Metachronous metastasis was seen in 30.2% of pts, occurring after a median follow-up of 36 mo. Median OS after diagnosis of metastasis was 19.0 mo. Systemic therapy was given to 92.9% of pts with inoperable/metastatic disease. The most common 1st line therapy was doxorubicin single agent (57.7% of pts), achieving responses in 13.3% of pts. Second line therapies included ifosfamide and pazopanib (31.3% of pts each), 3rd line treatment was very heterogeneous.

Conclusion: SFT is an orphan malignancy with a variable clinical course, a low incidence of distant spread at first diagnosis but a considerable risk of local failure and metachronous metastasis. Surgery is the only curative option at diagnosis, time of relapse and in case of resectable metastasis. Palliative systemic therapy is considered in pts with inoperable/metastatic disease but achieves low response rates. The natural course and survival outcomes of SFT cases treated with palliative intent tend to be better than in non-selected STS pts.

Poster #278 3251890

NEOADJUVANT RADIATION AND DUAL CHECK POINT BLOCKADE IN RESECTABLE SOFT TISSUE SARCOMA: INITIAL OUTCOMES IN FIRST 5 PATIENTS ON STUDY

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Objective: The role of systemic therapy in patients with localized soft tissue sarcoma (STS) is evolving, particularly in patients with intermediate risk disease or who may be poor candidates for or refuse anthracycline + ifosfamide based chemotherapy. Given evidence of benefit with immunotherapy in metastatic STS and synergistic effects when combined with radiation in other solid tumors, we sought to characterize the safety profile and outcomes of adding ipilimumab + nivolumab to standard neoadjuvant radiation in STS. Here we report the safety and initial clinical outcomes of the first 5 patients on treatment.

Methods: Eligible adults with STS recommended for neoadjuvant radiation followed by surgical resection were offered participation. Intermediate to high-grade sarcomas (excluding GIST, Ewing's, rhabdomyosarcoma) in adults with ECOG 0-2 and resectable primaries were included. Limited metastases were allowed on protocol if neoadjuvant radiation and resection of the primary were recommended as standard of care for symptom control. Goal enrollment is 12 patients on the treatment arm and 12 patients on a non-randomized, non-blinded control arm. Treatment consists of ipilimumab 1mg/kg IV q6 weeks + nivolumab 240mg q2 weeks x6 weeks total, concurrent with the start of radiation. Surgical resection is planned 2-4 weeks after completing neoadjuvant treatment. The primary outcome is the safety and adverse event profile of neoadjuvant dual checkpoint blockade with concurrent STS radiation. Secondary outcomes include pathologic response as well as patient reported outcomes using the validated FANLTC tool. Exploratory outcomes include changes in peripheral blood immunologic profile and tumor environment as well as progression free survival.

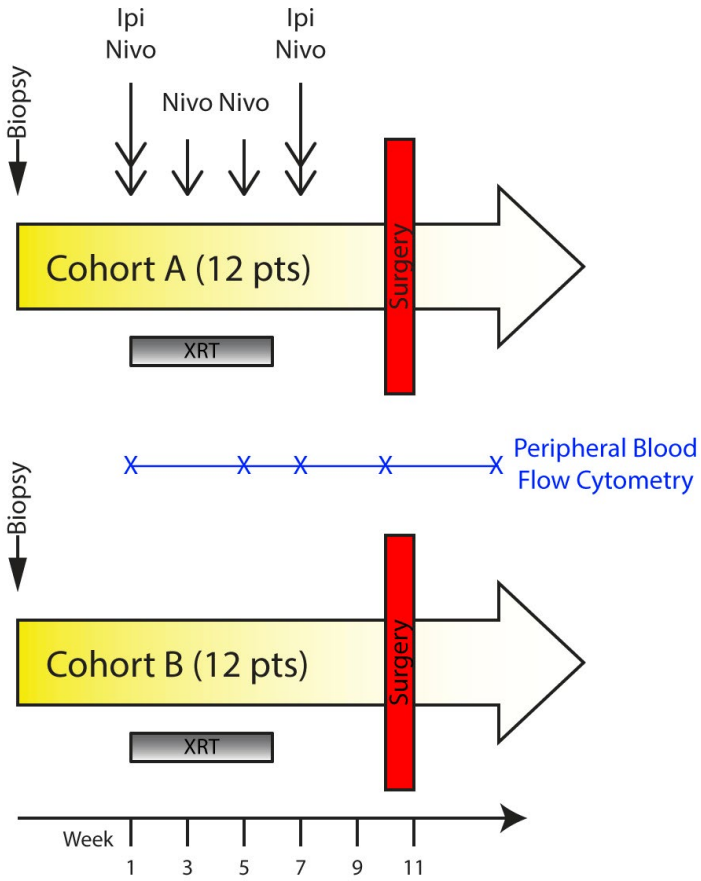
Results: Seven patients have enrolled to date, 5 on the treatment arm and 2 on the control arm. In the treatment arm, 1 patient is currently undergoing neoadjuvant treatment and 2 are pending surgery. There were no serious immune related adverse events (irAEs) in the treatment group to date. In 3 patients with extremity sarcomas, treatment was tolerated very well in 2 cases, however 1 patient developed necrotic tumor rupture requiring hospitalization and IV antibiotics until surgical resection of the primary was performed. In 2 patients with retroperitoneal sarcomas, treatment was associated with significant fatigue and anorexia; one patient had a feeding tube placed to maintain nutrition and another experienced grade 4 anorexia and weakness despite disease control and ultimately elected for hospice. This patient received one dose of ipilimumab/nivolumab, but developed diarrhea and diagnosed with C. diff colitis; further immunotherapy was held due to decline in function, though the patient did complete planned radiation. One patient in the treatment arm has undergone surgery, 2 are pending surgery, and surgery was canceled in 2 patients with retroperitoneal sarcoma. Of 5 patients on the treatment arm, 2 are alive and no evidence of disease. Another patient is alive but developed metastatic lung nodules by the end of treatment. This patient underwent surgery for a highly symptomatic primary with >90% necrosis on pathology but not a pathologic complete response. The 2 patients on the control arm both have extremity sarcomas. One has undergone surgery and is currently no evidence of disease and the second is currently undergoing radiation, both with good tolerance to date.

Conclusion: Dual checkpoint blockade was generally well tolerated when added to neoadjuvant radiation therapy for STS without serious immune-related adverse events in 5 patients treated to date. However, 3 patients experienced grade 3-5 treatment related adverse events. As these adverse events were not auto-immune in nature, it is unclear if these were related to radiation alone or if the addition of immunotherapy exacerbated these side effects, particularly in 2 patients with retroperitoneal sarcomas. This study is ongoing and additional subjects may provide further insight.

Safety and initial outcomes in 5 patients treated with neoadjuvant dual checkpoint blockade and concurrent radiation

ID	Sarcoma subtype	Location	Metastasis at start of treatment?	Completed neoadjuvant treatment?	Adverse events	Oncologic outcomes
001	Dedifferentiated liposarcoma with rhabdoid differentiation	Retroperitoneum	No	Yes	Grade 3 anorexia and fatigue requiring feeding tube placement. No irAEs.	On posttreatment imaging primary was stable and pain from primary improved with treatment., but developed widespread lung metastasis. Biopsy confirmed metastatic disease and surgery to the primary was aborted. On subsequent therapy, poor tolerance to doxorubicin as well as progression; enrolled on hospice and deceased 5 months after start of treatment.
002	Undifferentiated pleomorphic sarcoma.	Extremity	Possible	Yes	Grade 3 tumor necrosis/ rupture. No irAEs.	On posttreatment imaging, lung nodules progressed despite neoadjuvant treatment. Developed necrotic tumor rupture/ leakage of primary prior to planned surgical resection requiring hospitalization and antibiotics. Tumor with >90% necrosis but not pCR. On subsequent therapy, good tolerance but progression on doxorubicin; good tolerance and response to gemcitabine + docetaxel. Currently maintained on chemotherapy. No local recurrence at primary site.
003	Dedifferentiated liposarcoma.	Retroperitoneum	Biopsy confirmed local lymph node metastasis.	No: stopped checkpoint therapy after first dose due to diarrhea, ultimately dx C. diff. Did not resume due to severe anorexia and fatigue. Completed radiation as scheduled.	Grade 4-5 anorexia and malaise; became unable to swallow and enrolled on hospice. No irAEs.	Posttreatment imaging with interval decrease in size of primary and local metastasis, however given severe functional decline further treatment aborted and enrolled on hospice. Deceased 2 months after starting treatment.
005	High-grade sarcoma / undifferentiated pleomorphic sarcoma	Extremity	No	Yes	Grade 1 exacerbation of preexistent rash, possibly due to irAE. Managed with topical hydrocortisone cream, resolved by the end of treatment.	Felt generally improved at the end of neoadjuvant treatment compared with start, with improved function of limb. Posttreatment imaging with interval slight decrease in size of primary. Pending surgical resection.
006	Dedifferentiated liposarcoma	Extremity	No	In progress	No irAEs to date.	Pending posttreatment imaging and surgical resection.

Abbreviations: irAE = immune related adverse event, NOS = not otherwise specified, pCR = pathologic complete response.



Schema for neoadjuvant dual checkpoint blockade with concurrent radiation in soft tissue sarcoma, trial in progress.

Poster #279 3254560

CLINICAL OUTCOMES OF SOLITARY FIBROUS TUMOR: A SINGLE INSTITUTION EXPERIENCE OF 54 CASES

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Objective: Solitary fibrous tumor (SFT) is a rare fibrous neoplasm with limited information about its clinical features and outcomes. Data on the presentation, clinical features, and natural history and prognosis of solitary fibrous tumors are nearly entirely reported by retrospective case series and case reports because of its rarity. Moreover, changes in diagnostic terminology and subclassifying tumor by histology over the years have resulted in a disorganized, unsystematic approach to solitary fibrous tumor. We conducted a retrospective analysis to investigate clinical charateristics and treatment outcomes.

Methods: Between January 1998 and December 2018, a total of 54 patients with pathologically proven solitary fibrous tumor were identified from the database of Asan Medical Center reviewed retrospectively. We analyzed overall patients baseline characteristics, tumor anatomical distribution, pathologic characteristics, and treatment flow. Furthermore, we compared oncologic outcomes of localized disease patients with distant metastatic disease patients.

Results: A total of 54 patients were diagnosed with solitary fibrous tumor. Overall, the median age was 57 (range, 30–84) years, and 55.4 % of patients were men. The frequency of primary tumors in head and neck, thorax, abdomen-pelvis, genitourinary organ, extremities and skeletal system was 18.5%, 44.4%, 31.4%, 3.7%, 1.9%, respectively. In contrast to previous reports, lung parenchymal solitary fibrous tumor was most common (35.1%), and pleural SFT was only 7.4%. Mean initial tumor size was 6.01 (range,1-21.6) cm, and 14.8% was over 10 cm at diagnosis. Forty-five out of 54 patients (83.3%) underwent surgery only as initial treatment, 6 (11.1%) underwent surgery followed by adjuvant radiotherapy and 3 (5.6%) of patients underwent palliative treatment (chemotherapy, radiotherapy, surgery followed by chemotherapy) as initial treatment. Recurrence occurred in 10 patients (18.5%), either local recurrence or distant metastasis. Median recurrence free interval was 53.4 (range, 6.6-250.5) months. Patients received ifosfamide based regimen (MAID, VIP) or adriamycin based regimen (CYVADIC) as palliative chemotherapy. No tumor responded to chemotherapy and median progression free survival after palliative chemotherapy was only less than 2 months (55days).

Median follow up duration is 50.5 months and 5- year overall survival (OS) of all patients was 87.9%. The patients with localized disease showed longer OS for distant metastasis compared to patients with distant metastasis either at diagnosis or recur with metastasis (5- year OS 92.9% vs. 64.0%). Thoracic solitary fibrous tumor showed shorter overall OS (5-year OS 78.6% vs. 96.4%) than those with other sites.

Conclusion: Localized solitary fibrous tumor showed relatively long and stable survival outcome after surgery compared to patients with distant metastasis. Patients with palliative setting solitary fibrous tumor patients had little clinical benefit from palliative chemotherapy.

Poster #280 3254837

POTENTIAL PREDICTORS OF TUMOR RESPONSE TO NEOADJUVANT SYSTEMIC THERAPY IN PATIENTS WITH RETROPERITONEAL SARCOMA – A MULTI-INSTITUTIONAL TARPSWG STUDY

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Objective: Surgery is the mainstay of treatment for patients with retroperitoneal sarcoma (RPS), but this can be challenging and histologic subtype-specific local and distant recurrence rates remain high. The hypothetical benefits of neoadjuvant systemic therapy include tumor response (e.g. shrinkage) to facilitate resection and upfront control of distant and possibly local microscopic disease, but there is a paucity of data on such outcomes. In this exploratory study, we sought to determine the frequency and potential predictors of radiologic tumor response in non-metastatic, high risk primary RPS patients who received neoadjuvant systemic therapy at sarcoma referral centers across the United States and Europe.

Methods: Retrospective clinicopathologic data was collected from 6 institutions, each with at least 5 patients with RPS who had received neoadjuvant systemic therapy with or without radiation therapy from 2008-2018. Standard descriptive methods were used to characterize the study patients in general and by specific histologic subtype. For each patient, preoperative best objective response based on RECIST1.1 criteria was reported independently by each institution. Univariable and multivariable logistic models were performed to determine potential predictors of response (partial response, PR versus stable disease, SD / progression of disease, PD).

Results: In total, 121 RPS patients were included in this study with 74 (61%) of them from a single institution. A median of 3 cycles (interquartile range: 2-4, range: 1-20) of neoadjuvant systemic therapy were given. The intended treatment course was completed in 89 patients (74%). Fifty-three patients (44%) also received neoadjuvant radiation therapy. No radiologic complete responses were observed. PR was seen in 20 patients (17%) overall. Among 29 patients who received 5 or more cycles, PR was seen in 10 (34%). Tumor response by histologic subtype is shown in the **Table 1**. Notably, SD was observed in the majority of patients with leiomyosarcoma (72%) and well differentiated liposarcoma (83%). PR was seen in 50% of patients with undifferentiated pleomorphic sarcoma (MDM2-negative), although patient numbers were limited. The systemic therapy regimen(s) given by histologic subtype are shown in **Table 2**. On univariable modeling, more cycles of neoadjuvant systemic therapy were positively associated with PR ($p = 0.04$) but statistical significance was lost with multivariable modeling ($p = 0.07$). Gender, age, tumor size, histologic subtype and receipt of radiation therapy were not predictive of PR. All patients ultimately underwent complete (R0/R1) resection. Concomitant organ resection was performed in almost all patients (118, 98%). Complications of any severity occurred in 46 patients (38%) and major complications (Clavien-Dindo grade 3 or higher) occurred in 34 patients (28%).

Conclusion: Tumor response to neoadjuvant systemic therapy appears to be associated with more treatment cycles in patients with RPS. Reasons for discontinuation of therapy (e.g. intolerance, disease progression) and the value of histologic subtype-specific regimens (e.g. Gronchi et al., Lancet Oncol 2017) in RPS patients deserve further study.

Table 1	N*	PR (%)	SD (%)	PD (%)
DD	53	7 (13)	30 (57)	16 (30)
LMS	36	4 (11)	26 (72)	6 (17)
WD	12	2 (17)	10 (83)	0 (0)
UPS	10	5 (50)	4 (40)	1 (10)

**not shown: MPNST (N = 6), SFT (N = 4)*

Table 2	A+I	A	I	A+DTIC	G+T	A+DTIC+Cys	Other^
DD	32	1	8	0	3	3	6
LMS	11	1	6	12	3	1	2
WD	4	1	7	0	0	0	0
UPS	5	0	2	1	0	0	2

A = adriamycin or epirubicin; I = ifosfamide; G = gemcitabine; T = taxotere; Cys = cyclophosphamide
^includes A+Cys, A+Olara, G+DTIC, G-alone, VIDE, trabectedin, PEB and multiple regimens (2 pts)

Poster #281 3254980

AN EVALUATION OF A MULTI-DISCIPLINARY PRECEPTORSHIP (MDTP) FOR ONCOLOGY TRAINEES IN NATIONAL CANCER CENTRE SINGAPORE (NCCS)

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Objective: Sarcoma is a challenging and rare disease that is difficult to manage. Education and shared experiences are important to manage sarcoma competently. The department has ongoing efforts to continually improve sarcoma knowledge. Clinical preceptorships have been documented as effective learning methods. Building on our previous experiences, an improved international sarcoma MDTP was carefully designed and delivered. This was an intensive 2-day program with carefully selected lectures and challenging real-life clinical case discussions. The objective of the preceptorship was to raise clinical competence of oncology trainees in sarcoma management.

Methods: A pre- and post-test were conducted at the beginning and end of the MDTP, held on 26-27 October 2018 in Singapore. The test consists of 20 scenario-based multiple choice questions of equal weightage. The participants are required to select the best out of the 4 options. To examine the effectiveness, we used the same set of questions for both tests. Evaluations were carried out to identify areas for improvements.

Results: A total of 15 trainees attended. 3 were Taiwanese, 2 were Indonesians, and the rest were local attendees. All of them were oncology trainees of different specialties (8 medical, 2 surgical, 2 orthopaedic, and 3 radiation oncologists). On average, the number of years of training is 3.88 (Range: 3 to 5). 12 attendees completed the pre- and post-test (80%). The mean score for the pre-test was 9.3, median is 9.5 (Range: 6 to 14). For post-test, the mean score is 11.5, median 11.5 (Range: 9 to 14). 83.3% of the attendees showed improvement from the pretest (mean increment score 2.17; p value <0.001). None of the attendees scored worse. All the participants found the program helpful, with the interactive clinical case discussions very relevant.

Conclusion: This program sought to enhance learning and the results revealed positive outcomes. The attendees also benefited from challenging clinical cases discussion with sarcoma specialists. Being an international conference, our attendees were able to gain a wider perspective and insight in the management of this very difficult disease, thereby improving the overall clinical competence.

Poster #282 3254984

COMORBIDITIES IN CASES WITH SOFT TISSUE SARCOMA-IMPACT ON THE COMPLETION OF STANDARD THERAPY AND ONCOLOGICAL OUTCOME

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Objective: With progression of aging, comorbidities have become consequent problem in soft tissue sarcoma treatment. There have been limited studies as to the impact of comorbidities in sarcoma patients on oncological outcomes.

Methods: 232 sarcoma patients without metastasis at presentation were subject to the present study. Frequency of comorbidities, impact of comorbidities on the completion of standard therapy and survival were analyzed. Comorbidities were evaluated based on Charlson Comorbidity Index (CCI,Quan H et al. 2010). Standard therapy for soft tissue sarcoma was defined as completion of wide resection (marginal resection was allowed only for well differentiated liposarcoma) and systemic chemotherapy (only for cases of high grade, deep located and diameters > 50mm).

Results: Fifty three cases (22.8%) were evaluated as having comorbidities. The frequent comorbidities included congestive heart failure in 24 (10.3%), diabetes mellitus with chronic comorbidities in 16 (6.9%) and dementia in 15(6.4%) cases. Risks of incomplete therapy included higher CCI (p=0.003), congestive heart failure(p=0.03) and dementia (p=0.0002). Cases with higher CCI≧4(p<0.0001), cases with congestive heart failure(p=0.02) and cases with dementia (p<0.0001) had significantly worse overall survival. Among candidate risks including age (>75), FNCLCC grade and CCI, grade (p<0.0001) and CCI (p<0.0001) proved to be independent risks for lethal event in multivariate model.

Conclusion: The present data showed comorbidities, especially heart disease and dementia, rather than age, had impact on treatment quality and oncological outcome of soft tissue sarcoma.

Poster #283 3255122

LONG-TERM OUTCOMES EFFICACY OF MULTIDISCIPLINARY TREATMENT OF EPITHELIOID SARCOMA

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Objective: Data on the clinical presentation and optimal multidisciplinary treatment as well as long-term outcomes of patients (pts) with epithelioid sarcoma (ES) is still limited and guidelines for optimal treatment are not yet established. Until today surgery is considered as effective treatment for early stage cases and outcomes of systemic treatment seem unsatisfactory. This study analyze the outcomes of multidisciplinary treatment of ES in a reference sarcoma clinic in Poland. We aimed to describe the potential role of neoadjuvant radio- and chemotherapy in ES, as well as efficacy of sequential palliative chemotherapy in prolongation of survival in these pts.

Methods: We retrospectively reviewed all consecutive pts with ES treated in the Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie Institute-Oncology Center in Warsaw between 01/1999 and 05/2019. Histopatology of ES was confirmed in all cases by a designated sarcoma pathologist. Surviving and progression-free patients were censored at data cut-off (15.06.2019). Survival curves were calculated according to Kaplan-Meier method and compared with the log-rank test or a Cox proportional hazard model, with R package.

Results: 36 ES patients (median age 36 years, 67% male) were eligible. Clinical presentation at first visit included 83% pts with extremity localization, median tumour diameter 6.2 cm, all were higher pathological grade, 47% nodal metastases, 8% distant metastases, and 42% pts was referred with local recurrence from regional hospitals. 25% patients presented with unresectable tumor in our center. 27 patients were operated in our center, including 74% R0 resections. 4 patients underwent surgery alone, 20 surgery and radiotherapy and 6 received neoadjuvant chemotherapy, surgery and radiotherapy treatment. 19 patients were treated due to advanced or metastatic disease. After initial treatment local recurrence (n = 7) and distant recurrence (n = 13) was diagnosed. Median local relapse-free survival (LRFS) was 104m . 2-year disease-free survival (DFS) rates was 63% (95% CI: 39-100%) when the primary surgery was performed in our center, and 80% (95% CI:52%-100%) if after primary resection in regional hospital re-resection was performed in our sarcoma department. In patients referred to our center with local recurrence after resection in regional hospital 2-year DFS rate reached 29% (95% CI: 9-92%). Resection margin status and adjuvant radiotherapy did not correlated with LRFS and DFS in this cohort.

6 received chemotherapy as first-line palliative treatment (2 doxorubicin/dacarbazine, 2 doxorubicin/ifosfamide, 1 gemcitabine/docetaxel, 1 high-dose ifosfamide), 4 received second line therapy and 2 third line later. The median age of patients treated systemically was 33 years. Median progression-free survival (PFS) in 1st-line palliative treatment was 6.1 month (95% CI: 2.1-NA) No regiment was statistically superior in this dataset, but doxorubicin/ifosfamide regiment had numerically longest PFS of 13 months (95%CI: 6.1-NA). Most often best response in palliative treatment was SD. 15 patients died due to disease progression. After a median follow-up of 53 (range: 32-103) months, the 5-yr-RFS was 41% (CI 95% [25-69]) and the 5-yr overall survival (OS) rate was 58% (CI 95% [42-81]) . The ES proximal subtype, nodal involvement and unresectable primary tumor were associated with unfavorable OS in patients without metastases at presentation.

Conclusion: Proximal ES require multimodal treatment. Follow-up after radical treatment should be intensified in first 3 years. Development of novel systemic therapies for epithelioid sarcoma remain an unmet medical need. Sequential chemotherapy in fit patients may result in longer OS of these patients although objective responses are rarely achieved with currently used regimens. Multicenter cooperation is crucial in order to provide robust statistical analysis of predictive and prognostic factors in rare tumors such as ES.

Poster #284 3255194

EVALUATION OF LATERAL EXTENT OF THE TUMOR INFILTRATION AREA AROUND SUBCUTANEOUS MYXOFIBROSARCOMA BY ULTRASONOGRAPHY

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Objective: Subcutaneous myxofibrosarcoma (MFS) tends to have a reactive layer that might contain tumor cells. Wider resection including the reactive layer is recommended to achieve complete tumor resection. Contrast-enhanced magnetic resonance imaging (MRI) is widely used for evaluating the extent of subcutaneous MFS. Since the imaging direction of MRI is limited, it is difficult to evaluate the lateral extent of the reactive layer in all directions, except for axial and sagittal plane.

Ultrasonography (US)is widely used as an image evaluation method of inflammation or edema of subcutaneous tissues. US can evaluate the condition of subcutaneous tissue in any cross section. In this study, the utility of ultrasonography in the evaluation of lateral extent of the tumor infiltration around the subcutaneous MFS was examined.

Methods: Patients who underwent surgery with subcutaneous MFS from January 2015 to October 2018 were included. US examination was done 1 or 2 days before surgery. The distance from the tumor surface to the outer edge of the region where the increased subcutaneous tissue echogenicity is observed in 0 o'clock, 3 o'clock, 6 o'clock, 9 o'clock direction was measured (U-dist). The distances from the tumor surface to the outer edge of the radiological infiltrated area on T1 enhanced MRI were measured in 0 o'clock, 3 o'clock, 6 o'clock, 9 o'clock direction (R-dist). Similarly, on hematoxylin and eosin staining of the resected tumor specimens, the distances from the tumor surface to the outer edge of the atypical tumor cell infiltration area were measured in the same four directions (H-dist). E-dist, R-dist and H-dist of the same section were compared statistically.

Results: Seven patients were enrolled (male/female : 6/1), ranging in age from 66 to 87 years (mean age 74 years). Increased echogenicity was observed in the subcutaneous tissues around the tumor in all directions. The mean U-dist, R-dist and H-dist, were 24 (8-54) mm,18 (1-40) mm and 12(1-25) mm respectively. U-dist were strongly correlated with R-dist (R2=0.60), and E-dist ware significantly longer than R-dist ($p<0.01$, paired t-test). Moreover, U-dist was more strongly correlated to H-dist (R2=0.22) than R-dist(R2=0.08). U-dist was shorter than H-dist only in 3 directions of 3 cases (range 3 – 6 mm), while R-dist was shroter than H-dist in 8 directions of 5 cases (range 1-18 mm).

Conclusion: US can evaluate the lateral extent of the reactive layer in subcutaneous tissue. Moreover, US is less likely to underestimate the size of the histological infiltrated area than MRI.

Poster #285 3255214

DERMATOFIBROSARCOMA PROTUBERANS - A UNICENTRIC RETROSPECTIVE ANALYSIS OF A 10-YEAR PERIOD AT A TERTIARY TEACHING HOSPITAL

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Objective: Dermatofibrosarcoma protuberans (DFSP) is a rare skin tumor with an indolent growing pattern. It is characterized by the translocation t(17;22)(q22;q13), which leads to the production of COL1A1-PDGFB fusion transcripts. Despite DFSP having a low risk of distant dissemination, there is a high rate of local recurrence and, therefore, elevated morbidity. Mohs' micrographic surgery is the treatment of choice for primary and recurrent DFSP, but radiotherapy may play a role in local control in some cases. Systemic treatment for disseminated disease was limited in the past, but today, due to better understanding of tumor biology and molecular alterations, the use of multikinase inhibitors and other specific target agents is an effective option. These patients should be treated in reference medical centers and treatment planning should be discussed by a multidisciplinary team.

The aim of this study is to review and characterize the histopathological and clinical features of 19 patients presenting with the diagnosis of dermatofibrosarcoma protuberans, during a ten-year period at a tertiary teaching hospital.

Methods: Retrospective study of all patients with the histological diagnosis of dermatofibrosarcoma protuberans between January 1st, 2009 and June 30th, 2019, at Hospital de Santa Maria (Lisbon, Portugal). Data was obtained by reviewing histopathology registries and the clinical records of dermatology, general and plastic surgery and oncology visits.

Results: Nineteen patients diagnosed with DFSP were identified. The mean age at the diagnosis was 51 years (+- 18.5), with a range of 30-97 years. A female predominance was observed (n=13; 68.4%). The most common location was the upper limb and the thorax (n=4 each; 21,0%), followed by lower limb (n=3; 15,8%), inguinal region, back, abdomen and neck (n=2 each; 10,5%). Most tumors presented with a small size (T1 n=15; 78,9% vs. T2 n=2; 10,5%) and all without node or distant metastasis (N0; M0). All patients were submitted to complete excision. One patient was treated with radiotherapy following surgery, and no patient was submitted to chemotherapy. Two patients had local recurrence, with relapse-free survival of 3 and 11 months. All patients are still alive and there are no cases of distant metastases.

Conclusion: DFSP is an uncommon malignancy of the skin with a high risk of local recurrence. Patients should be referred to specialized medical centers with experience and high volume of cutaneous sarcomas cases for optimal treatment, better survival and functional outcomes.

Poster #286 3255873

FIRST INTERIM RESULTS FROM A GERMAN RETROSPECTIVE STUDY OF SARCOMA PATIENTS TREATED WITH TRABECTEDIN (RETRASARC)

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Objective: Despite the growing amount of published data regarding clinical experiences of sarcoma patients treated with trabectedin (Yondelis®), many questions still remain unanswered. Collection of effectiveness and safety data in a large real-world population of sarcoma patients treated with trabectedin can certainly help us to shed some more light on some of the open questions. The retrospective multicenter study ReTraSarc was initiated in 2016 with the aim to evaluate the use and course as well as effectiveness and safety of trabectedin in a large (n=>500) real-life patient population with soft tissue or bone sarcoma in Germany (ClinicalTrials.gov Identifier: NCT03284320).

Methods: ReTraSarc was conducted in 12 sites across Germany. Eligible patients were those with confirmed diagnosis of soft tissue or bone sarcoma who had previously received at least one cycle of trabectedin. The patients' clinical histories were analyzed from the first diagnoses of sarcoma until patients' death or loss-to-follow-up. The cutoff date for the collection of patients' clinical data ends in June 2019.

Results: To date 504 patients (236 females) treated with trabectedin were retrospectively analyzed in ReTraSarc. The median year for the 1st sarcoma diagnosis was 2010 (range 1987 – 2019; interquartile range (IQR): 2007; 2013). Overall, 475 patients (94.2%) had a soft tissue sarcoma (STS), whereas the resting 29 patients (5.8%) had bone sarcoma. The most prevalent type of sarcoma were leiomyosarcoma (n=129, 27.2%) and liposarcoma (n=97, 20.4%). Histological subtypes of STS in >2% of patients are shown in Table 1. Patients had a mean age of 54 years (10-87) at first diagnosis. Trabectedin as 1st-line treatment was administered to 31 patients (6.2%), as 2nd-line therapy to 192 patients (38.4%), as 3rd-line therapy to 144 patients (28.8%), whereas 130 patients (26%) have been exposed to trabectedin as ≥4th-line therapy. Patients being ever exposed to trabectedin had a median overall survival (OS) after initial diagnosis of 36.3 months (95% confidence interval [95% CI: 32.7; 39.3]). Analyses of effectiveness (e.g. response rates, progression free survival) and safety are in progress for the whole study population and stratified per sarcoma subtypes.

Conclusion: The results of this real-life study, with a large number of patients and long-term follow-up, allow us to better analyze progression-free survival (PFS) and OS in sarcoma patients treated with trabectedin, given in different treatment lines and after dose modifications and/or cycle delays. Additionally, the results of this study enable us to evaluate the real-life impact of rechallenge with trabectedin in a further therapy line after disease progression. Final descriptive results and first effectiveness and safety analyses stratified per sarcoma subtypes will be presented at the conference.

Table 1. Soft tissue sarcoma histology

Subtype STS	N	Percent
Leiomyosarcoma	129	27.2
Liposarcoma	97	20.4
Pleomorphic sarcoma NOS*	79	16.6
Synovial sarcoma	45	9.5
Spindle cell sarcoma NOS*	25	5.3
Fibrosarcoma	22	4.6
Malignant peripheral nerve sheath tumor	13	2.7
Rhabdomyosarcoma	12	2.5
Diagnoses	53	11.2
Total	475	100

*NOS, not otherwise specified; **Includes among other: angiosarcoma, chondrosarcoma, histiocytoma, carcinosarcoma, hemangioma, endometrial stromal sarcoma.

Poster #287 3256569

DETECTION OF APO10 AND TKTL1 FOR FOLLOW AND POST TREATMENT SCREENING IN SARCOMA PATIENTS

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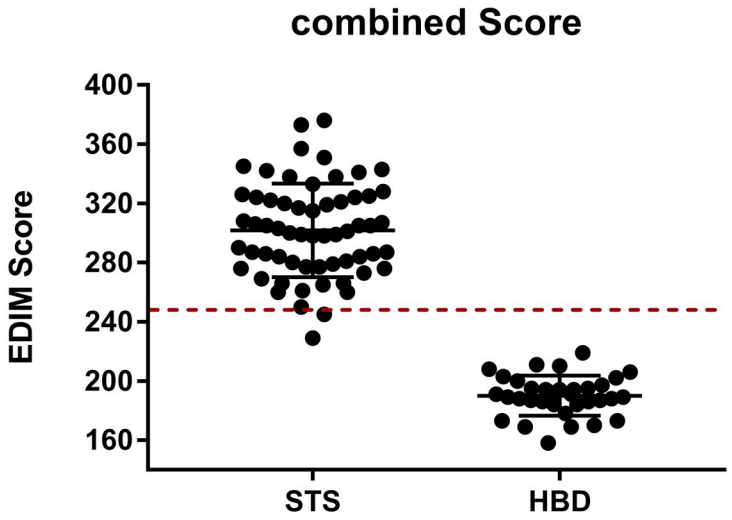
Objective: Tumor markers are used in primary diagnostics, for staging or for follow-up in several malignant diseases. Some of these markers have high sensitivity and specificity and some have prognostic potential. Up todate, there are no suchmarkers established for soft-tissue and bone sarcomas. The aim of this pilot study was to evaluate whether an EDIM test (epitope detection in macrophages) of Apo10 and TKTL1 could be a reliable test for the follow-up of soft-tissue and bone sarcomas.

Methods: The EDIM test is based on two biomarkers (Apo10 and TKTL1). Apo10 is an epitope of DNaseX (Desoxyribonuclease X), which plays a role in apoptosis. It accumulates in tumor cells and is associated with apoptosis resistance and proliferation. TKTL1 (Transketolase-like protein 1), on the other hand, plays a crucial role in the anaerobic glycolysis of tumor cells. Increased lactate production leads to destruction of the basal membrane and facilitate metastasis.

Results: In total, blood samples from 75 patients with a high-grade (stage III) bone or soft-tissue sarcomas could be included. The mean age of all patients was 58.9 years (14-88). 35 of the patients were male. All patients had an increased EDIM-Apo10 as well as a elevated TKTL1 score before biopsy. After completion of the therapy, the values in the follow-up controls normalized. In an independent control group of healthy volunteers, only normal values were measured.

Conclusion: All patients with high-grade sarcoma had an increased EDIM-Apo10 and TKTL1 score. After successful curative therapy, the values normalize. We believe that this approach could to be very useful technique for follow-up monitoring. Further work is being undertaken with a larger cohort.



Poster #288 3258032

CHEMOTHERAPY IN ADVANCED MALIGNANT PHYLLODES TUMOR (PT) OF THE BREAST: A MULTI-INSTITUTIONAL EUROPEAN RETROSPECTIVE CASE-SERIES ANALYSIS

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Objective: Data on chemotherapy are limited in breast PT, a rare fibroepithelial neoplasm accounting for less than 1% of all breast neoplasms, with a low metastatic potential. Herein we report on the results of a multicentric retrospective collaborative study aimed at investigating the activity and efficacy of chemotherapy in locally advanced/metastatic PT.

Methods: Cases of advanced PT of the breast treated with chemotherapy in several european centres from 2000 to 2018 were retrospectively reviewed. Responses are provided according to RECIST. Survival curves were calculated using Kaplan-Meier method.

Results: From 2000, 51 female patients were identified (two with locally advanced disease and 49 with metastatic disease). Median age was 51 years (range: 25-80 years). Patients received a median number of 2 chemotherapy lines (range 1-4). Most used chemotherapy regimens included: antracyclines + ifosfamide (AI), antracyclines alone, high-dose ifosfamide given as a continuous infusion for 14 days (HD-IFX), gemcitabine +/- docetaxel (GD), trabectedin. In particular, 26 patients received AI (all as first-line), 11 patients received an antracycline alone (as first, second and further line in 9, 1 and 1 cases, respectively), 14 patients received HD-IFX (as first, second and further line in 2, 9 and 3 cases, respectively), 16 patients received GD (as first, second and further line in 4, 6 and 6 cases, respectively), 12 received trabectedin (as first, second and further line in 2, 6 and 4 cases, respectively). Best responses according to RECIST were: 10 (40%) PR, 6 (24%) SD, 9 (36%) PD with AI; 1 (9%) PR, 3 (27%) SD, 7 (64%) PD with anthracyclines alone; 2 (14%) PR, 3 (21%) SD, 9 (65%) PD with HD-IFX; 1 (6%) PR, 3 (19%) SD, 11 (69%) PD with GD (with 1 patient not evaluable); 1 (8%) PR, 1 (8%) SD, 9 (75%) PD with trabectedin (with 1 patient not evaluable). Median progression-free survival were: 5.6 months with AI, 2.4 months with anthracycline alone, 2.6 months with HD-IFX, 2.8 months with gemcitabine-based chemotherapy; 2 months with trabectedin. With a median follow-up of 32 months, overall survival from the start of first-line chemotherapy was 15.2 months.

Conclusion: In this series of advanced PT patients (to our knowledge, the largest reported so far), though with the limitations of a small retrospective analysis, the patterns of response of PT looked similar to STS overall, possibly with a relatively high rate of responses to AI, but a low duration.

Poster #289 3231289

GENERATING SOFT TISSUE SARCOMA PATIENT-DERIVED XENOGRAFT (PDX) MODELS FROM CORE-NEEDLE BIOPSY: A PROSPECTIVE CLINICAL TRIAL

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Objective: Patient-derived xenograft (PDX) models provide an opportunity to identify personalized treatment for patients with aggressive soft tissue sarcoma (STS). While STS PDX models are successfully generated from surgical specimens (≥62% in untreated high-grade STS), there is no data regarding STS PDX establishment from percutaneous core-needle biopsies (CNBx). We aimed to determine the feasibility of generating PDX models from clinical core-needle biopsy specimens in patients with sarcoma.

Methods: Beginning August 2018, patients undergoing an image-guided CNBx for a potential STS were eligible for participation in this ongoing study. Additional tissue was obtained for implantation in female NOG mice (Taconic Biosciences). One core was subcutaneously implanted into the rear flank. Tumors were passaged into new NOG mice when they reached 500 mm^3. Tumors that could be serially passaged were considered established. Clinicopathologic characteristics were obtained and summarized.

Results: To date, 15 patients have been enrolled. One patient was excluded as CNBx revealed lymphoma. The overall success rate for PDX model generation from core-needle biopsy was 14% (2 of 14), with median time to first passage was 82.5 days (62 and 103 days, respectively). The success rate among high-grade untreated STS was 33% (2 of 6). The two successful PDX models were generated from 14g CNBx, none from 18g or 19g CNBxs. The two histologies were UPS and sarcoma NOS. Of the PDX model generation failures, 58% were low or intermediate grade, and 58% had undergone treatment prior to CNBx. The histologies included slow-growing sarcoma subtypes, such as WDLPS and solitary fibrous tumor (Table 1).

Conclusion: Preliminary trend is that large caliber CNBx in high-grade untreated STS offers the greatest likelihood of PDX model generation. While further refinement of patient selection criteria and model generation methods is needed, early results demonstrate that PDX from CNBx biopsy is feasible, but with lower success rates than from surgical specimens.

Table 1: Patient and tumor characteristics for all patients and by PDX model success.

		All (n = 14)	Success (n = 2)	Failure (n = 12)
Age (yr)		53.5 (31-81)	60 (39-81)	53.5 (31-78)
Grade				
	Low	4 (28.6)	0 (0.0)	4 (33.3)
	Intermediate	3 (21.4)	0 (0.0)	3 (25.0)
	High	7 (50.0)	2 (100.0)	5 (41.7)
Presentation				
	Primary	6 (42.9)	2 (100.0)	4 (33.3)
	Recurrent or metastatic	8 (57.1)	0 (0.0)	8 (66.7)
Location				
	Lung	2 (14.3)	0 (0.0)	2 (16.7)
	Abdomen/pelvis/RP	4 (28.6)	0 (0.0)	4 (33.3)
	Extremity/trunk	8 (57.1)	2 (100.0)	6 (50.0)
Size (cm)		5.6 (1.2-11.4)	7.8 (4.1-11.4)	5.6 (1.2-10.3)
Subtype				
	Epithelioid sarcoma	1 (7.1)	0 (0.0)	1 (8.3)
	Sarcoma, NOS	3 (21.4)	1 (50.0)	2 (16.7)
	Myxoid liposarcoma	2 (14.3)	0 (0.0)	2 (16.7)
	WDLPS	2 (14.3)	0 (0.0)	2 (16.7)
	MPNST	1 (7.1)	0 (0.0)	1 (8.3)
	Leiomyosarcoma	2 (14.3)	0 (0.0)	2 (16.7)
	UPS	1 (7.1)	1 (50.0)	0 (0.0)
	Solitary fibrous tumor	1 (7.1)	0 (0.0)	1 (8.3)
	Angiosarcoma	1 (7.1)	0 (0.0)	1 (8.3)
Pre-biopsy therapy				
	No (None)	7 (50.0)	2 (100.0)	5 (41.7)
	Yes (CT, XRT, CT+XRT)	7 (50.0)	0 (0.0)	7 (58.3)
Needle size (gauge)				
	14g	9 (64.3)	2 (100.0)	7 (58.3)
	18g + 19g	5 (35.7)	0 (0.0)	5 (41.7)

Continuous variables expressed as median (range) and categorical variables expressed as n (%).

Poster #290 3240354

ESTABLISHMENT OF A NOVEL HUMAN CIC-DUX4 SARCOMA CELL LINE, KITRA-SRS, WITH AUTOCRINE IGF-1R ACTIVATION AND METASTATIC POTENTIAL TO THE LUNGS

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Objective: *CIC* rearrangement is the genetic abnormality that is generally identified in approximately 60-70% of *EWSR1*-negative small blue round cell sarcomas. This rearrangement most commonly connects *CIC* (19q13) to *DUX4* (4q35 or 10q26); some tumours harbour *CIC* rearrangements with non-*DUX4* partner genes, including *FOXO4*, *LEUTX*, *NUTM1*, and *NUTM2A*. *CIC-DUX4* sarcoma (CDS) is an aggressive and often fatal high-grade sarcoma appearing predominantly in children and young adults. Novel therapeutic strategies are needed to improve patient prognosis. Although cell lines and their xenograft models are essential tools for basic research and development of antitumour drugs, few cell lines currently exist for CDS. In the present study, we successfully established a novel human CDS cell line designated Kitra-SRS and used it to establish orthotopic tumour xenografts in nude mice.

Methods: Kitra-SRS cells was derived from the surgically resected tumor of a 9-year-old girl and has been growing in standard 2D culture for more than 100 passages (more than 24 months). The chimeric transcript and karyotype were analysed. Xenografts were established in nude mice and characterized by morphology and immunohistochemical reactivity. Subsequently, the antitumor effects of inhibition of IGF-1R, which was activated in Kitra-SRS cells, were assessed *in vitro* and *in vivo*.

Results: The *CIC-DUX4* fusion transcript was detected in Kitra-SRS cells by RNA-seq experiment and RT-PCR. Sequence analysis revealed that the *CIC* and *DUX4* breakpoint in Kitra-SRS cells was coincident with the insertion of six nucleotides and was confirmed within exon 20 of *CIC* and exon 1 of *DUX4*, respectively. Moreover, the *CIC* sequence of the fusion transcript corresponded to the wild-type sequence, and the *DUX4* sequence was identical to sequences of several *DUX4* pseudogene components on chromosomes 4q35.2 or 10q26.3. In chromosomal analysis using multiplex fluorescence in situ hybridization (M-FISH), the following karyotypes were found: 48, XX, del(1)(p32), +8, t(12;19)(q13;q13), +20. In addition, three chromosome breakpoints within 19q13.2, including *CIC*, were demonstrated using the bacterial artificial chromosome cloning system. These results suggest that the *CIC-DUX4* fusion gene in Kitra-SRS cells was generated by t(12;19) complex chromosomal rearrangements with an insertion of a chromosome segment including a *DUX4* pseudogene component. Kitra-SRS xenograft tumours in nude mice were histologically similar to the original tumour and exhibited metastatic potential to the lungs. Kitra-SRS cells displayed autocrine activation of the insulin-like growth factor 1 (IGF-1)/IGF-1 receptor (IGF-1R) pathway by western blotting and enzyme-linked immunosorbent assay. Treatment with the IGF-1R inhibitor, linstinib, suppressed cell proliferation of Kitra-SRS cells in a dose-dependent manner (IC_{50}: 1.43μM). In addition, flow cytometric analyses revealed that exposure to linstinib for 48 h increased the population of Kitra-SRS cells in the G0/G1 phase in a dose-dependent manner. Consistent with *in vitro* experiments, linstinib treatment markedly attenuated Kitra-SRS cell growth and the activation of IGF-1R/AKT signalling in nude mouse models; furthermore, lung metastases were not found in linstinib-treated mice.

Conclusion: In conclusion, the present study describes the establishment of a novel human CDS cell line, Kitra-SRS cells, with autocrine activation of IGF-1/IGF-1R signalling and metastatic potential to the lungs. Kitra-SRS will be a meaningful model for investigating the molecular pathology of CDS and developing novel strategies to treat patients with CDS.

Poster #291 3241614

CONTINUOUS INFUSIONAL IFOSFAMIDE FOR MANAGEMENT OF SOFT-TISSUE AND BONE SARCOMA: A SINGLE CENTRE RETROSPECTIVE COHORT ANALYSIS

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Objective: Ifosfamide is routinely used to treat both soft tissue sarcoma (STS) and bone sarcoma (BS) with demonstrated clinical efficacy at doses greater than 9 g/m^2/cycle. In an attempt to mitigate the toxicity associated with high dose ifosfamide, continuous infusional ifosfamide is increasingly being used. However, data on clinical outcomes from patients treated with infusional ifosfamide, particularly patients with bone sarcoma, remains limited.

Methods: We present a retrospective cohort analysis of sarcoma patients treated with 4-weekly infusional ifosfamide (dosed at 14g/m^2/14 days) between August 2012 and February 2019. Clinical data were analysed to evaluate radiological responses where available, clinical benefit rate (CBR; defined as the proportion of patients with radiological improvement or disease stability), progression free survival (PFS), overall survival (OS) and CTCAE toxicities ≥ grade 2 (G2).

Results: Eighty patients commenced treatment; 46 with soft tissue sarcoma (STS) and 34 with bone sarcoma (BS). Patient demographics including number of previous chemotherapy lines, proportion of patients who received prior ifosfamide, and the median number of treatment cycles given, can be found within table 1.

For those patients with STS, 15 patients (33%) had synovial sarcoma (SS), 13 (28%) had liposarcoma and 18 (39%) had other STS subtypes. Overall CBR was 50% (23 patients; 13 (28%) with radiological improvement and 10 (22%) with disease stability) with 6 patients proceeding to consolidation treatment with surgery or radiotherapy. Eleven patients (24%) had progressive disease (PD) and the remaining 12 patients (26%) were non-assessable. For all STS pts, median PFS was 3.8 months, and median OS was 13.0 months. CBR in SS (15 patients) was 80% (12 patients), median PFS was 8.1 months and median OS was 20.9 months; whilst for liposarcoma (13 patients), CBR was 38% (5 patients), median PFS was 3.4 months and median OS was 11.2 months. For remaining STS patients (18), CBR was 33% (6 patients), median PFS was 2.7 months and median OS was 12.7 months.

For patients with BS, 16 patients (47%) had Ewing sarcoma (ES), 13 patients (38%) had osteosarcoma, and 5 (15%) had other subtypes. Overall CBR was 30% (10 patients; 6 (18%) with radiological improvement and 4 (12%) with disease stability) with 3 patients proceeding to consolidation treatment. Seventeen patients (50%) had PD and 7 (21%) were non-assessable. For all BS patients, median PFS was 2.5 months and median OS was 6.2 months. In ES (16 patients), CBR was 38% (6 patients), median PFS was 3 months and median OS was 8.3 months; whilst for osteosarcoma (13 patients), CBR was 15% (2 patients), median PFS was 2.5 months, and median OS was 6.9 months. For the remaining patients (5), CBR was 40% (2 patients), median PFS was 2.1 months and median was OS 3.9 months. Results are summarised in table 1.

For all 80 patients, 21 (26%) had treatment terminated early due to toxicity, and 18 patients (23%) had a dose reduction. Fourteen patients (18%) experienced ≥G2 thrombocytopenia and 27 (34%) experienced ≥G2 neutropenia. Twelve patients (15%) experienced neutropenic sepsis/febrile neutropenia, one resulting in death. Forty-nine patients (61%) experienced at least 1 non-haematological ≥G2 toxicity, most commonly nausea and vomiting (20, 26%), non-neutropenic infection (12, 15%) and fatigue (9, 12%). Six patients (8%) had suspected encephalopathy (3 at G3/4) (including one admission to intensive care), 3 (4%) experienced haematuria, 3 (4%) had electrolyte disturbances and 2 (3%) had confirmed acute kidney injury.

Conclusion: Infusional Ifosfamide is a viable treatment option in STS with notable clinical efficacy in SS patients with a median PFS of 8 months and median OS of 20 months. In BS, approximately 30% of patients gain clinical benefit, with likely greater efficacy in ES. Treatment is associated with toxicity that requires adequate supportive care and should be given in specialist centres.

Summary of patient demographics, radiological responses, clinical benefit rate (CBR), PFS and OS.

	Soft Tissue Sarcoma			Bone Sarcoma		
Number of Patients	46			34		
Median Age (range)	43 (18-72)			23 (12-64)		
% Male	48%			62%		
Median previous chemotherapy lines (range)	1 (0-4)			2 (0-5)		
Median number of cycles (range)	4 (1-24)			3 (1-8)		
% CBR PD non-assessable	50% (23) 11 (24%) 12 (26%)			30% (10) 17 (50%) 7 (21%)		
Median PFS	3.8 months			2.5 months		
Median OS	13.0 months			6.2 months		
Prior ifosfamide	24 (52%)			23 (68%)		
Subgroup Analysis	Synovial Sarcoma (15)	Liposarcoma (13)	Other (18)	Ewing Sarcoma (16)	Osteosarcoma (13)	Other (5)
% CBR	80%	38%	33%	38%	15%	40%
Median PFS	8.1 m	3.4 m	2.7 m	3 m	2.5 m	2.1 m
Median OS	20.9 m	11.2 m	12.7 m	8.3 m	6.9 m	3.9 m

For those patients with liposarcoma, 7 patients had de-differentiated liposarcoma, 3 were myxoid, 2 were well-differentiated and 1 was pleomorphic. Other histological subtypes for STS include spindle cell sarcoma (NOS) (4), malignant peripheral nerve sheath tumour (3), epithelioid sarcoma (3), fibrosarcoma (2), leiomyosarcoma (2), rhabdomyosarcoma (1), round cell tumour (1), intimal sarcoma (1) and unclassifiable STS (1). Other subtypes for BS were mesenchymal chondrosarcoma (3), de-differentiated chondrosarcoma (1) and unclassifiable BS (1).

Poster #292 3247644

INFLAMMATORY TYPE UNDIFFERENTIATED PLEOMORPHIC SARCOMA TREATED WITH DOXORUBICIN, IFOSFAMIDE AND PREDNISOLONE. REPORT OF TWO CASES

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Objective: Undifferentiated pleomorphic sarcoma (UPS) is one of the most common soft tissue sarcomas in late adult life. Inflammatory subtype of UPS, formerly referred to as inflammatory malignant fibrous histiocytoma (MFH) have been reported to demonstrate systematic inflammatory symptoms, such as fever, leukocytosis with neutrophilia, and elevated C-reactive protein (CRP) level. These paraneoplastic symptoms (PNS) have been reported to be associated with poor prognosis. Treatment consists of surgery while the role of radiotherapy and chemotherapy remains controversial. There are no reports for treatment specifically for inflammatory UPS. We here report two cases of inflammatory UPS, which had good response to neoadjuvant chemotherapy consisting of doxorubicin, ifosfamide and prednisolone.

Methods: Two cases of inflammatory UPS treated at our institute were reviewed. Clinical, image, surgical and histological details were collected and analyzed.

Results: Case 1. A 45 year old male presented with a 18 cm soft tissue tumor of the right upper arm. Biopsy revealed UPS. Patient presented with high fever (39.5°C) and pretreatment blood test showed elevated CRP (21.04 mg/dl) and leukocytosis (WBC 15400/mm^3). Neoadjuvant chemotherapy consisting of doxorubicin and ifosfamide (AI) was administered. After two cycles, tumor grew to 20 cm and PNS persisted. From the third cycle, prednisolone (20 mg oral daily) was added to AI. After five cycles, tumor shrunk to 14 cm and PNS subsided. Blood test showed normal CRP (0.16 mg/dl) and WBC (3000/mm^3) counts. Wide resection surgery of tumor was performed and histology revealed 90% tumor necrosis. Two cycles of adjuvant chemotherapy and radiotherapy was administered. The patient is CDF at 40 months. Case 2. A 47 year old female presented with a 10 cm soft tissue tumor of the right thigh. Biopsy revealed UPS. Patient presented with high fever (38.1°C) and pretreatment blood test showed elevated CRP (25.87 mg/dl) and leukocytosis (WBC 10300/mm^3). Neoadjuvant chemotherapy (AI) was administered. After two cycles, tumor grew to 15 cm and PNS persisted. From the third cycle, prednisolone (30 mg oral daily) was added to AI. After seven cycles, tumor shrunk to 8 cm and PNS subsided. Blood test showed normal CRP (0.09 mg/dl) and WBC (4700/mm^3) counts. Wide resection surgery of tumor was performed and histology revealed 80% tumor necrosis. The patient is CDF at 9 months.

Conclusion: We experienced two cases of inflammatory UPS which did not initially respond to chemotherapy but had good response after prednisolone was added.

Poster #293 3248538

BCOR SARCOMAS: A CASE SERIES WITH A NEWBCOR/CCNB3 FUSION GENE VARIANT

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Objective: To analyze the incidence of BCOR alterations in the population of Ewing-like sarcomas referred to Department of Pathology, Aghia Sofia Children's Hospital.

Methods: We included 13 patients with the diagnosis of a Ewing-like sarcoma.

Histopathology: Although round cell morphology was a predominant feature of the neoplasms, cell spindling, clear cell cytology and myxoid stroma were frequent and suggestive features of undifferentiated sarcomas with BCOR alterations. Moreover, the heterogeneous CD99 immunohistochemical expression, mainly cytoplasmic, the diffuse membranous expression of CD56 and absence of Fli-1detection supported the morphological suspicion. All cases were negative for EWSR1/ETS fusions.

Genetics: Total RNA was extracted from FFPE sections using NucleoSpin total RNA FFPE Mini Kit (Macherey-Nagel,GmbH, Germany), according to the manufacturer's instructions. Approximately 500ng of total RNA was reverse transcribed using the SuperScript II Reverse Transcriptase (Invitrogen, Carlsbad USA) and random hexamers. cDNA was subjected to PCR analysis, for the detection of the BCOR/CCNB3 fusion gene using Platinum TAQ Polymerase (Invitrogen, Carlsbad USA), with specific primers, as listed:

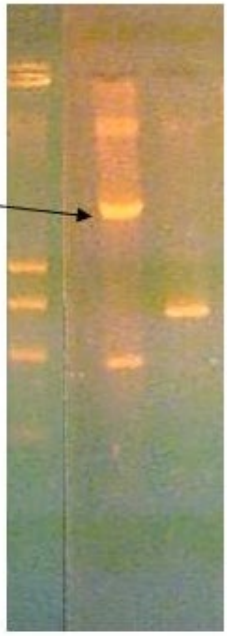
BCOR3.1F: 5'-GGCAGGTTTCTGCAAGTCTC-3'
CCNB3.1R: 5'-AGATGCCTCCTCAGTGTTGG-3'
CCNB3.1R NEW: 5'-GCTTCAGACGGGACCTCTTC-3'

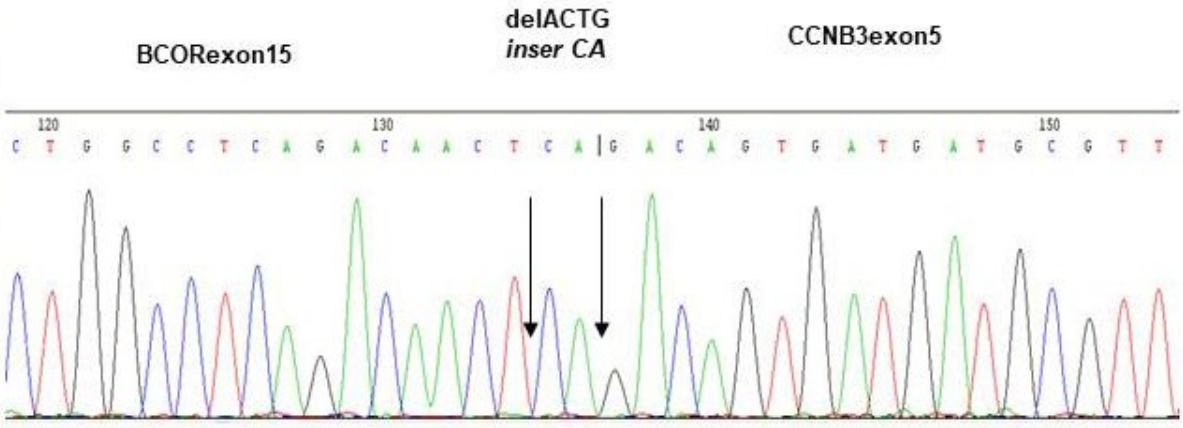
PCR conditions were: 40 cycles of 94°C for 50sec, 60°C for 40sec and 72°C for 1min. PCR products were analyzed in agarose gel electrophoresis and subjected to Sanger sequencing analysis. GAPDH was also transcribed as housekeeping gene to monitor the integrity of the isolated RNA material.

Fluoresence in situ hybridization (FISH): Formalin-fixed, paraffin-embedded biopsy blocks from the specimen selected by pathologist were analyzed for the detection of translocations involving the BCOR gene at Xp11.4. A section of 4 μm was cut from the selected block and applied to silinized slides. For hybridization procedures, the FISH probe "BCOR split FISH probe by Abnova" was used. Probe mixture was applied onto the areas of interest on the slides according to the manufacturer's instructions. Hybridization signals were counted by the use of a Zeiss Axioplan fluorescence microscope equipped with the appropriate filter combination and the ISIS digital imaging system and software (Metasystems, Germany).

Results: Histopathology favored the diagnosis of Ewing-like sarcomas in 13 cases. Among these samples, 5 were found to express the BCOR/CCNB3 chimeric gene with FISH analysis and reverse transcription PCR. The fusion gene products detected in 4 of the examined cases were similar to the previously reported BCOR exon 15 CCNB3 exon5. In one of these 5 samples, an alternative chimeric product of the same two partners was detected. When PCR products were analyzed in agarose gel, there was a product of 500bp as anticipated and a second band of a higher molecular weight, approximately 700bp. To further clarify this, PCR products were analyzed by Sanger sequencing, which revealed the existence of the well described fusion product (500bp) and of an alternative chimeric product (700bp). The latter is the result of the fusion of the same two partners in a different break point for the CCNB3 gene, giving rise to a slightly longer transcript. This alternatively spliced variant consists of the first fifteen exons of BCOR joined to a part of the CCNB3 exon 5. The new fusion gene was also found to present a 4 nucleotide deletion with a synchronous 2 nucleotide insertion in the BCORexon15 CCNB3 exon 5 junction leading to an out of frame fusion product.

Conclusion: Herein we report the experience of referral center in Greece of undifferentiated sarcomas sharing BCOR alterations. We present 5 cases with BCOR-CCNB3 fusion. One of the latter cases appeared with a not previously described alternative fusion variant.




BCORexon15
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Poster #294 3252967

HEPATIC METASTASES FROM SOFT TISSUE SARCOMA

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Objective: Hepatic metastases from soft-tissue sarcoma is rare compared to lung metastases. Although hepatic metastases are more frequently found in the abdominal cavity and the retroperitoneum, the evidence in the literature is scarce. We examined the difference in the incidence of hepatic metastasis based on the site of occurrence and histologic type.

Methods: Between 2007 and 2017, we examined patients with soft-tissue sarcomas who were registered in the Hospital-based Cancer Registry of the Hokkaido Cancer Center. The exclusion criteria were as follows: gastrointestinal stromal tumors, tumors of unknown origin, and follow-up periods of less than 1 month. Outcome measures included age, gender, size, site of occurrence, histologic type, follow-up period, outcome, presence or absence of hepatic metastasis, and timing of indication for hepatic metastasis. SPSS 25 was used for statistical analysis.

Results: Of 687 cases of soft-tissue sarcomas, 13 cases were gastrointestinal stromal tumors, 1 case was of an unknown primary site, and 15 cases were censored at less than 1 month. A total of 658 cases remained after these exclusions, comprising of 323 males and 335 females with a median age at first visit of 65.0 years (range, 1-96). Two hundred and seventy-six were 10 cm or more in size. The main sites of occurrence included 376 extremities, 124 superficial layers of the body, and 74 retroperitoneal cavities. Hepatic metastases were observed in 14 extremities, 13 retroperitoneums, and 6 thoracoabdominal organs, occurring more frequently in the retroperitoneum (hazard ratio, 5.981; 95% confidence interval, 2.793-12.808) and thoracoabdominal organs (hazard ratio, 3.355; 95% confidence interval, 1.283–10.390). The histological types were as follows: 209 cases of adipocytic tumors, 170 cases of undifferentiated/unclassified sarcomas, and 69 cases of smooth muscle tumors (leiomyosarcoma). Hepatic metastases were found in 13 cases of leiomyosarcoma, 8 cases of undifferentiated/unclassified sarcoma, and 5 cases of adipocytic tumors, with metastases occurring more frequently from leiomyosarcomas (hazard ratio, 4.303; 95% confidence interval, 1.782-10.390). According to multivariate analysis, the incidence of liver metastasis was high in leiomyosarcoma (hazard ratio, 4.546; 95% confidence interval, 2.275-9.086) and retroperitoneal onset (hazard ratio, 4.588; 95% confidence interval, 2.280-9.231) (Table). The 1-year survival rate after detection of hepatic metastasis was 36.1%.

Conclusion: Retroperitoneal sarcomas and leiomyosarcomas had a high incidence of hepatic metastases. Although chest CT is often utilized in screening, staging, and follow-up of metastasis, additional abdominal CT should be considered for retroperitoneal sarcoma and leiomyosarcoma.

Cox proportional hazard model

	Univariate			Multivariate		
	Hazard Ratio	95% CI	P value	Hazard Ratio	95% CI	P value
Leiomyosarcoma	6.975	2.836 – 17.155	<0.001***	5.589	2.223 – 14.053	<0.001***
Retroperitoneal	5.739	2.339 – 14.081	<0.001***	4.505	1.797 – 11.296	0.001**
Thoracic and peritoneal	2.154	0.627 – 7.399	0.223	—	—	—

CI; Confidence interval

Poster #295 3253032

RETROSPECTIVE ANALYSIS OF ADJUVANT TREATMENT FOR LOCALIZED, OPERABLE UTERINE LEIOMYOSARCOMA

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Objective: 1. To Evaluated the influence of clinical characteristics and adjuvant therapy on outcomes
2. To Identify variables independently associated with DFS

Methods: We reviewed the medical records of patients with uterine leiomyosarcoma who underwent upfront surgery between 2000-2018. We evaluated the influence of clinical characteristics and adjuvant therapy on outcomes. Patient characteristics and treatment outcomes were described using descriptive statistics. Kaplan-Meier survival analysis was used to estimate disease-free survival(DFS) and comparisons between groups were by the log-rank test. To identify variables independently associated with DFS, variables with a *p*-value<0.05 in univariate analysis were included in multivariate analyses by Cox proportional hazard regression. A two-tailed *p*-value less than 0.05 was considered statistically significant for all tests.

Results: 59 patients with a median age of 52 years were analyzed and the median time from surgery to adjuvant treatment was 47 days. 48/59 (81.4%) underwent TAH-BSO. 64.4% were FIGO stage I, 16.9% were stage II and 6.7% were stage III. The median tumor size was 11 cm (range: 3-21cm) and the median mitotic rate was 13 mitoses/ 10 high-power fields (HPF), (range: 1-63). 34/59 (57.6%) of patients received adjuvant chemotherapy +/- radiation therapy and 25 patients (42.3%) did not receive adjuvant treatment. With a median follow-up time of 42.8 months, 42 patients (71.2%) had disease relapse and 15 (35.7%) had pulmonary metastases. The median disease-free survival (mDFS) for all patients was 23.1 months. Any adjuvant treatment (chemotherapy or radiation) had a trend toward longer mDFS than no adjuvant treatment (36.6 vs 13.6 months, p=0.14). Patients who had adjuvant chemotherapy had a non-significant longer mDFS compared with those who did not receive any adjuvant treatment (33.8 *vs* 13.6 months, p=0.18). Subgroup analysis of patients with stage I disease showed that, though there was a trend towards higher mDFS in the chemotherapy group, it was not statistically significant (29.7 vs 16.6 months, p=0.59). Multivariate analysis found that the independent prognostic factors for worse DFS included tumor size larger than 10 cm, and mitotic rate over 10/ 10HPF. More morcellated specimens were found in non-adjuvant treatment arm (36%) compare to 8% in adjuvant arm. In the non-treatment arm, 14 patients had recurrences within 6 months.

Conclusion: In a retrospective uLMS population, the mDFS was 23.1 months. Tumor size >10cm and mitotic rate >10/10 HPF were independent prognostic factors for lower DFS. The non-treatment group had a significantly higher number of patient who underwent morcellization and relapsed within 6 months, confounding analyses of the impact of adjuvant chemotherapy.

Table 1. Patient and disease characteristics of localized uterine leiomyosarcoma

Characteristic	Value
Type of surgery, n (%) - TAH with BSO* - Total hysterectomy - Supracervical hysterectomy - TAH with BSO and extended debulking surgery Morcellated specimen, n (%)	48 (81.4) 3 (5.1) 1 (1.7) 7 (11.1) 12 (20.3)
Median tumor size (range), cm. Not applicable, n (%)	11(3-21) 10(16)
Median mitotic rate/10HPF (range) Not applicable, n (%)	13 (1-63) 11 (18)
Margin, n (%) - R0 - R1 - R2 - Not applicable	36 (61) 6 (10.2) 2 (3.4) 15 (25
FIGO stage, n (%) - I - II - III - Not applicable	38 (64.4) 10 (16.9) 4 (6.7) 7 (11.9)
Any adjuvant treatment, n (%) Adjuvant chemotherapy, n (%) - Chemotherapy alone - Chemotherapy plus radiation Chemotherapy agent, n (%) - Gemcitabine + Docetaxel - Gemcitabine + Docetaxel followed by Doxorubicin - Doxorubicin + Ifosfamide - Chemoradiation with Ifosfamide followed by Gemcitabine + Docetaxel - Aldoxorubicin - Immunotherapy (unknown) Adjuvant radiation alone, n (%) Adjuvant letrozole, n (%) No adjuvant treatment, n (%)	34 (57)) 31 (52) 23 (38.9) 8 (13) 25 (80.6) 2 (6.5) 1 (3.2) 1 (3.2) 1 (3.2) 1 (3.2) 2 (3.3) 1 (1.6) 25 (42.3)

Table.2 Baseline characteristics according to adjuvant treatment

	Any adjuvant treatment (chemo +/- radiation) (n= 34)	No adjuvant treatment (n= 25)
FIGO stage, n(%) - I - II-III - Missing data	21 (21/34, 61.7%%) 10 (10/34, 29.4%) 3 (3/24, 8.8%)	21 (21/29, 72.4%) 4 (4/29, 13.7%) 4 (4/29, 13.7%)
Median tumor size, cm.(range) - Missing data	10.0 (4-21) 5	10.5 (3-16) 6
Median mitotic rate, per10HPF (range) - Missing data	13.0 (1-60) 5	15 (1-63) 7
Margin, n (%) - R0 - R1 - R2 - Not applicable	18 (52.9) 5 (14.7) 1 (2.9) 10 (29.4)	18 (72) 1(4) 1(4) 5 (20)
Morcellated specimen, n	3(8)	9(36)

Poster #296 3253257

ASSOCIATIONS BETWEEN TREATMENT PATTERNS AND DISTANCE TO TREATING FACILITY AMONG PATIENTS WITH SOFT TISSUE SARCOMA OF THE EXTREMITY

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Objective: The impact that distance travelled to a treatment facility has on treatment patterns and outcomes among patients with soft tissue sarcoma (STS) of the extremity have yet to be thoroughly investigated.

Methods: Information on patients treated for STS of the extremity between 2006 and 2015 was obtained from the National Cancer Database (NCDB). The median distance between patients' residence and their treatment facility was calculated and used to stratify patients into two groups: those who travelled less than the median distance and those who travelled greater than the median distance. Chi-square tests were used to test associations between categorical variables and distance to treatment. Kaplan-Meir survival estimates were calculated, and Cox regression was used to estimate the risk of cause-specific death.

Results: The sample included 21,763 patients with STS of the extremity. Mean age was 59.3 years, 54.6% were male, and 83.2% were white. The median distance travelled to treating facility was 15.6 miles. When stratified by distance to treatment, 49.0% travelled < 15 miles and 51.0% travelled ≥ 15 miles. Patients who travelled ≥ 15 miles were more likely to have undifferentiated rather than well-differentiated tumors (OR=1.21; 95% CI: 1.11-1.33), and stage II (OR=1.16; 95% CI: 1.07-1.25) or stage III (OR=1.22; 95% CI: 1.13-1.32) disease rather than stage I disease compared to patients who travelled < 15 miles. Also, patients who travelled ≥ 15 miles to treatment were more likely to be treated at an academic rather than non-academic facility (OR=2.44; 95% CI: 2.30-2.59), undergo limb-sparing resection (OR=1.60; 95% CI: 1.46-1.77) or amputation (OR=1.96; 95% CI: 1.69-2.28) rather than no surgery, and receive chemotherapy (OR=1.26; 95% CI: 1.18-1.35) compared to patients who travelled < 15 miles. There was no difference in the risk of cause-specific death between patients who travelled ≥ 15 miles and those who did not (HR=1.00; 95% CI: 0.93-1.06).

Conclusion: Further research into reasons why greater distance travelled is associated with more advanced disease but comparable survival is warranted.

Poster #297 3253345

BRAIN METASTASIS FROM SARCOMA

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Objective: Sarcomas are rare heterogeneous malignancies of mesenchymal origin, which comprise merely 1 % of all forms of cancer in the adult population. The lung is the most common site for distant metastases for most sarcomas, and brain metastasis from sarcoma is very rare. Early detection and early start of treatment should be important because brain metastasis is directly linked to patients' prognosis and quality of life. However, literature regarding sarcoma brain metastasis is limited, and the characteristics of brain metastasis from sarcoma is still unknown. In this study, we aimed to analyze the clinical characteristics of brain metastasis in sarcoma patients, and to ascertain the treatment options for brain metastasis from sarcoma.

Methods: We retrospectively reviewed a total of 650 sarcoma patients (561 patients with soft tissue sarcoma and 89 patients with osteosarcoma) treated in Kobe University and Hyogo Cancer Center between 1998 and 2016. 6 of 650 soft tissue sarcoma and osteosarcoma patients developed brain metastasis. We collected clinical, pathological and survival data of the patients, and seek to characterize the incidence, treatments and prognosis of brain metastasis from sarcoma.

Results: Of 650 sarcoma patients, 6 patients (0.92%) were identified with brain metastasis (5 males and 1 female). Mean age at a diagnosis of primary tumor was 49.3 years (36-77), and the overall time from primary tumor diagnosis to the brain metastasis was 31.3 months[KT1] (8-59). Among 6 patients, 5 different histologic subtypes were identified; 2 synovial sarcoma, 1 myxoid liposarcoma, 1 alveolar soft part sarcoma (ASPS), 1 rhabdomyosarcoma, and 1 osteosarcoma. In histologic subtypes, ASPS may tend to metastasize to brain with a 25% incidence (1/4) compared to other subtypes, although there were limited cases. The incidence in others was 4.44% in synovial sarcoma (2/45), 1.82% for myxoid liposarcoma (1/55), 7.69% in rhabdomyosarcoma (1/13) and 1.12% in osteosarcoma (1/89). In all 6 patients, brain metastasis was solitary, and distant metastasis in other sites, the most frequent in the lung, was observed prior to brain metastasis. The treatments for brain metastasis were varies, surgery only (n=1), radiation only (n=2), surgery and post-operative radiation (n=2), and none (n=1).[KT2] The mean duration of survival in 5 patients who underwent treatment was 5.7 months (1-14). The duration in 2 patients who were treated by surgery and post-operative radiation (11 months) was significantly longer compared to other 3 patients (2.2 months) (p=0.01) and the brain metastasis free period in 2 patients who were treated by surgery and post-operative radiation (37.5 months) was also significantly longer compared to other 3 patients (16.8 months) (p=0.04). Age at initial diagnosis and maximum size of primary tumor were not significantly differences between these two groups. Five of 6 patients died during follow-up, and 1 patient survives without a recurrence of brain metastasis at eight months after treatment.

Conclusion: In the present study, we revealed that brain metastasis from sarcoma is very rare with 0.92% incidence for 19 years period. Although the incidence is very low, we should be careful with the patients' symptoms to keep in mind that brain metastasis can occur in sarcoma patients, especially ASPS patients. In treatment options, we revealed that surgery and post-operative radiation may offer survival benefit for the patients. Although further investigation is needed, the findings in the current study suggest that surgery and post-operative radiation should be considered as a therapeutic option for sarcoma brain metastasis.

Poster #298 3253682

IDENTIFYING TUMOR SPECIFIC ANTIGENS IN SARCOMA PATIENTS WITH TUMOR REACTIVE T-CELLS: AN ANALYSIS OF MUTATIONS, NEOANTIGEN PEPTIDES AND EFFECTOR FUNCTIONS

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Objective: From selected sarcoma patients with high autologous tumor reactive TILs:
1) Identify tumor mutational burden (TMB) in sarcomas with both simple and complex karyotypes
2) Determine HLA I expression and predict neoantigens
3) Screen for T-cell specificity against candidate neoantigens in tumor reactive TIL cultures

Methods: *In vitro* expanded TILs from 20 sarcoma patients were screened for recognition of autologous tumor cells using ELIspot and flow cytometry.

Tumor samples and established tumor cell lines underwent whole exome sequencing (WES) wherefrom neoantigens were predicted. The data were analyzed using a custom pipeline in which sequencing reads were initially aligned using the bwa-mem algorithm to the latest version of the reference human genome (hg38/GRCh38). Only somatic variants were kept in the downstream analysis and neoantigen peptides of 8-11 amino acids which contain the variants were designed. Moreover, the WES data were used to extrapolate the HLA type/allele information for each patient using optitype v.1.3.2. Subsequently, the binding affinities of the HLA alleles to the neoantigen peptides were calculated using the NetMHCpan v.4.0 software. Finally, the MuPeXI v.1.2.0 was used to predict immunogenicity by providing a priority score for each neoantigen peptide.

Results: TILs from 10 sarcoma patients showed recognition of autologous tumor. Tumor samples from four patients (two undifferentiated pleomorphic sarcomas, one myxofibrosarcoma, and one inflammatory myofibroblastic sarcoma) were selected for prediction of potential neoantigens. Generally, the TMB in the four tested samples were low (range 1.20e-05 to 6.40e-06). The number of potentially neoantigens for the HLA-A, HLA-B an HLA-C alleles varied in the 4 patients. We identified 14988 unique neoantigens for patient S1, 3707 unique neoantigens for patient S14, 3592 unique neoantigens for patient S5 and 1843 neoantigens for patient S26.

A range of candidate epitopes will be selected from each patient for synthesizing peptides, and screening for recognition among tumor reactive TILs using ELIspot and flow cytometry.

Conclusion: We have found tumor reactive, *in vitro* expanded TILs in 50% of the screened patients with various sarcoma subtypes. TILs from four patients were highly tumor reactive, and tumor samples were selected for WES and RNA sequencing. As expected, the TMB were low and the predicted potential neoantigens ranged from 1843 to 14988 unique antigens for the HLA-A, -B and -C alleles. Next, we aim at defining relevant epitopes and determining the quality/relevance of a given set of neoepitopes in tumor recognition by analyzing T-cell effector function. Our findings could potentially improve adoptive cell transfer based treatments of sarcoma patients, for which early results from single epitope (NY- ESO 1) targeted therapy are promising.

Poster #299 3253949

POPULATION PHARMACOKINETIC ANALYSIS FOR COMPARISON OF PEXIDARTINIB EXPOSURE IN ASIAN AND NON-ASIAN PATIENTS

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Objective: Pexidartinib is a novel, small molecule tyrosine kinase inhibitor that targets colony-stimulating factor 1 receptor and shows significant antitumor activity in patients with tenosynovial giant cell tumor (TGCT). We previously reported a pooled population pharmacokinetic (PK) analysis of pexidartinib in healthy subjects and patients with TGCT or other solid tumors. This updated analysis included three additional studies with Asian patients to further evaluate the population PK and the exposure of pexidartinib and its glucuronide metabolite (ZAAD-1006a) in Asian and non-Asian patients.

Methods: Data were from twelve clinical studies with a total of 422 subjects who had PK data available, i.e., seven phase 1 clinical pharmacology studies in healthy subjects (n=159), four phase 1 studies (including the three additional studies) in patients with TGCT or other solid tumors (n=179), and one phase 3 study in patients with TGCT (n=84). In healthy subjects, pexidartinib was given as a single oral dose of 200 mg to 2400 mg, and in patients it was given as multiple oral doses of 200 mg/day to 1200 mg/day. Overall, 30 of 422 subjects (7.11%) were Asian, of whom 3 were healthy subjects enrolled in phase 1 clinical pharmacology studies and 27 were patients. Analysis was performed by using nonlinear mixed effects modeling (NONMEM), where pexidartinib and ZAAD-1006a PK was described separately by a two-compartment model with sequential zero- and first-order absorption with a lag time and linear elimination. Among the assessed covariate effects in the final selected model, Asian race and body weight effects on pexidartinib and ZAAD-1006a clearance (CL/F) were included. Steady state exposures of pexidartinib and ZAAD-1006a in individual subjects were obtained using the corresponding individual PK parameters from the final PK model and a dose regimen of 400 mg twice daily (800 mg/day). Comparison of pexidartinib and ZAAD-1006a exposure was made between Asian and non-Asian patients, since there were only 3 Asians in the healthy subject population.

Results: Observed concentrations of pexidartinib and ZAAD-1006a in Asian subjects were within the overall concentration range in all subjects. Pexidartinib CL/F is estimated to be 6.20 L/hr for a typical Asian patient with body weight of 63 kg, comparable to the estimated value of 5.79 L/hr for a typical non-Asian patient with body weight of 80 kg. When comparing Asian versus non-Asian patients, model-predicted steady state area under the concentration-time curve over 24 hours (AUC_{0-24}) of pexidartinib and ZAAD-1006a were found to be similar between the two groups (Figure). The median AUC_{0-24} of pexidartinib was 145 µg ● hr/mL (5th–95th percentile: 63.4–231 µg ● hr/mL) and 138 µg ● hr/mL (5th–95th percentile: 82.3–250 µg ● hr/mL), respectively, in Asian (n=27) and non-Asian (n=236) patients; whereas the median AUC_{0-24} of ZAAD-1006a was 273 µg ● hr/mL (5th–95th percentile: 145–526 µg ● hr/mL) and 271 µg ● hr/mL (5th–95th percentile: 144–595 µg ● hr/mL), respectively, in Asian (n=16) and non-Asian (n=109) patients.

Conclusion: Analysis suggests that pexidartinib and its glucuronide metabolite (ZAAD-1006a) exposures are similar between Asian and non-Asian patients.

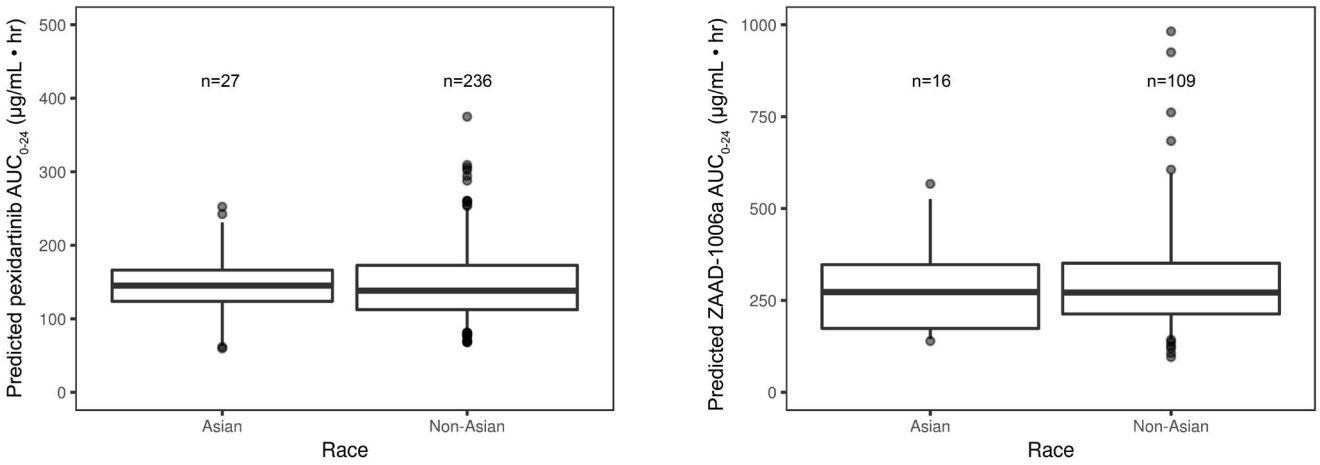

Figure. Steady state exposure of pexidartinib (left panel) and ZAAD-1006a (right panel) in Asian and non-Asian patients.

n=number of patients with available exposure value in each category. Box refers to the first (Q1) to third quartiles (Q3), and horizontal line within the box is median or second quartile (Q2). Whisker is 5th and 95th percentiles.

Poster #300 3254451

REAL WORLD CLINICAL PROGNOSITC FACTORS AND EFFICACY OF UPFRONT WEEKLY PACLITAXEL FOR ADVANCED ANGIOSARCOMA PATIENTS

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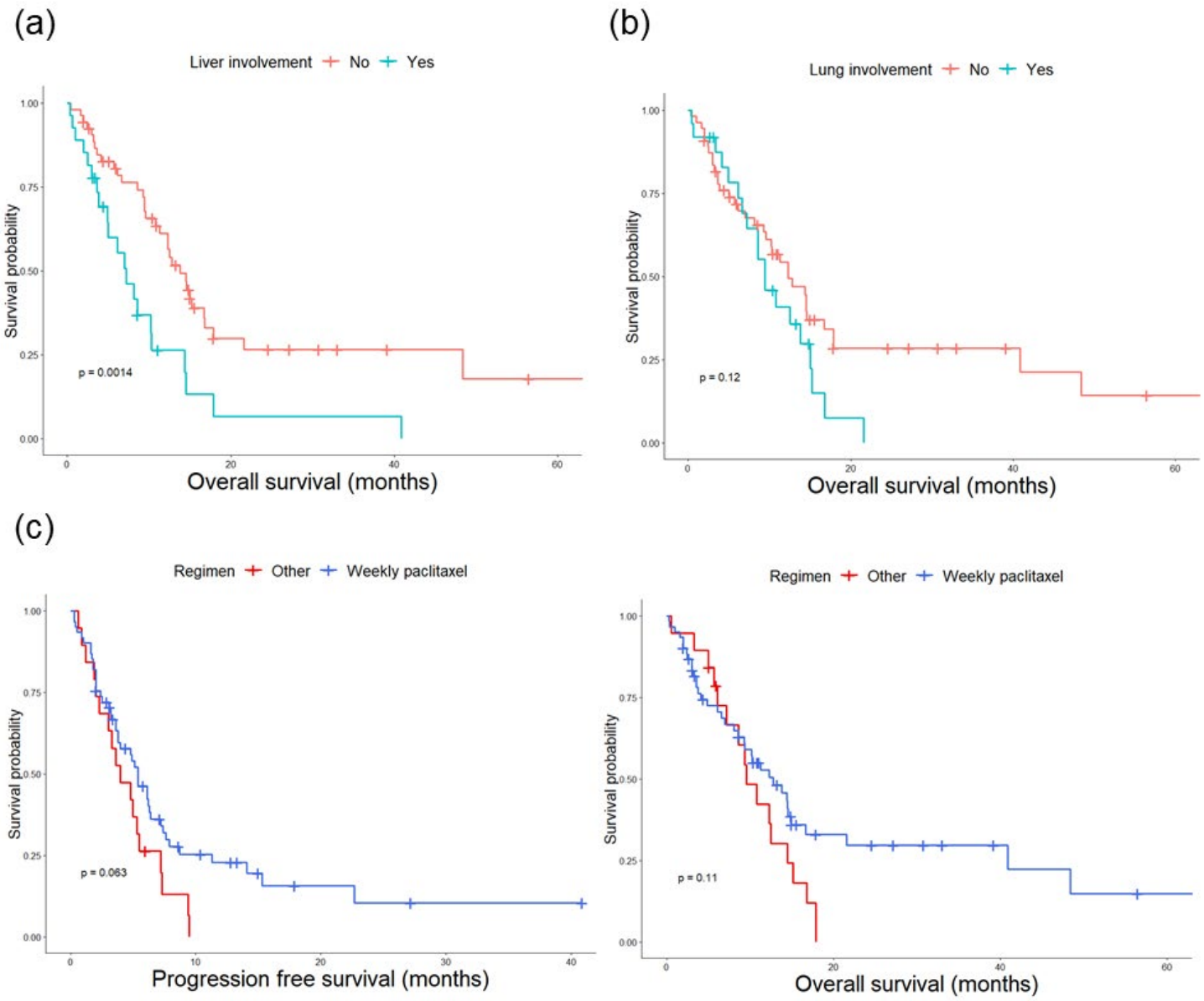
Objective: Angiosarcoma is a rare mesenchymal malignant tumor with a highly aggressive clinical course. Although weekly paclitaxel and doxorubicin-based chemotherapy regimens are widely used for advanced angiosarcoma, standard of care remains controversial. Here we describe single center retrospective analyses of clinical outcome of advanced angiosarcoma.

Methods: We reviewed electronic medical records of 80 patients with angiosarcoma at Seoul National University Hospital who were treated with systemic chemotherapy for at least once in the setting of advanced stage, defined as inoperable or metastatic disease. Demographic, pathologic, radiologic and treatment data were collected and analyzed to determine prognostic factors. Tumor responses were evaluated using RECIST 1.1 criteria.

Results: Among the 80 patients, median age was 61.5 (range 27 ~ 80) and 53 patients (66.3%) were male. Scalp was the most common primary site (N = 19, 23.8%), followed by liver (N = 16, 20%). Liver, lung and bone involvements were found in 27 (33.8%), 25 (31.3%) and 25 (31.3%) patients, respectively. Median overall survival (OS) was 12.3 months (95% confidence interval 9.4 ~ 14.6 months). Liver and lung involvements were significant independent prognostic factors for OS ($p < 0.001$ and $p = 0.038$ respectively in multivariate analysis) while primary sites and bone involvements were not significant prognostic factor ($p = 0.58$ and $p=0.54$, respectively). Total of 61 patients received weekly paclitaxel as 1st line chemotherapy, and the rest of the patients received either one of doxorubicin-based chemotherapy (n = 9) or non-doxorubicin-based chemotherapy (n = 10). Objective response rate was 27.9% for weekly paclitaxel not statistically different to 21.6% for the other regimens ($p = 0.77$). Progression free survival (PFS) and OS tended to be longer in the patients who received weekly paclitaxel than other regimens (median PFS 5.4 vs 4.0 months, $p = 0.063$ and median OS 12.8 vs 9.6 months, $p=0.11$). The survival differences were significant in the patients without liver involvement, favoring weekly paclitaxel (median PFS 6.1 vs 3.5 months, $p = 0.03$ and median OS 15.0 vs 12.3 months, $p = 0.05$). However, treatment regimens were not associated with survival in patients with liver involvement (weekly paclitaxel vs other regimens, median PFS 3.8 vs 5.0 months, $p = 0.9$ and median OS 8.1 vs 6.1 months, $p = 0.7$).

Conclusion: In the advanced angiosarcoma patients, not the primary site but the involved sites especially the liver and lung were significantly associated with poor prognosis. Treatment with upfront chemotherapy with weekly paclitaxel regimen seems effective and may provide survival benefit especially for patients advanced angiosarcoma without liver involvement.



Kaplan-Meier curves showing survival of advanced angiosarcoma patients. (a) Survival curves showing overall survival according to involvement of liver, blue(red) line representing patients with(without) liver involvement. (b) Survival curves showing overall survival according to involvement of lung, blue(red) line representing patients with(without) liver involvement. (c) Survival curves showing progression free survival and overall survival of 1st line chemotherapy. Blue line represents patients who received weekly paclitaxel and red line represents patients who received other regimens. Each of log rank p-value calculated by univariate analysis is shown on the bottom left of the plots.

Poster #301 3242595

VALUE OF A COMMUNITY-BASED MULTIDISCIPLINARY SARCOMA CASE CONFERENCE IN AN INTEGRATED HEALTHCARE SYSTEM

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Objective: Management of soft tissue and bone sarcoma is extremely challenging and requires multidisciplinary collaborations. Such collaborations, while critical for quality care, are often difficult to implement in both the academic and community settings.

Methods: We established a multidisciplinary sarcoma case conference in 2013 to routinely discuss all newly diagnosed and relapsed cases in Northern California Kaiser Permanente. This service was also provided to several other Kaiser Permanente regions including Hawaii and the Mid-Atlantic. The case conference is coordinated by a sarcoma medical oncologist, with participation from musculoskeletal oncology, surgical oncology, radiation oncology, pathology, pediatric oncology, musculoskeletal radiology, and genetics. We have also created a rapid case ascertainment system for identifying newly diagnosed sarcoma cases in a timely fashion.

Results: More than 1,300 cases have been discussed in the multidisciplinary sarcoma case conference. Approximately 50% of the cases were men and 50% women, with a median age of 57. Majority of cases were referred by medical oncology, musculoskeletal oncology and surgical oncology. More than 32 different histologic subtypes of sarcoma have been discussed. The most common histologic types were liposarcoma (16%), undifferentiated pleomorphic sarcoma (14%), and leiomyosarcoma (11%).The number of cases referred to the case conference increased substantially every year (more than 300 cases per year in 2017 and 2018). We performed three surveys for feedback by the referring physicians, approximately 6 months, 2 years and 6 years after the case conference was established. The results from thesurveys showed that the vast majority of the referring physicians felt the case conference improved the quality of care as well as their confidence in providing care to patients with sarcoma. The case conference often changed the management of patients. The survey also showed our sarcoma case conference has improved patient satisfaction as well.

Conclusion: Our multidisciplinary sarcoma case conference in an integrated healthcare system has improved the care quality, physician confidence in the management of the disease, as well as patient satisfaction. This can serve as a model for other healthcare systems in the management of rare and complex diseases such as sarcoma.

Poster #302 3245232

PROGNOSIS IN RECURRENT/METASTATIC SOFT TISSUE SARCOMA PATIENTS WI RETROPERITONEAL/ INTRA-ABDOMINAL ORIGIN RECEIVING SYSTEMIC CHEMOTHERAPIES COMPARED TO THOSE WITH EXTREMITIES/TRUNK ORIGIN

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Objective: To soft tissue sarcoma (STS) patients, there are differences of clinical benefits in perioperative chemotherapy by their primary sites, such as extremities, retroperitoneum or other visceral organs. In terms of salvage chemotherapy for recurrent/metastatic STS patients, however, whether there are differences of clinical benefits by their primary sites are unknown yet.

Methods: We retrospectively reviewed clinical records of STS patients consulting the department of medical oncology between June 2011 and March 2018, and extracted patients with primary site of retroperitoneum/intra-abdomen (cohort R) and extremities/trunk soft tissue (cohort E) who received systemic chemotherapies as recurrent/metastatic setting. The characteristics, details of chemotherapy and prognoses of each cohort were compared.

Results: Of all 337 STS patients, 49 patients in cohort R and 77 patients in E cohort were enrolled in the analyses. Liposarcoma was most frequently observed in cohort R (51.0%); in cohort E, liposarcoma was also observed in relatively high rate (22.1%), but the frequency was lower than in cohort R. Median chemotherapy treatment line was 2 cycles (range: 1-6) in cohort R and 3 cycles (range: 1-9) in cohort E. Doxorubicin was highly used in cohort R (90.0%) in than cohort E (54.5%) in recurrent/metastatic setting because many patients in cohort E had treatment history of preoperative chemotherapy (6.1% in cohort R and 50.6% in cohort E) and doxorubicin was had been already used in preoperative treatment setting. Median overall survival from the start of salvage chemotherapy was 31.9 months (95%CI: 20.9-42.8) in cohort R and 24.2 months (95%CI: 19.3-29.1) in cohort E (p=0.698).

Conclusion: Between retroperitoneal/intra-abdominal and extremities/trunk sarcoma patients in recurrent/metastatic setting, there were differences in distributions of pathology or antitumor drugs used as salvage setting, but prognoses with salvage chemotherapy were similar in both groups.

Poster #303 3253268

ESTABLISHMENT OF AN ACADEMIC TISSUE MICROARRAY PLATFORM AS AN EFFICIENT TOOL FOR SOFT TISSUE SARCOMA RESEARCH

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Objective: Soft tissue sarcoma (STS) is a rare and heterogeneous family of mesenchymal tumors, characterized by morphological and genetic diversity. Histopathology and molecular profiling, relying on the availability of archival material, is used in both clinical routine and in sarcoma research. Tissue microarrays (TMAs) from sarcoma tissue blocks have potential advantages over conventional tissue analysis from individual patients in terms of efficiency and cost-effectiveness. Since 2015 we have built TMAs in the Laboratory of Experimental Oncology at KU Leuven (Leuven, Belgium), using left-over archival material available from STS patients.

Methods: For the TMA construction, donor blocks were selected according to the following criteria: blocks with sufficient tumor tissue and height at least 3 mm from STS patients diagnosed at the University Hospitals Leuven, Leuven, Belgium; Leiden University Medical Center, Leiden, The Netherlands and University Hospital Zürich, Zürich, Switzerland, and STS patients enrolled in EORTC phase 2 trial 90101 "CREATE". Cases included in the TMAs are well annotated in terms of pathological diagnosis, treatment and clinical follow-up. Each TMA block contains duplicate or triplicate 1.0-1.5 mm tissue cores from representative areas selected by reference sarcoma pathologists. The construction of TMAs was performed with TMA Grand Master (3DHistech) at the Translational Research Unit at University of Bern, Switzerland or in Leiden, The Netherlands.

Results: At present we have created TMAs from the following STS subtypes: clear cell sarcoma (CCSA, 22 and 32 cases per TMA block), alveolar soft part sarcoma (ASPS, 12 and 47), inflammatory myofibroblastic tumor (IMFT, 12 and 21), alveolar rhabdomyosarcoma (24) and leiomyosarcoma (55). For CCSA, ASPS and IMFT we have separate TMAs from local clinical cases and from EORTC 90101 "CREATE". For drug- and target-screening purposes in a broader range of STS we also made TMAs representing multiple, most common subtypes: angiosarcoma, dedifferentiated, pleomorphic and myxoid liposarcoma, leiomyosarcoma, malignant peripheral nerve sheath tumor, myxofibrosarcoma, rhabdomyosarcoma, synovial sarcoma and undifferentiated pleomorphic sarcoma, with 7-11 individual cases per tumor type. TMA construction is still ongoing in other relevant sarcoma subtypes.

Conclusion: We have built and are currently expanding a ready to use TMA platform representing the broad heterogeneity of STS. TMAs are available for rapid and cost-effective morphological, immunohistochemical and molecular characterization and identification of novel diagnostic markers as well as drug targets. The platform is readily available to academic and commercial partners for collaboration (contact: patrick.schoffski@uzleuven.be).

Poster #304 3253417

SURGICAL OUTCOMES IN ELDERLY PATIENTS OVER 80 YEARS OF AGE WITH SOFT TISSUESARCOMAS

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Objective: In Japan, the population over 80 years has reached to 10 million, and the ratio of which has increased to 8.5% of the total population in 2017. In elderly patients with soft tissue sarcomas (STS), it is necessary to decide the optical treatment strategy considering not only the comorbidity or performance status (PS) but also the residual function after surgical excision. In this study, we assessed the surgical outcomes of STS that occurred in elderly patients over 80 years of age.

Methods: The present study included 50 patients who underwent surgical treatment for STS (excluding dermatofibrosarcoma protuberans and well-differentiated liposarcoma) at our institutions between 1995 and 2018. There were 29 males and 21 females. The mean age at the surgery was 83.3 (80-97) years old and the mean follow-up period was 23 (1-90) months. Before surgery, there were 25 patients with PS0, 15 with PS1, six with PS2, three with PS3, and one with unknown status. The histological subtypes included 23 undifferentiated pleomorphic sarcomas, 10 myxofibrosarcomas, six leiomyosarcomas, six liposarcomas, and others in five. The location of STS was an upper extremity in 16 patients, a lower extremity in 24, and a trunk in 10. Thirty-nine patients had high-graded tumors.

Results: At the first visit, distant metastasis was found in three patients, and unplanned excision was performed in seven. Histological evaluation of the resected specimens in our institutions was R0 in 41 cases, R1 in six, and R2 in three. Thirty-three patients required the reconstruction for the defect of soft tissues. Four patients received chemotherapy as neo-adjuvant/adjuvant therapy and 13 were irradiated. Post-operative complications occurred in 18 patients, which were not associated with fatal outcomes. After surgery, local recurrence was observed in seven patients (14%) and distant metastasis in 11 (22%). Fourteen patients discontinued to follow due to a transfer to other hospitals or an onset of other diseases. At the last follow-up, oncologic outcome was CDF in 27 patients, NED in four, AWD in seven, and DOD in eight. Four patients died by other causes. The overall survival rate was 73% and 59% and disease-free survival rate was 63% and 50% at 2 and 5 years, respectively. PS (0-1 vs. 2-3) and age (less than 85 vs. over 85) associated with neither overall nor disease-free survivals.

Conclusion: In patients with STS over 80 years of age, surgical treatment is the mainstay because the administration of chemotherapy is usually thought to be difficult for them. The present study showed that the surgical treatment for STS provided a good prognosis in patients over 80 years of age if oncological and biological status allows to receive surgery. Even in these patients, the maintenance of ADL and the preservation of function should be considered. In order to elucidate the accurate prognosis of these patients, a survey for patients who are unable to go to the hospital due to their healthy condition is necessary.

Poster #305 3254145

RAPID AND COMPLETE REMISSION OF CHEMOTHERAPY/TYROSINE KINASE INHIBITOR RESISTANT RELAPSED SPONTANEOUS AND RADIATION INDUCED ANGIOSARCOMA FOLLOWING TREATMENT WITH COMBINED ANTI-CTLA-4 AND ANTI-PD-1 THERAPY

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Objective: The primary objective was to assess the activity of combined anti-CTLA-4 and anti-PD-1 therapy in patients with relapsed and resistant spontaneous and radiation-induced angiosarcoma not amenable to complete surgical excision.

Methods: Two patients, an 88-year-old male with spontaneous head and neck angiosarcoma and a 73-year-old female with radiation-induced breast angiosarcoma were both treated with conventional surgery, radiation therapy (spontaneous patient), chemotherapy and tyrosine kinase inhibition (Sunitinib). Both were initially treated with surgery but rapidly relapsed and deemed ineligible for subsequent complete resection. Both went on to receive chemotherapy with sunitinib with both achieving good partial responses. Both suffered a rapid relapse while on therapy so received compassionate combined anti-CTLA-4 and anti-PD-1 therapy.

Results: The male patient first presented with spontaneous angiosarcoma of the right temple on 11/30/15 that was biopsied (Stage IIB) but with positive margins (R2). Consequently, he received liposomal doxorubicin (20 mg/m2 Q 3 weeks) initially responding but then progressed locally while on therapy (2/22/16). He then received involved field radiation therapy and achieved a clinical complete response. A second recurrence outside of the radiation field led to another surgery (3/13/17) with clear margins but a third recurrence (4/25/17) now with submental adenopathy prompted weekly paclitaxel (80 mg/m2) combined with sunitinib (25 mg) resulting in stable disease. Rapid and disfiguring growth occurred while on therapy associated with right eye closure and a large painful submental lesion starting in 1/19. Combination Anti-CTLA-4 (Ipilimumab) 1mg/kg and Anti-PD-1 (Nivolumab) 240 mg administered every 3 weeks x 4 was started on compassionate use consent (1/14/19) followed by Nivolumab 240 mg q 2weels. He achieved a clinical complete response after cycle 3 of combined therapy (3/11/19) that persist while on therapy as of 6/15/19. He experienced a grade II local rash that responded to topical steroids.

The female patient with a history of a right breast lumpectomy for breast cancer in 2012, followed by radiation therapy, first presented in 2018 after a one-year history of noting a small single lesion on her right breast that expanded to multiple sites on biopsy (9/11/18) showing angiosarcoma with positive margins. On 10/4/18 weekly paclitaxel (80 mg/m2) and carboplatin (AUC 2) with sunitinib (25mg) was started with a partial response achieved. An R0 resection (11/28/19) was followed by two recurrences, both resected, the second (3/5/19) being R1. Sunitinib was resumed but she developed field cancerization with rapidly growing bulk disease while on sunitinib. Combination Anti-CTLA-4 (Ipilimumab) 1mg/kg and Anti-PD-1 (Nivolumab) 240mg was started to be administered every 3 weeks and a clinical complete response was achieved at week 3 after the first cycle. She has not experienced an adverse immunologic event to date and remains on therapy.

Conclusion: Chemotherapy and tyrosine kinase resistant angiosarcoma not amenable to complete surgical resection invariably leads to suffering and death. Here we report on two patients, one with spontaneous and the other, radiation-induced angiosarcoma who failed conventional therapies, and both achieved complete clinical remissions within 3 cycles of combination Anti-CTLA-4 (Ipilimumab) 1mg/kg and Anti-PD-1 (Nivolumab) 240mg therapy with no serious adverse immunologic events experienced to date. Anecdotes of responses to single agent check point inhibitors (Shindu, J Immunother Cancer. 2017 18;5(1):58) have been reported but to our knowledge, this is the first report of active combination Anti-CTLA-4/AntiPD-1 therapy. Longer follow up is required to assess durability of response and a complete toxicity assessment, however, the rapidity an extent of responses observed in this population of resistant relapsed patients warrants further study.

Poster #306 3254295

ADULT GENITOURINARY SARCOMA: CANCER INSTITUTE HOSPITAL OF JAPANESE FOUNDATION FOR CANCER RESEARCH EXPERIENCE

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Objective: To examine the clinical characteristics, treatment, and survival of adult patients with genitourinary sarcoma at our institution during recent 14 years.

Methods: We retrospectively retrieved the medical records of adult patients who were potential candidates for soft tissue sarcoma, primary sites of which were prostate, kidney, urinary bladder, and paratesticular structures between March 2005 and May 2019. Any patients with retroperitoneal sarcoma were not included in this study. The probability of survival was estimated by the Kaplan-Meier method and the statistical significance of differences between patient subgroups were assessed by the log rank test.

Results: The data on 28 adult candidates for primary genitourinary sarcomas were extracted. However, the disease of four patients were found to be benign. Moreover, the primary sites of five patients were organs other than genitourinary ones. They had recurrent and/or metastatic diseases in genitourinary sites. After all, 19 patients had primary genitourinary sarcomas. Of the 19 patients, 16 (84%) were male and 3 (16%) were female. The median age was 41 years, ranging from 20 to 79. The median tumor size was 5.2 cm, ranging from 1.8 to 22. The primary sites were the prostate in 8 (42%), the urinary bladder in 5 (26%), paratesticular region in 3 (16%), and the kidney in 3 (16%). The median prostate-specific antigen value for the 8 patients with prostate origin was 1.23 ng/ml, ranging from 0.51 to 3.76. The most common histological subtypes were leiomyosarcoma in 5 (26%), followed by rhabdomyosarcoma in 3 (15.8%), carcinosarcoma in 2 (10.6%), Ewing sarcoma, Ewing-like sarcoma, liposarcoma, synovial sarcoma, prostatic stromal sarcoma, myxofibrosarcoma, desmoplastic sarcoma, extraskeletal myxoid chondrosarcoma, not otherwise specified-type sarcoma in 1 (5.3%) each. The overall survival rate at 1, 3 and 5 years was 61.5%, 34.4% and 25.8%, respectively. On univariate analysis, absence of metastasis at diagnosis and complete surgical resection were predictive of favorable survival. Meanwhile, any chemotherapeutic therapy could not show sufficiently beneficial effect (objective response rate [ORR] 21.1% in total) on treatment of adult patients with genitourinary sarcoma, except for the regimen including vincristine, adriamycin, actinomycin D, cyclophosphamide, ifosfamide, and etoposide which are key drugs for small round cell sarcomas such as Ewing sarcoma and rhabdomyosarcoma. Pazopanib was used in 9 patients mainly as an optional drug in the late-line setting, and the ORR was 11.1%. Of the nine patients, six high-grade (grade 3 or 4) adverse events were observed in three patients.

Conclusion: Inoperable metastatic disease remains difficult to treat, although the number of therapeutic agents to use for sarcoma has increased compared with before. In the field of genitourinary malignancy, therapeutic agents for carcinoma have been enriched, however, those for sarcoma are still insufficient. Further investigation of genitourinary sarcomas, and development of novel agent for sarcoma would be needed.

Poster #307 3252932

ANALYSIS OF DEDIFFERENTIATED LIPOSARCOMA ARISING FROM THE EXTREMITIES AND SURFACE OF THE TRUNK

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Objective: Dedifferentiated liposarcoma (DDL) is adipocytic neoplasm and contain two components, well differentiated liposarcoma and non-lipogenic sarcoma. DDL presents most frequently in the retroperitoneum. However, cases of the extremities are relatively rare, and few reports have examined clinical features. In this study, we analyzed clinical features of DDL arising from the extremities and surface of trunk.

Methods: The participants included ten patients treated in our institutes from 2012 to 2016. All these patients were treated with surgical treatment. The tumor size, localization, surgical margin and distant metastases were evaluated by preoperative examination. In addition, the recurrence rate, metastatic rate, presence of adjuvant radiotherapy or adjuvant chemotherapy, and oncological outcomes were examined. We used the resection margin as defined by the Japanese Orthopedic Association.

Results: The patients group consisted of six males and four females, with a median age of 73 years (range, 55-86 years). Five patients were initial cases and five patients were recurrent cases. Five patients were de-novo tumor and five were secondary. All patients received primary operation as lipoma. One patient had lung metastasis at initial presentation. The mean follow-up period from the start of treatment was 18 months (4-94months). Four tumors were located in the thigh, three in the lower leg, one in the shoulder, one in the axially fossa, and one in the back. The median length of tumor was 11.5 cm (3-24 cm). In the evaluation of surgical margin, five patients had wide resection, three had marginal resection, one had intralesional resection, one had amputation. Adjuvant radiotherapy was performed in three patients with an inadequate wide margin, a marginal margin, and an intralesional resection. Adjuvant chemotherapy was performed in two patients with local recurrence or lung metastasis. Local recurrence occurred in one patient. Distant metastases occurred in two patients, one of these patients died 46 months after the start of treatment. One patient was alive with disease. Five-year overall survival rate was 90%.

Conclusion: It is reported that the 3-year recurrence rate of DDL is 83% in the retroperitoneum and 6% in the extremities. Moreover, it is reported that the 5-year overall survival rate of DDL in the retroperitoneum is 20-44% and 61.1% in the extremities. In this study, the 3-year recurrence rate was 10% and overall survival was 90%. Our results suggest that sufficient surgical resection is possible for DDL in the extremities, and adjuvant radiotherapy may provide good local control without wide resection margin. Even cases that have been diagnosed as lipoma in the past, it is important to consider the possibility of dedifferentiation for recurrent cases.

Poster #308 3255188

SITES OF DISTANT METASTASES AND FACTORS AFFECTING OVERALL SURVIVAL: A STUDY OF 159 PATIENTS WITH METASTATIC LIPOSARCOMA

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Objective: To assess the association between site of distant metastases and overall survival in metastatic liposarcoma and identify clinical prognostic factors in this group of patients.

Methods: Data was obtained for patients with liposarcoma from the SEER database between 2010 and 2016. Patients with previous malignancy or records from recurrent disease were excluded. Univariate and multivariate Cox proportional hazard models were used to identify variables associated with overall survival. Survival times between groups were compared using Kaplan-Meier analysis and log-rank tests. Site of metastasis ($p<0.01$), whether the patient received surgery to primary site ($p<0.01$) and/or radiotherapy ($p=0.02$) were significantly associated with overall survival and were included in a multivariate model. Age, sex, site of primary, whether the patient was given chemotherapy and primary tumour size were not significantly associated ($p>0.1$). Tumour grade ($p=0.1$) and histological subtype ($p=0.06$) were of borderline significance and were included in a multivariable model.

Results: We analysed 159 patients with details on sites of metastasis. The most common distant metastatic site was lung, followed by liver, and then brain. Survival was poorer for lung or multiple sites of metastasis (n=99, median 6 months) compared to bone or liver metastasis (n=60, median 16 months). Myxoid liposarcoma (HR 0.47, $p=0.025$), mixed liposarcoma (HR 0.2, $p=0.013$), and patients receiving surgery to primary site (HR 0.41, $p <0.01$) were associated with improved overall survival whereas metastasis to lung or multiple sites (HR 1.58, $p=0.041$), and poorly differentiated (HR 2.99, $p=0.029$) or anaplastic (HR 2.68, $p=0.047$) liposarcoma was associated with poor overall survival.

Conclusion: The site of distant metastases affects overall survival in metastatic liposarcoma. The identified factors can help clinicians evaluate the prognosis for liposarcoma patients with distant metastases and aid patient consultation regarding goals of care.

Poster #309 3212091

MOLECULAR PROFILE IN SOFT TISSUE SARCOMAS (STS): USEFULNESS FOR SPECIFIC DIAGNOSIS OF PLEOMORPHIC SARCOMA?

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Objective: Evaluar las alteraciones moleculares somáticas descritas en la literatura y determinar patrones genéticos que permitan un diagnóstico molecular preciso de los sarcomas pleomórficos (PS).

Methods: <Estudio descriptivo de mutaciones de genes en sarcomas de datos publicados en la World Wide Web basado en bases de datos certificadas como Catálogo de mutaciones somáticas en cáncer, referencia genética en el hogar y Centro Nacional de Información Biotecnológica.

Results: Las mutaciones somáticas fueron frecuentemente fundadas en 23 STS.
Se describieron un total de 338 mutaciones, con un promedio de 13 (r2-25) por sarcoma.
Clasificamos el Grupo 1 (tumores con menos de 7 mutaciones): sarcoma del estroma endometrial, liposarcoma mixoide, melanoma de células claras y sarcoma epitelial.
El grupo 3 incluyó tumores con el mayor número de mutaciones (≥ 20): angiosarcoma, liposarcoma desdiferenciado, leiomiosarcoma y sarcoma de Ewing.
Se fundaron 74 mutaciones específicas y 64 mutaciones no específicas, en más de 5 se fundaron STS: ATRX, BRAF, CDKN2A, CIC, FAT1, KMT2D, KRAS, MED12, NF1, PIK3CA, PTEN, RB, TERT Y TP53.
El análisis final se realizó para identificar específicos o no específicos en PS.
Se fundaron 20 mutaciones, 3 específicas (KMT2A 8%, PTPRT 7%, FLT3 5%) y 17 no específicas (presentes a ≥ 5 STS: TP53 27%, KRAS 11%, PIK3CA Y FAT1 7%, BRAF 6%, NF1 Y CIC 5%.

Conclusion: Las alteraciones moleculares que se encuentran en las bases de datos disponibles son una herramienta más para la clasificación precisa de los sarcomas pleomorfos de muchos otros que se clasifican como tales de manera equívoca, teniendo en cuenta la identificación de mutaciones específicas como KMT2A, PTPRT, FLT3 que podrían establecer un molecular específico. patrón de ps.

Otras mutaciones no específicas también podrían ayudar en el diagnóstico final de PS.

Poster #310 3230196

EARLY BRAIN-ONLY METASTASES AFTER COMPLETE RESPONSE TO NEOADJUVANT THERAPY FOR HIGH-RISK LOCALIZED PLEOMORPHIC SARCOMA

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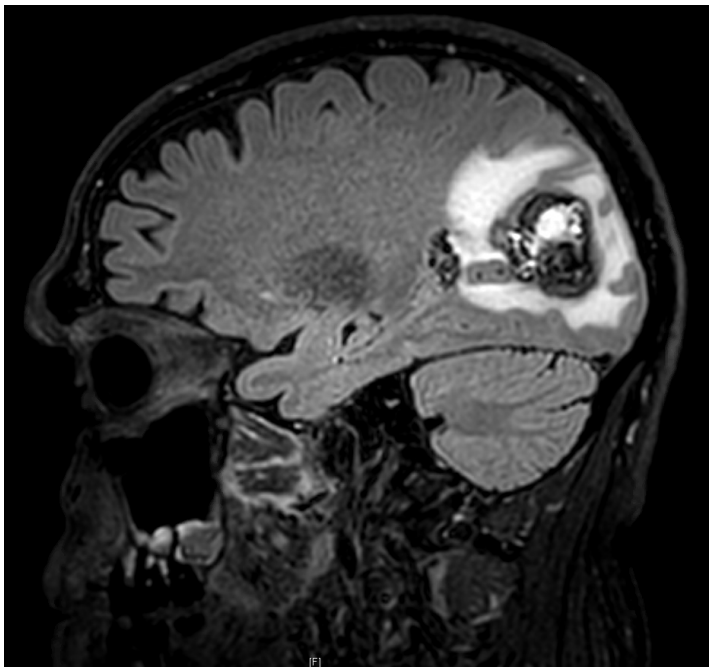
Objective: 63 year old optometrist had a rapidly growing mass on right thigh as he was getting ready to retire. MRI 5/25/2017 showed 13.2 cm mass emanating from soft tissues around quadriceps. Core needle biopsy proved high-grade pleomorphic sarcoma. CT chest/abdomen/pelvis (c/a/p) 6/7/2017 was negative for metastatic disease.

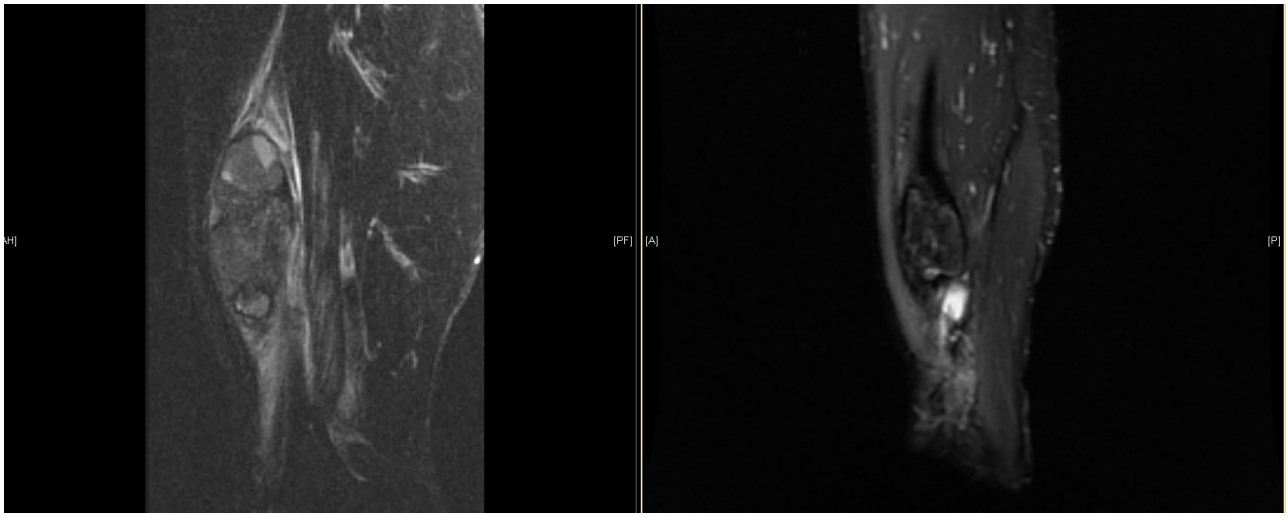
Methods: We chose neoadjuvant MAI (adriamycin 75mg CIVI over 48 hrs plus ifosfamide 2.5g/m2 IV days 1-4 with mesna and G-CSF support as outpt) with first cycle starting 6/20/17. After 3 cycles, his thigh mass was markedly smaller, yet chemo was weighing on him physically. Restaging CT scan and MRI right thigh 8/27/17 showed no signs of metastases with marked decrease in thigh mass. Therefore, he was transitioned to neoadjuvant intensity modulated radiotherapy (IMRT), completing 25 Fxs, 50 Gy late Oct 2017.

Results: On 11/3/17, he, being an optometrist, called to tell me he had a "right homonymous hemianopsia". He was sent to the local emergency room that night and MRI head showed multifocal brain metastases, including a large left occipital mass (image 1). CT c/a/p 11/6/17 still showed no metastases elsewhere, and MRI thigh showed continued response (image 2). He underwent craniotomy mid Nov 2017 (biopsy-proven undifferentiated sarcoma - PDL-1 0%/ negative; microsatellite stable), followed by stereotactic body radiotherapy (SBRT) in Dec 2017 to operative bed and other smaller lesions in L cerebellum. He stabilized neurologically and underwent definitive surgical resection of the primary thigh mass 12/20/17. This showed no residual sarcoma with complete pathologic response (image 3). Repeat MRI head 1/26/18 showed two new extraaxial dural-based mets, while restaging CT 1/26/18 showed no evidence of other metastases. He was started on temozolomide 150mg/m2 days 1-5 of 28 day cycle early Feb 2018. By 2/13/18, his family called in stating that he had a sudden headache with word-finding difficulties and worsening vision changes. He was started on decadron 8mg PO BID, with outpatient MRI head 2/15/18 showing moderate-sized extra-axial hematomas associated with dural-based metastases, as well as small left convexity subdural hematoma. The hope was that this bleeding was a sign of response, so he started second cycle of Temodar late Feb 2018. By 3/25/18, MRI brain w/ and w/o showed multiple metastases, with hemorrhaging noted in L occiput, L temporal area, L inferior frontal lobe with 2-3mm midline shift and minimal uncal herniation. He was taken for L pterional craniotomy and evacuation of clot on 3/27/18. He worked with rehab team to regain some functionality, but obviously temozolomide did not appear to be working. Consideration for more SBRT versus whole brain radiotherapy was given, but it was decided to pursue home hospice. He passed away peacefully at home 4/27/18.

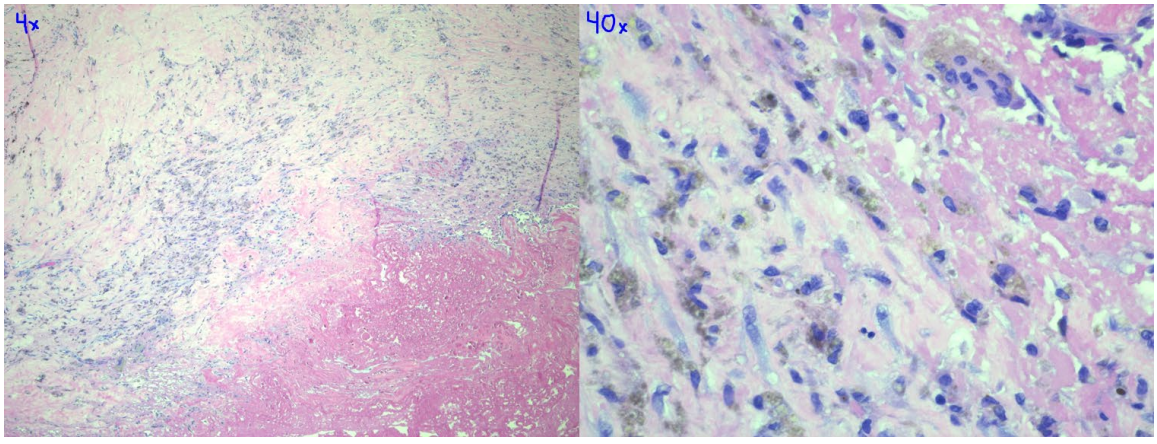
Conclusion: Here, we present a patient with complete pathologic response to three cycles of neoadjuvant MAI followed by IMRT for a large, localized high grade undifferentiated sarcoma of thigh. Unfortunately, he developed symptomatic brain metastases within weeks of finishing neoadjuvant radiation and succumbed of this brain disease within six months. Intriguingly, he showed no evidence of other metastatic deposits throughout. Brain metastases with undifferentiated sarcomas have certainly been described in the literature, but typically happen late in the setting of widespread systemic metastases, in which the patient has outlived the expected prognosis. There has been noted to have a slight predominance in males, involving extremities, with undifferentiated sarcomas. In the largest cohort described, over 28 years of review at MD Anderson, the median interval from primary sarcoma diagnosis to brain metastasis was 2.2 years and from systemic disease to brain metastasis was 1.1 year (Al Sannaa et al 2016). This case brings into question the role, if any, for staging the brain in a newly diagnosed localized high grade undifferentiated sarcoma of the extremity in a male.



MRI Sagittal FLAIR images of left occipital brain metastasis early Nov 2017



Change in sagittal STIR MRI characteristics of right thigh sarcoma from May 2017 (left) to Nov 2017 (right) after 3 cycles of neoadjuvant MAI followed by 50 Gy radiation



Complete pathologic response seen in primary thigh sarcoma. At 4x magnification on the left, there is necrotic tumor in lower right quadrant with tumor bed in upper left. At 40x magnification on the right, tumor bed is showing fibrosis, hemosiderin-laden macrophages and few lymphocytes but no active tumor. (4x magnification on left, 40x magnification right)

Poster #311 3240092

CLINICAL STUDY OF SOFT TISSUE SARCOMA WITH ANTECEDENT PRIMARY MALIGNANCIES

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Objective: We retrospectively reviewed 21 soft tissue sarcoma cases with antecedent primary malignancies (STS-APM) and compared their survival to those of 107 soft tissue sarcoma only (STS-O) from 2008 to 2017 in our institution.

Methods: Overall survival was estimated using Kaplan-Meier survival curves and prognostic factors were analyzed using logistic regression analyses and contingency table analyses.

Results: As the final status of STS-APM patients, 12 patients were in disease free survival, 5 were alive with disease, 3 have died of disease and 1 has died of another disease. There was no case that died of antecedent primary malignancy. The 5-year overall survival rates were 88% in STS-APM and 78% in STS-O, showing no statistical significant ($p = 0.65$). The 5-year overall survival rates in each stage of STS-APM and STS-O were 100/100% in stage I, 100/85% in stage II, 86/72% in stage III, and the three-year overall survival rates were 67/51% in stage IV, with no statistical significance. With regard to prognostic factor, histological grade of STS was the only significant factor. Although antecedent radiotherapy tended to show a high odds ratio, the association was not statistically significant. Antecedent chemotherapy did not show any estimated prognostic risk.

Conclusion: Our study suggested that antecedent primary malignancy in STS patient would not be a negative prognostic factor.

Poster #312 3230600

PHASE II STUDY OF NEOADJUVANT CHECKPOINT BLOCKADE IN PATIENTS WITH SURGICALLY RESECTED UNDIFFERENTIATED PLEOMORPHIC SARCOMA AND DEDIFFERENTIATED LIPOSARCOMA-PRELIMINARY SAFETY DATA

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Objective: The recently published SARC028 and Alliance A091401 trials reported promising activity of checkpoint blockade in select histologic types of advanced soft tissue sarcomas (STS), including dedifferentiated liposarcoma (DDLPS) and undifferentiated pleomorphic sarcoma (UPS). We hypothesize that immune checkpoint blockade will be safe and effective when administered in the neoadjuvant setting. Here, we report preliminary safety and radiographic response data for an on-going phase II trial of neoadjuvant checkpoint blockade in patients with resectable retroperitoneal DDLPS or extremity/trunk UPS (NCT03307616).

Methods: NCT03307616 is a randomized, phase II non-comparative trial evaluating neoadjuvant checkpoint blockade in patients with resectable DDLPS of the retroperitoneum (RP) or UPS of the trunk or extremity (ET) treated with concurrent neoadjuvant radiotherapy (RT). A total of 40 patients will be enrolled in 4 arms: 20 patients with treatment-naïve resectable primary or locally recurrent retroperitoneal DDLPS will be randomized 1:1 to: (Arm A) 3 doses of nivolumab (3mg/kg) prior to surgical resection or (Arm B) combination ipilumumab (3 mg/kg) & nivolumab (1 mg/kg) x 1 dose followed by 2 doses of nivolomab (3mg/kg) prior to surgical resection. Arm C & D will randomize 20 patients with treatment-naïve resectable primary or locally recurrent extremity or trunk UPS will be randomized 1:1 to receive preoperatively either: (Arm C) 1 dose of nivolumab (3mg/kg) followed by concurrent nivolomab (3mg/kg) and RT prior to surgical resection or (Arm D) combination ipilimumab (3 mg/kg) & nivolumab (1mg/kg) x 1 dose followed by concurrent nivolomab (3mg/kg) and RT prior to surgical resection. Radiation is delivered as standard of care preoperatively to a dose of 50 Gy in 25 fractions in Arms C & D. The primary endpoint is objective pathologic response as operationally defined by percent hyalinization. Secondary endpoints include: safety and toxicity of nivolumab and combination ipilimumab/nivolumab in the neoadjuvant setting; objective response by RECIST and immune-related reposnse criteria (irRC); recurrence-free survival; overall survival and patient-reported outcomes. Longitudinal blood, tissue and microbiome samples are collected pre-treatment, prior to dose 2 and at the time of surgical resection.

Results: At the time of this submission, 14 patients had completed therapy through surgery and had safety and toxicity data available. All patients proceeded to surgical resection without delay. One patient developed metastatic disease during treatment but underwent palliative resection (Arm C). Three patients (23%) did not complete all courses of preoperative immunotherapy, all in the combination arm due to toxicity (Arm B: n=1, Arm D: n=2). By RECIST, the majority of patients had stable disease (69%) and 4 patients (31%) had progressive disease during the neoadjuvant period, none of which significantly changed the planned surgery. Treatment related Gr ≥3 AEs included: colitis: n=1, renal failure: n=1, cardiac: n=2, fatigue: n=1, and pruritus: n=1. The most common related Gr 1/2 AEs were fatigue: n=5, rash: n=4, colitis: n=3, fever: n=3, myaligias: n=3, hypothyroid: n=2. There were no perioperative deaths. One patient required reoperation for small bowel fistula, possible-related to therapy (Arm A). Due to observed toxicity in dual checkpoint blockade arms, a voluntary dose-reduction of ipilimumab was implemented to ipilimumab (1mg/kg)/nivolumab (3mg/kg) after these 14 patients.

Conclusion: Preoperative nivolumab with or without RT did not show unexpected toxicities in patients with retroperitoneal DDLPS and extremity/trunk UPS. Combination with ipilimumab at the initial dose tested led to higher toxicity but did not interfere with surgical planning.

Arm: Histology; number (N=)	Treatment	Grade 1/2 N; (%)	Grade 3-related N; (%)	Median RECIST response (%, range)
A: DDLPS (4)	Nivo	2 (50)	1 (25)	5.5 (-8 – 26)
B: DDLPS (5)	Ipi + Nivo	4 (80)	0	24 (7-74)
C: UPS (3)	Nivo/RT	3 (100)	1 (33)	-21 (-25 – 16)
D: UPS (2)	Ipi/Nivo + Nivo/RT	2 (100)	2 (100)	9.5 (-4 - 22)

Nivo: nivolumab; Ipi: ipilimumb; RT: 50Gy external beam radiation

Poster #313 3256138

BONE CEMENT IMPLANTATION SYNDROME IN BONE TUMOR SURGERIES: INCIDENCE, RISK FACTOR, AND CLINICAL EXPERIENCE

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Objective: Bone cement implantation syndrome (BCIS) is an important cause of intraoperative morbidity and mortality in patients undergoing cemented hip arthroplasty. The clinical presentation includes hypotension, hypoxia, arrhythmia, loss of consciousness and even cardiac arrest. A few studies have shown that its incidence ranges from 27.8% to 38%. The risk factors include old age, osteoporosis, bony metastasis, among others. However, studies on BCIS only involved patients who underwent hip arthroplasty. In addition to hip arthroplasty, bone cement is also widely used in surgeries for bone tumors. Patients with bone tumors, especially malignant tumors, are likely to be weaker and vulnerable to hemodynamic instability. Thus, BCIS should also be studied specifically for these patients. Bone cementation provides immediate structural stability and possibly causes thermal necrosis of tumor cells in the surgical margins. Therefore, cementation is not only used for joint reconstruction procedures but also for tumor curettage and/or internal fixation in bone tumor surgeries. The peak and mean intramedullary pressures have been shown to be much lower in cementation without prosthesis insertion[3], which should lower the rate of BCIS. However, bony metastasis has been shown to be a risk factor of BCIS in hip arthroplasties. The relative hypervascularity of bone metastasis and worse patient condition may be the associated causes. Taking these factors into account, we speculated that cementation in bone tumor surgeries may result in considerable incidence rate of BCIS even without intramedullary device. This retrospective observational study aimed to investigate the incidence of BCIS in bone tumor surgeries and compare the incidence rates of BCIS between those patients with and without possible risk factors. Furthermore, we will also share our experience and strategies to lessen the severity of BCIS in bone tumor surgeries. To our knowledge, this is the first study to address this issue.

Methods: We performed a retrospective observational study at the corresponding author's hospital. We included patients who underwent bone tumor surgeries requiring cementation as part of the surgery between March 2016 and January 2018. We reviewed medical records including formal anesthesia records and operation notes. Patients with complete data files were included. We also compared the incidence rates of BCIS between those patients with and without possible risk factors. All procedures were performed by the senior author, who has been a specialist in orthopedic oncological surgeries for about 30 years.

Results: Eighty-eight patients were included. The characteristics of bone tumors and types of surgery are shown in Table 1. The average age was 55.0±16.3. BCIS occurred in 23 patients, with an incidence of 26.1%. Among them, 19 had grade I and 4 had grade II, and there was no grade III BCIS. Only one grade I patient presented with hypoxia and the others presented with hypotension.
The lowest blood pressure occurred within 10 minutes in 21 (87.5%) patients and within 20 minutes for all the patients. Nine grade I BCIS were self-limiting. Ten grade I hypotension cases and all grade II hypotension cases recovered after administration of a vasoconstrictor medication.
The comparison of the incidence between patients with and without each risk factor is shown in Table 2. The occurrence rate of BCIS was significantly higher when there was a pre-existing lung cancer or lung metastasis (p=0.008). With regard to other factors, there was no significant difference between two groups.

Conclusion: BCIS is not unusual in bone tumor surgeries, even without prosthesis insertion. The incidence is similar to that of cemented arthroplasties. Pre-existing lung malignancy further increases the risk. Surgeons and anesthesiologists should pay attention to this condition and be well-prepared before and during the operation.

Table 1. Characteristics of bone tumors and types of surgery

		BCIS grade			Total
		N/A	Grade I	Grade II	
Types of tumor	Bone metastasis	40	15	3	58
	Primary bone cancer	10	4	1	15
	Benign bone tumor	11	4	0	15
Types of surgery	Cementation alone	10	2	0	12
	Cementation + plate and screws	29	10	1	40
	Cementation + intramedullary nail	2	0	0	2
	Cementation + arthroplasty	24	7	3	34
Location of tumor	Femur	39	13	3	55
	Humerus	9	5	1	15
	Tibia	9	0	0	9
	Acetabulum	3	1	0	4
	Acetabulum + femur	2	0	0	2
	Radius	2	0	0	2
	Foot	1	0	0	1

There was no grade III BCIS.

Table 2. Comparison of BCIS incidence in patients with and without possible risk factors

		Bone cement implantation syndrome		p value
		Yes	No	
Age (years)	≥60	13	28	0.333
	<60	10	37	
Arthroplasty	Yes	10	24	0.624
	No	13	41	
IM device	Yes	10	26	0.809
	No	13	39	
Lung morbidity	Yes	16	24	0.008
	No	7	41	
Blood loss (mL)	≥200	13	24	0.141
	<200	10	41	
Tumor location	Femur	16	41	0.622
	Other	7	24	
Gender	Male	11	23	0.326
	Female	12	42	

IM device: Any intramedullary device, including prosthesis and intramedullary nail.
Lung morbidity: Primary lung cancer or lung metastasis.

Poster #314 3256521

LONG TERM OUTCOMES AFTER SURGICAL MANAGMENT OF DERMATOFIBROSARCOMA PROTUBERANS: A SINGLE INSTITUTION EXPERIENCE

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Objective: Dermatofibrosarcoma protuberans (DFSP) is a locally aggressive rare dermal soft tissue tumor. Though the vast majority of disease exhibits low-grade malignant behavior 10-15% may undergo high-grade sarcomatous transformation with metastatic potential. Our Objective is to review pre-referral management and outcomes after definitive surgical treatment.

Methods: A retrospective review of DFSP patients treated at our tertiary cancer center over a 17-year period was performed. We examined clinicopathological parameters with special emphasis on initial biopsy method, resection margin, and reconstruction techniques. Main endpoints were recurrence-free (RFS) and overall survival (OS).

Results: Forty-two patients underwent oncologic excision of DFSP. Median follow-up was 44 months (IQR 11-83). Median age at diagnosis was 43 (IQR 32-50) years. Twenty-seven (64%) were Caucasian, 11 (26%) Black/African America, 3 (7%) Hispanic, and 1 (3%) Asian American. Primary sites of disease were extremity 17 (41%), truncal in 13 (31%), and head/neck in 12 (29%). Median tumor size was 5 cm (IQR 3-7). Eighteen (43%) patients had non-oncologic/failed resections prior to referral and underwent re-excision at our institution. 24 patients underwent definitive resection after incisional biopsy at our center: 31 (74%) wide local excisions, and 11 (29%) narrow excision with Mohs surgery. Median surgical gross margin was 2 cm (IQR 1-3). Margin negative (R0) resection was obtained in 37 (88%) patients, 5 (12%) patients had R1 resection, of which 4 (80%) had prevous non-oncologic resections. 24 (57%) defects were closed primarily, 8 (19) with autologous skin graft, 10 (24%) with free/rotational flaps. 4 (10%) patients were found to have fibrosarcomatous transformation (FST) and all four were treated with either adjuvant chemotherapy and/or radiation. 2 (5%) patients developed recurrent disease. One patient recurred after R0 resection (RFS= 72.6 mos), the other had R1 resection with FST and developed metastatic disease (RFS=7.2 mos) but is alive with disease (OS = 30.70 mos).

Conclusion: DFSP is a rare tumor with low metastatic potential but creates a clinical challenge of achieving local control. Complete excision of the tumor with wide surgical margin widths of at least 2 cm is recommended. Patients undergoing non-oncologic resections are at highest risk for margin positive (R1) resection. However, in the setting of focal margin positivity durable RFS may still be achieved.

Poster #315 3256560

REVISION RATES FOR MEGAPROSTHESES: REVIEW OF LITERATURE AND META-ANALYSIS

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Objective: Outcomes of megaprotheses vary by anatomical site and design. We conducted a meta-analysis of megaprostheses of major joints over more than 30 years to look for design variables affecting the outcomes. Objectives: report survival, revision for mechanical/recurrence/infectious causes for proximal humerus (PH), proximal femur (PF), distal femur (DF), and proximal tibia (PT) megaprostheses and assess risk factors of revision for mechanical cause in knee protheses including fixation, modularity, and hinge type.

Methods: Using PRISMA recommendations, English-written peer-reviewed articles reporting megaprostheses outcomes were included. Titles and abstracts which were selected were then retrieved for full-text inclusion and exclusion criteria assessment.

Random effects meta-analyses were used to estimate pooled rates of events with the DerSimonian–Laird estimate. Simple approximation of 95 % confidence intervals is reported. Between studies variability was assessed with the I-squared statistics. Meta-regression models were built to assess the effect of moderators (anatomic site and modularity/fixation/hinge variables) on t outcomes.

Results: A total of 102 articles were retrieved giving 178 identifiable series (according to anatomical site and design) reporting on 6830 patients. The median follow-up was 45 months [first quartile - third quartile: 27 - 60]. The 5-year revision rate (40 series included) was 20% [17% - 23%] (ie, 5yr survival 80%). Over follow-up, the proportion of revision for mechanical reason was 11% [9% - 13%] with significant differences between anatomical sites (14%, 5.5%, 7.6%, 13% for distal femur, proximal femur, proximal humerus, and proximal tibia; P<0.001). The proportion of revision for infection was 6% [5% - 7%] with significant differences between anatomical sites (6.5%, 4%, 4.3%, 11% for distal femur, proximal femur, proximal humerus, and proximal tibia; P<0.001). The proportion of local recurrence was 7.5% [6% - 9%] with no difference between anatomical sites (P=0.48). Fixation (cemented/uncemented, P=0.83), modularity (custom-made/modular, P=0.31), and hinge (fixed/rotating, P=0.19) had no effect on the risk of revision for mechanical reason.

Conclusion: The 5-year survival rate of major joints is 80%. Revision rate for mechanical reason is significantly different between anatomical sites (6% for PF to 15% for DF) so as for infection (5% for proximal humerus to 17% for proximal tibia). There is no significant effect of common design variables (fixation, modularity, or hinge) on the risk of mechanical revision.

Poster #316 3256707

DISTRACTION OSTEOGENSIS SPECIFIC SURGICAL COMPLICATIONS IN RECONSTRUCTION OF OSSEOUS TUMORS

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Objective: Long-term functional outcomes and rates of complications of traditional reconstructive options after bone tumor resection are well established. The use of distraction osteogenesis (DO) via bone transport to treat large bone defects is common in situations of trauma or infection, but less reported in patients for oncological diagnoses. The aim of this study was to critically assess safety and efficacy of DO, and compare rates of complication and functional outcome to standard oncologic reconstructions.

Methods: We evaluated 38 cancer patients who underwent DO reconstruction of the upper and lower extremity at our institution. Data were collected regarding demographics, oncologic characteristics, treatment details, and postoperative complications. Functional outcomes were assessed using the Musculoskeletal Tumor Society (MSTS) scores. Our data were compared to previously published rates of complications and functional outcome of allograft, megaprostheses, modular endoprostheses, and vascularized fibular graft reconstructions in cancer patients (Aponte-Tinao et al. 2015; Ippolito et al. 2019; Capanna et al. 2015; Ahlmann et al. 2006; Ghoneimy et al. 2019; Gebert et al. 2006).

Results: In our study, DO was used for reconstruction of bone defects in the upper and lower extremity; most of the reported studies focused on one anatomic location. The rate of limb survival in our study is comparable to that of other studies. The rates of local recurrence and negative margins in DO patients are better than in most of the reported series. Infections requiring wash-outs occurred in 53% of our patients, which can be explained by the use of external fixators for DO. Rates of structural failure and nonunion in our series are slightly higher than in the reported studies. Functional outcome of our patients is the best compared to the reported series. See Table 1.

Conclusion: This is the largest series of patients reported undergoing DO for reconstruction after osseous tumos. Despite early complications, specifically infection, DO is an effective method for biological reconstruction of large bony defects in patients after resection of osseous sarcomas. Excellent intermediate term functional results and high rate of limb survival are achieved with DO. We found no enhanced risk of local recurrence in our series. We postulate that the use of DO is safe and effective for the reconstruction after resection of malignant bone neoplasms, supporting other smaller published series.

Table 1 - Complications in different reconstructive techniques

Author/year	n	Reconstructive technique	Anatomic location	Mean follow-up	Mean age at surgery	Limb survival	Local recurrence	Negative margins	Infection rate	Structural failure	Non-union	MSTS score (mean)
Aponte-Tinao et al[1], 2015	35	Allograft	Lower Extremity	108 months (1-23 years)	17 years (2-50 y.)	97%	9%	100%	3%	31%[a]	9%	26
Ippolito et al[2], 2019	74	Allograft	Upper + Lower Extr.	105 months	32 years (5-71 y.)	NA	7%	NA	7%	8%[a]	23%	23.6
Capanna et al[3], 2015	199	Megaprostheses	Lower Extremity	67 months (24-149 m.)	43 years (12-90 y.)	95.5%	4%	NA	9.5%	29%[b]	3%	NA
Ahlmann et al[4], 2006	211	Modular endoprostheses	Lower Extremity	37.3 months (1-204 m.)	50 years (11-86 y.)	97.6%	2.8%	100%	5.2%	8.1%[b] 0.5%[c]	NA	22.3
Ghoneimy et al[5], 2019	41	Vascularized fibular graft	Lower Extremity	48.7 months (12-104 m.)	10.3 years (5-17 y.)	NA	4.8%	95.2%	0%	33.3%[a]	13.8%	24.3
Gebert et al[6], 2006	21	Vascularized fibular graft	Upper Extremity	43.6 months (6.0-131.9 m.)	15.4 years (5.1-27.5 y.)	NA	0%	100%	5%	24%[a]	0%	25.5
MSKCC series, 2019	38	Distraction osteogenesis	Upper + Lower Extr.	29.2 months (12-53 m.)	18 years (6-61 y.)	97%	0%	100%	53%	7.9%[a] 42.1%[b]	26.3%	26.4

[a]Graft/regenerate fracture; [b]Hardware failure/loosening/instability/dislocation; [c]periprosthetic/prosthetic fracture

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Poster #317 3223323

THE IMPACT OF SURVEILLANCE INTERVAL FOLLOWING RESECTION OF PRIMARY WEL DIFFERENTIATED LIPOSARCOMA OF THE RETROPERITONEUM

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Objective: Recurrent retroperitoneal well differentiated liposarcoma (RP WDLPS) is unlikely to be cured with surgical resection. Thus many clinicians will delay surgery after detection of recurrence until the time of significant symptoms or if there is noted to be a rapid rate of disease progression. The current consensus of the multidisciplinary sarcoma group at MD Anderson Cancer Center (MDACC) is to examine and image patients following primary sarcoma resection every 3 months for the first 2 years postoperatively, although level 1 data supporting this practice are lacking. The aim of this study was to determine whether longer follow-up intervals (q4-6 months) might be feasible in this patient population without impacting outcomes or delaying treatment in those who developed recurrence.

Methods: A retrospective review of all patients (n=90) with primary RP WDLPS who underwent surgical resection at MDACC between April 1996 and April 2017 and received follow-up care and surveillance at MDACC was performed. Dates of postoperative follow-up, surveillance visits, diagnosis of recurrence, and surgery for recurrence were collected. For patients who developed recurrence, time to recurrence and time to surgery for recurrence were determined in order to assess the potential impact of surveillance interval on timing of surgery or initiation of systemic therapy for recurrence.

Results: Median age at diagnosis was 62 years (range 32-82). 52.2% of patients were male (47/90). Median tumor size was 29cm (range 6-70) with 18.9% (17/90) of patients having multifocal primary tumors. R0/R1 resection was achieved in 85 patients (94.4%), R2 in 3 (3.3%), unknown in 2 (2.2%). Median follow-up was 66.4 months (65.3 for survivors) with a median overall survival of 66.8 months (range 11.2-283.5). 55 patients (61.1%) developed local recurrence with median time to recurrence of 24.6 months (range 2.5-123.6). Of the patients who recurred, 39 (70.9%) underwent resection of recurrent disease at a median of 6.3 months (range 0.9-58.0) from diagnosis of recurrence and 31.0 months (range 7.2-118.5) from primary WDLPS resection. Most recurrences occurred at or beyond 1 year (38/55 [69.1%] patients with RFS ≥12 months, 28/55 [50.9%] RFS ≥24 months). In this cohort, surveillance imaging at 4 month intervals (compared to 3 months) would not have impacted management of WDLPS recurrence in the majority of patients (89, 98.9%). In 1 patient (1.1%) a longer interval would have delayed initiation of treatment (chemotherapy). Surveillance imaging at 6 month intervals (compared to 3 months) would not have impacted management of WDLPS recurrence in the majority of patients (87, 96.7%) but would have delayed initiation of treatment (chemotherapy) in 1 patient (1.1%) and might have impacted timing of operation in 2 patients (2.2%) who underwent surgery for recurrence within 1 year of primary tumor resection.

Conclusion: Surgical resection is standard management for patients with primary RP WDLPS. In a cohort of 90 patients who underwent resection of primary RP WDLPS, 61.1% developed local recurrence with median time to recurrence of 24.6 months. The timing of surveillance imaging (3 vs 4 or 6 month intervals) in the first 2 years following primary WDLPS resection is unlikely to significantly impact timing of surgery or systemic therapy for recurrent disease. Prospective studies evaluating the timing of follow-up and imaging with patient outcomes are needed. Standardized practice patterns could result in decreased anxiety and cost for patients and the healthcare system overall.

Poster #318 3224146

CAN THE KATAGIRI SCORING SYSTEM PREDICT SURVIVAL FOR PATIENTS WITH METASTATIC BONE DISEASE TREATED SURGICALLY?

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Objective: Bone is one of the most common sites of metastasis from many types of cancers. Skeletal metastasis can be associated with pain, pathologic fracture, and spinal cord compression. Surgical treatment is only performed in selected patients for pain control and to improve quality of lives. Survival prediction is critical in determining the surgical treatment options to balance the risk and benefit. Many prognostic scoring systems exist for patients with skeletal metastasis, with one of the most popular being the Katagiri scoring system. However, it has not been validated in surgical patients since vast majority of the patients in the original cohort were treated non-surgically. The objective of this study was to evaluate the predicting power of the Katagiri scoring system in a cohort of patients with skeletal metastatic tumor treated with surgery.

Methods: We performed a retrospective study involved in cohort of patients who underwent surgical management for skeletal metastatic disease at a single institution over 10 years. A smaller cohort of medically managed patients was also included for comparison. Patients were stratified into low risk (score 1-3), intermediate risk (score 4-6), and high risk (score 7-10) groups based on Katagiri score. The length of survival time was calculated by chart review. Survival rates at 6, 12, and 24 months were compared with the original cohort analyzed by Katagiri. The non-surgical group treated in our institute was used as control.

Results: We identified 186 patients with skeletal metastatic disease treated surgically and 52 patients treated medically. For low risk surgical patients, survival at 6, 12, and 24 months was 83.3%, 71.8%, and 43.6% for our cohort, and 97.9%, 91.5% and 77.2% for the Katagiri cohort, respectively ($p < 0.0005$, < 0.005, and < 0.0001 respectively). For intermediate risk patients, there was no significant difference in survival between our cohort and the Katagiri cohort at 6, 12, and 24 months respectively. For high risk surgical patients, survival at 6, 12, and 24 months was 70.1%, 50%, and 29.2% for our cohort and 27.2, 6.1%, and 2.2% for the Katagiri cohort ($p < 0.001$, < 0.001, and < 0.001 respectively). As an overall trend, the medically managed patients in our study were found to have similar survival outcomes as the Katagiri cohort (Table 1).

Conclusion: This study suggests that Katagiri score system predicts well for surgical patients with intermediate risk. However, it may over-estimate the survival for lower risk patients, but may also under-estimate that for higher risk patients. If the only major difference between our cohort and the Katagiri cohort is whether surgery was performed, the discrepancy can be attributed by the impact of surgery. Our study is limited by a smaller cohort relative to the Katagiri cohort. A future study with a larger cohort is needed in order to validate our findings. Despite the discrepancy in our findings, Katagiri score system remains a powerful predicting tool for patients with skeletal metastatic disease that are treated medically.

Table 1. Survival rates of our surgical cohort compared to Katagiri cohort

Katagiri Risk	Months of Survival	Surgical Alive	Surgical Deceased	Survival % of Surgically Managed Patients	Katagiri Alive	Katagiri Deceased	Survival % of Katagiri Patients	p-value
Score 1-3	6	65	13	83.3	99	2	97.9	0.0004
Score 1-3	12	56	22	71.8	92	9	91.5	0.0014
Score 1-3	24	34	44	43.6	78	23	77.2	0.00001
Score 4-6	6	50	28	64.1	260	92	73.9	0.08
Score 4-6	12	34	44	43.6	173	179	49.2	0.63
Score 4-6	24	24	54	30.1	97	255	27.6	0.57
Score 7-10	6	17	7	70.1	96	255	27.2	0.00001
Score 7-10	12	12	12	50	21	330	6.1	0.00001
Score 7-10	24	7	17	29.2	8	343	2.2	0.00001

Poster #319 3250165

CAN WE PREDICT RECONSTRUCTIVE SURGERY FAILURE IN SARCOMA PATIENTS?

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Objective: Given sarcoma heterogeneity, planning oncological treatment, and in what order, is complex. Although uncommon, reconstructive failure can delay or prevent delivery of adjuvant therapies where surgery is planned as first line treatment. We sought to try develop a clinical tool that would aid surgeons in predicting the likelihood of surgical and reconstructive success. Ideally identifying those who would incur surgical morbidity (and why), thus potentially jeopardising timing of adjuvant therapies.

Identifying high-risk patients could facilitate bespoke oncological care to ensure, on the balance of probability, all oncological modalities are delivered in a timely fashion. If clinicians and teams can achieve this, patients may be optimised through perioperative, enhanced rehabilitation and recovery programmes, or defer surgery till after medical and radiation based treatments are complete, without compromising disease free, and recurrence free survival. This is yet to be attempted and implemented in sarcoma care, and sarcoma patients in general, owing to heterogeneity, are well placed to be stratified according to risk. Reconstructive failure, delaying onward treatment, was rigidly defined.

Methods: Data compiled for thirty-two variables on 338 soft-tissue and bone sarcoma patients treated by The Northern Bone and Soft Tissue Sarcoma Unit based at Newcastle Upon Tyne Hospitals between 2000 to 2019, were analysed. Univariate analysis (Chi-Squared test, independent t-test, Fisher's exact test) identified important variables predictive of reconstructive failure. Variables within predefined cut-off on univariate analysis ($p<0.25$) included in binomial logistic regression. A preoperative clinical scoring-system was devised using multivariate analysis results.

Results: Reconstructive failure occurred in 21% of this cohort (71 of 338 patients). Five variables were significantly ($p<0.05$) associated with reconstructive failure on univariate analysis: reconstructive surgical method ($p<0.000$), number of major comorbidities ($p=0.042$), and, three variables relating to acute postoperative complications. Primary tumour depth and/or involvement was borderline statistically significant ($p=0.059$). Ten preoperative variables reached statistical cut-off ($p<0.25$) to be included in multivariate analysis. Number of major comorbidities (zero comorbidities: $p=0.023$, one comorbidity: p0.01, OR=2.689, two or more comorbidities: $p=0.094$, OR=2.763) and reconstructive method (direct primary closure: $p=0.005$, locoregional or pedicle flap: $p=0.002$, OR=3.29, free-flap: $p=0.008$, OR=3.948) are independent predictors of reconstructive surgery failure on multivariate analysis. The model has an acceptable level of discrimination between those who are high-risk of reconstructive failure and those who are not (c-statistic=0.748, 95% CI 0.6779 to 8.171 $p<0.001$). The Hosmer-Lemeshow test p-value is not statistically significant indicating the model is not a poor fit to cohort data ($X^2=5.194$, $p=0.983$). At optimal cut-off, 31% of the patients who had reconstructive failure were correctly predicted as high-risk. However, 93% of the patients who had reconstructive success were correctly predicted as low-risk.

Conclusion: The number of major comorbidities and reconstructive method are reconstructive failure independent risk factors in North of England sarcoma patients. However, the model significantly underestimates the number of high-risk patients for reconstructive failure. The model has an acceptable level of discrimination between high-risk and low-risk reconstructive sarcoma patients. Future studies will involve data collection for patients treated in North of England beyond 2019 to increase reconstructive failure patient sample size. Univariate and subsequent multivariate analysis on larger cohort will modify the model. We hope to collaborate with other populations and units to develop this tool.

Fisher's exact test results for preoperative variables

Categorical variable	Total number of patients with data collected for this variable	Fisher's exact test value	P-value (3 decimal places)	Inclusion of variable in logistic regression model based upon predefined cut-off (p
Histological subtype	338	25.866	0.364	Excluded
Neoadjuvant radiotherapy use	338	2.384	0.230	Included
Adjuvant radiotherapy use	338	2.832	0.226	Included
Reconstructive surgery type	338	20.263	<0.000	Included
Use of bone allograft in primary sarcoma surgery	338	20.263	0.409	Excluded
Type of prosthesis used in primary sarcoma surgery	338	7.090	0.103	Included
Number of major comorbidities (Charlson Score)	337	7.731	0.042	Included
Number of minor comorbidities (Charlson Score)	337	6.300	0.165	Included
WHO / ZOBRUD Score	335	3.555	0.491	Excluded
Clotting disorder or previous clot recorded	338	-	0.550	Excluded

Fisher's exact test results. Neoadjuvant radiotherapy, adjuvant radiotherapy, reconstruction type, prosthesis type, number of major and minor comorbidities are included in binomial logistic regression (p

VARIABLE NAME	TOTAL NUMBER OF PATIENTS WITH DATA COLLECTED FOR THIS VARIABLE	CHI-SQUARED GOODNESS OF FIT TEST RESULT ($?^2$)	P-VALUE	P VALUE IN RELATION TO CUT-OFF TO BE INCLUDED IN BINOMIAL LOGISTIC REGRESSION MODEL	INCLUSION OF VARIABLE IN BINOMIAL LOGISTIC REGRESSION MODEL BASED ON P < 0.25 CUT-OFF
GENDER	338	0.050	0.823	P > 0.25	EXCLUDED
SARCOMA CATEGORY	338	1.211	0.271	P > 0.25	EXCLUDED
SITE OF ORIGIN OF PRIMARY SARCOMA	338	6.580	0.160	P < 0.25	**INCLUDED**
TROJANI GRADE	223	1.405	0.495	P > 0.25	EXCLUDED
NEOADJUVANT CHEMOTHERAPY	338	1.485	0.223	P < 0.25	**INCLUDED**
ADJUVANT CHEMOTHERAPY	338	1.229	0.268	P > 0.25	EXCLUDED
POSTOPERATIVE TUMOUR MARGINS (FIRST RESECTION FOR PRIMARY SARCOMA). INCLUDES EXCISIONAL BIOPSY OR RESECTION. EXCLUDES INCISIONAL BIOPSY.	305	1.426	0.669	P > 0.25	EXCLUDED
PROSTHESIS USE FOR PRIMARY SARCOMA SURGERY	338	1.009	0.315	P > 0.25	EXCLUDED
SMOKING STATUS	321	3.195	0.202	P < 0.25	**INCLUDED**
CONCURRENT TUMOURS AT TIME OF PRIMARY SARCOMA DIAGNOSIS	338	1.406	0.236	P < 0.25	**INCLUDED**
PRIMARY TUMOUR DEPTH AND INVOLVEMENT WITH OTHER STRUCTURES	335	9.102	0.059	P < 0.25	**INCLUDED**
PRESCRIPTION OF ANTIPLATELET AND/OR ANTICOAGULATION BEFORE PRIMARY SARCOMA SURGERY	337	0.219	0.64	P > 0.25	EXCLUDED
PRESENCE OF AUTOIMMUNE DISEASE AT PRIMARY SARCOMA DIAGNOSIS	338	0.107	0.743	P > 0.25	EXCLUDED

Chi-square goodness of fit test results for preoperative variables. Primary sarcoma site of origin, neoadjuvant chemotherapy use, smoking status, concurrent tumours and primary tumour depth are included in binomial logistic regression model (p .
Primary tumour depth and involvement with other structure is borderline statistically significant at $p < 0.05$ level ($p = 0.059$).

CONTINUOUS VARIABLE		NUMBER OF PATIENTS WITHIN EACH SUBCATEGORY OF VARIABLE	MEAN	STANDARD DEVIATION	STANDARD ERROR MEAN	T-TEST	P-VALUE	INCLUSION OF VARIABLE IN BINOMIAL LOGISTIC REGRESSION MODEL BASED ON P < 0.25 CUT-OFF IN UNIVARIATE ANALYSIS
PATIENT AGE AT DIAGNOSIS OF PRIMARY SARCOMA (YEARS)	RECONSTRUCTIVE SUCCESS	267	51.31 YEARS	22.026	1.348	-0.783	0.434	EXCLUDED
	RECONSTRUCTIVE FAILURE	71	53.63 YEARS	23.055	2.736			
PREOPERATIVE PRIMARY TUMOUR SIZE (MM)	RECONSTRUCTIVE SUCCESS	151	80.18 MM	77.433	6.301	-0.238	0.812	EXCLUDED
	RECONSTRUCTIVE FAILURE	44	83.16 MM	55.225	8.325			
ANAESTHETIC TIME LENGTH FOR PRIMARY SARCOMA FIRST SURGERY (MINUTES)	RECONSTRUCTIVE SUCCESS	75	284.627 MINUTES	161.713	18.673	-0.449	0.654	EXCLUDED
	RECONSTRUCTIVE FAILURE	24	304.625 MINUTES	260.713	53.218			
FOLLOW-UP LENGTH (DAYS) - TIME INTERVAL BETWEEN FIRST SURGERY TO LAST ATTENDED CLINIC	RECONSTRUCTIVE SUCCESS	226	858.05 DAYS	903.747	55.412	0.665	0.506	EXCLUDED
	RECONSTRUCTIVE FAILURE	71	776.97 DAYS	943.063	111.921			

Independent t-test results for continuous variables. all variables were excluded from binomial logistic regression ($p > 0.25$). Equal variance was assumed for all variables as $p > 0.05$ in Levene's test for equality of variance.

Binomial logistic regression variables	B	S.E.	Wald	DF	P-value	Exp(B)	95% C.I.for(EXP(B)	
							Lower	Upper
Use of preoperative chemotherapy	.006	.494	.000	1	.991	1.006	.382	2.649
Zero major comorbidities			7.587	2	**.023**			
One major comorbidity	.989	.386	6.552	1	**.010**	2.689	1.261	5.735
Two or more major comorbidities	1.016	.607	2.802	1	.094	2.763	.841	9.083
Zero minor comorbidities			2.052	2	.358			
One minor comorbidity	-.591	.418	2.002	1	.157	.554	.244	1.256
Two or more minor comorbidities	-.390	.468	.694	1	.405	.677	.270	1.695
Use of postoperative radiotherapy	-.592	.380	2.427	1	.119	.553	.263	1.165
No prosthesis used			.488	2	.783			
Orthopaedic only prosthesis used	-.320	.525	.372	1	.542	.726	.260	2.031
Mesh and orthopaedic prosthesis, mesh only, tissue expander, breast implant prostheses	.142	.608	.055	1	.815	1.153	.350	3.794
Direct closure only			12.861	3	**.005**			
Skin graft without flap	.641	.670	.914	1	.339	1.898	.510	7.054
Locoregional or pedicle flap	1.191	.379	9.870	1	**.002**	3.290	1.565	6.915
Free flap	1.373	.521	6.936	1	**.008**	3.948	1.421	10.967
Site of origin: trunk			2.240	4	.692			
Site of origin: lower limb (knee and below)	-.362	.454	.635	1	.425	.696	.286	1.695
Site of origin: femur or thigh	-.035	.511	.005	1	**.945**	**.965**	.355	2.628
Site of origin: upper limb	-.672	.562	1.430	1	.232	.511	.170	1.536
Site of origin: head, face or neck	-.528	.599	.778	1	.378	.590	.183	1.907
Non-smoker			3.572	2	.168			
Previous smoker	-.466	.617	.571	1	.450	.627	.187	2.103
Current smoker	.766	.487	2.479	1	.115	2.152	.829	5.584
Superficial tumour – subcutaneous and/or cutaneous			4.159	4	.385			
Deep tissue tumour (involvement of tendons, deep fascia or muscle groups)	-.119	.438	.073	1	.786	.888	.377	2.094
Superficial / deep tissue tumour ard neurovascular involvement	-.023	.679	.001	1	.973	.977	.258	3.699
Composite tumour (superficial / cutaneous tumour / neurovascular involvement AND bone)	.614	.495	1.537	1	.215	1.848	.700	4.878
Bone tumour only (no mention of disrupting neurovascular or deep tissue structures)	-.356	.480	.550	1	.458	.700	.273	1.795
Concurrent cancer at time of primary diagnosis	-.230	.564	.167	1	.683	.794	.263	2.399
Constant	-1.556	.435	12.781	1	.000	.211		

Binomial logistic regression output using enter method variable selection. All variables included in multivariate analysis met predefined threshold (p

Poster #320 3253295

INTRAOPERATIVE ANGIOGRAPHY FOR PREDICTING WOUND COMPLICATION IN SOFT TISSUE SARCOMA OF THE EXTREMITIES: A PILOT STUDY

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Objective: For soft tissue sarcoma patients receiving preoperative radiation therapy, wound complications are common and potentially devastating; they may result in multiple subsequent surgeries and significant patient morbidity. The purpose of this study was to assess the feasibility of intraoperative indocyanine green fluorescent angiography (ICGA) as a predictor of wound complications in resections of irradiated soft tissue sarcoma of the extremities.

Methods: A consecutive series of patients of patients with soft tissue sarcoma of the extremities or pelvis who received neoadjuvant radiation and a subsequent radical resection received intraoperative ICGA with the SPY PHI device (Stryker Inc, Kalamazoo MI) at the time of closure. Three fellowship trained Orthopaedic Oncologic Surgeons were asked to prospectively predict likelihood of wound complications based on fluorescence. Retrospective analysis of fluorescence signal along multiple points of the wound length was performed and quantified. The primary endpoint was wound complication, defined as delayed wound healing or wound dehiscence, within 3 months of surgery. An *a priori* power analysis demonstrated that 5 patients were necessary to achieve statistical significance. Univariate and multivariate statistical analyses were performed to identify predictors of wound complications.

Results: 12 patients were consecutively imaged. The diagnosis was undifferentiated pleomorphic sarcoma in 8 (66.7%) of patients; 10 (83.3%) tumors were high grade. There were 5 patients with wound complications classified as "aseptic" in 4 cases and secondary to hematoma in 1 case. Using the ICGA, blinded surgeons correctly predicted wound complications in 75% of cases. In the area of wound complication, the mean % of maximal signal for wound complications was 49.1% during the inflow phase and 50.4% during the peak phase. The mean % maximal signal for peri-incisional tissue without wound complications was 77.5% during the inflow phase and 84.9% during the peak phase ($p=0.002$ and $p<0.001$). During the inflow phase, a mean ratio of normal of 0.62 maximized the area under the curve (AUC=0.91) for predicting wound complications with a sensitivity of 100% and specificity of 79.2%. During the peak phase, a mean ratio of normal of 0.55 maximized the area under the curve (AUC=0.95) for predicting wound complications with a sensitivity of 85.7% and a specificity 100%.

Conclusion: Intraoperative use of indocyanine green fluorescent angiography may help to predict wound complications in patients undergoing resection of preoperatively irradiated soft tissue sarcomas of the extremities and pelvis. Future studies are necessary to validate this technology in a prospective manner and to determine if interventions can be instituted to prevent predicted wound complications.

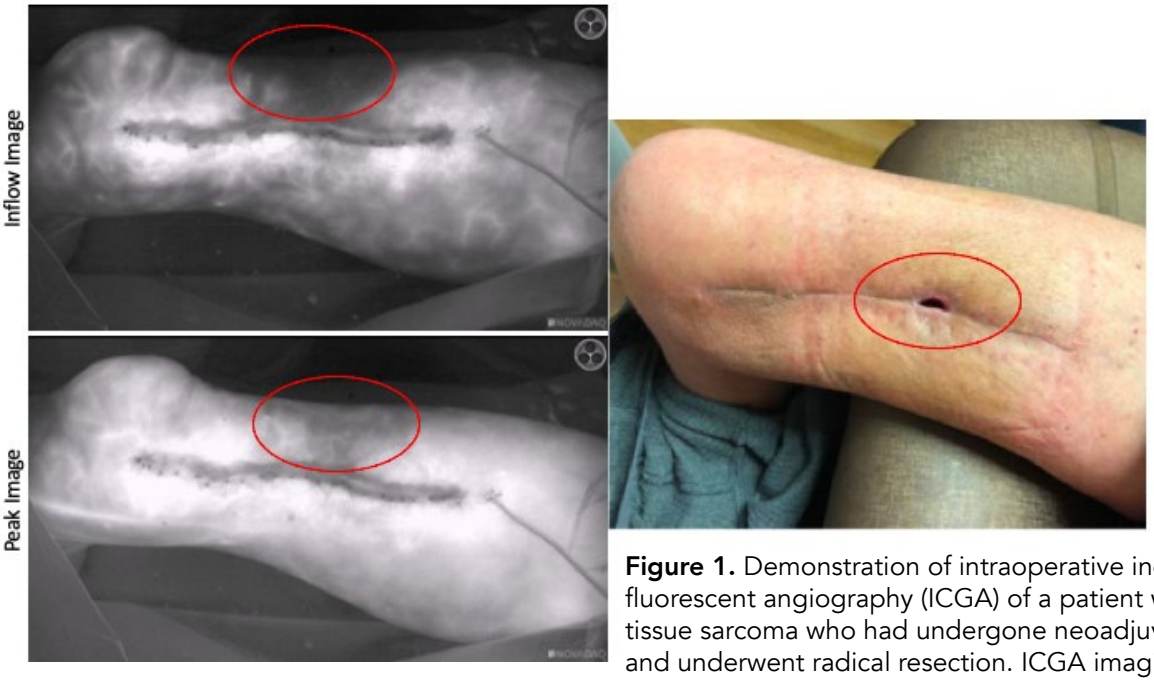

Figure 1. Demonstration of intraoperative indocyanine green fluorescent angiography (ICGA) of a patient with a diagnosis of soft tissue sarcoma who had undergone neoadjuvant radiation treatment and underwent radical resection. ICGA imaging demonstrates a perfusion deficit that correlates with the region of wound dehiscence, which was treated with wet to dry packings.

Poster #321 3255025

RECONSTRUCTION AFTER SOFT TISSUE SARCOMA OF THE LIMB USING MUSCLE SPARIN LATISSIMUS DORSI

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Objective: Schwabegger in 2003 first described a flap with a vertical skin component taking only the descending branch of the thoracodorsal artery as well as a muscular strip containing the artery. Since this study, the muscle sparing latissimus dorsi (MS-LD) is usually used in mammary reconstruction like described in Mojallal(2018) or Cook's study(2017). The evaluation of the functional recovery after muscle sparing latissimus dorsi (MS-LD) in comparison with latissimus dorsi (LD) pushes us to propose in a systematic way of this flap when the indication is posed in reconstruction of soft-tissue sarcoma (STS) of limbs and trunk wall.

Methods: We performed a retrospective analyze of our patients using MS-LD and LD with an analyze of their outcome with a specific questionnary : Quick DASH in pre and post operative time between 2016 to 2019 at the Institut Bergonié. The calculation of Quick DASH score = (sum of answers - 1) x 25 and the best score correspond to 0. We reported also characteristics of patients and tumors (size of coverage), presence of seroma, need and duration of drainage, time of hospitalization and time to resumption of activities of daily living.

Results: Out of a total of 22 patients, we chose to exclude the deceased patients and we were interested in the pateints who completed a questionnaire during the preoperative period. We thus distinguish 2 groups of 8 patients, one with MS LD the other with standard LD. The ratio of the questionnaire score before and after was sought and compared to those of the literature evaluated in breast reconstruction.

Our results of 16 patients showed a lower ratio of score after MS-LD vs standard LD and a shorter rehabilitation after MS-LD vs LD in the post operative time and allows the treatment of tumors of the same size and location in the same indications. So as in the article by Nassab et al, 2014 the realization of partial LD flap permit to reduce the use of analgesics, diminish the volume of seroma and duration of seroma and finally permit to obtain a shorter duration of hospitalization as part of the overall desire for rapid rehabilitation after surgery.

Conclusion: The muscle and nerve sparing LD flap appears to be a good and safe solution during reconstructive surgery for large defects and allows faster recovery after surgery.

Poster #322 3255197

ULTRASONOGRAPHY-GUIDED TUMOR EXCISION FOR IMPALPABLE AND ILL-DEFINED MALIGNANT SOFT TISSUE TUMOR

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Objective: The accurate excision of impalpable or ill-defined soft tissue tumors is usually thorny. In recent years, the image quality of ultrasonography (US) has improved considerably. The US has also an advantage regarding noninvasive and easy to get repeatable real-time imaging. We have used the US in the surgery of impalpable or ill-defined soft tissue tumors for the guide of tumor excision. The purpose of this study is to evaluate the usefulness of US-guided soft tissue excision.

Methods: The inclusion criteria of this study were the patient who was treated by ultrasonography-guided surgery at least 2 years follow-up or until death. Before the skin incision, all tumors were we detected the exact tumor location by the US. The probe and cable were wrapped in a sterile plastic cover to use in the operative field. This technique enabled the real-time identification of tumors. The tumor was monitored via adjacent fat tissue, fascia or muscle during the tumor excision (Fig. 1, 2). The histological surgical margins were evaluated in all tumors.

Results: Twenty patients (13 men & 7 women) were enrolled. The mean age was 53 years (35-70) and the mean tumor volume was 74.5 cm^3 (0.13−476.8). The mean follow-up term was 37 months (5-86) (Two tumors were primary and 4 were recurrent. The mean follow-up time was 35 months (24-54). Surgical margins were determined histologically as R0 in 19 patients and R1 in 1. Two local recurrences were detected, however both recurrences developed in the distance from the surgical field.

Conclusion: This study showed that the histological tumor-free margin was obtained by intraoperative use of the US for impalpable or ill-defined malignant soft tissue tumor excision. The limitation of this study is that the number of patients was rather small, so further analysis is necessary. US-guided surgery is simple, noninvasive, and useful to monitor the exact tumor location, and help to excise the tumor accurately.

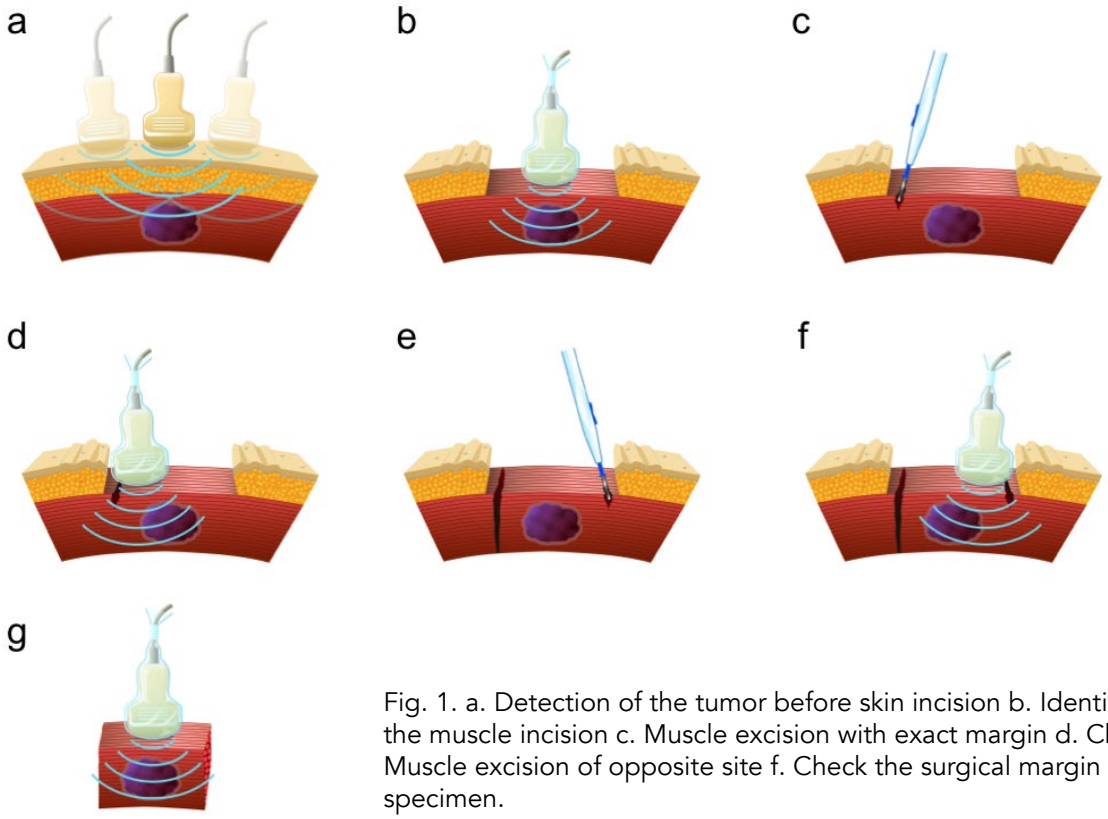

Fig. 1. a. Detection of the tumor before skin incision b. Identify the tumor for deciding the muscle incision c. Muscle excision with exact margin d. Check the surgical margin e. Muscle excision of opposite site f. Check the surgical margin g. Check the tumor in the specimen.

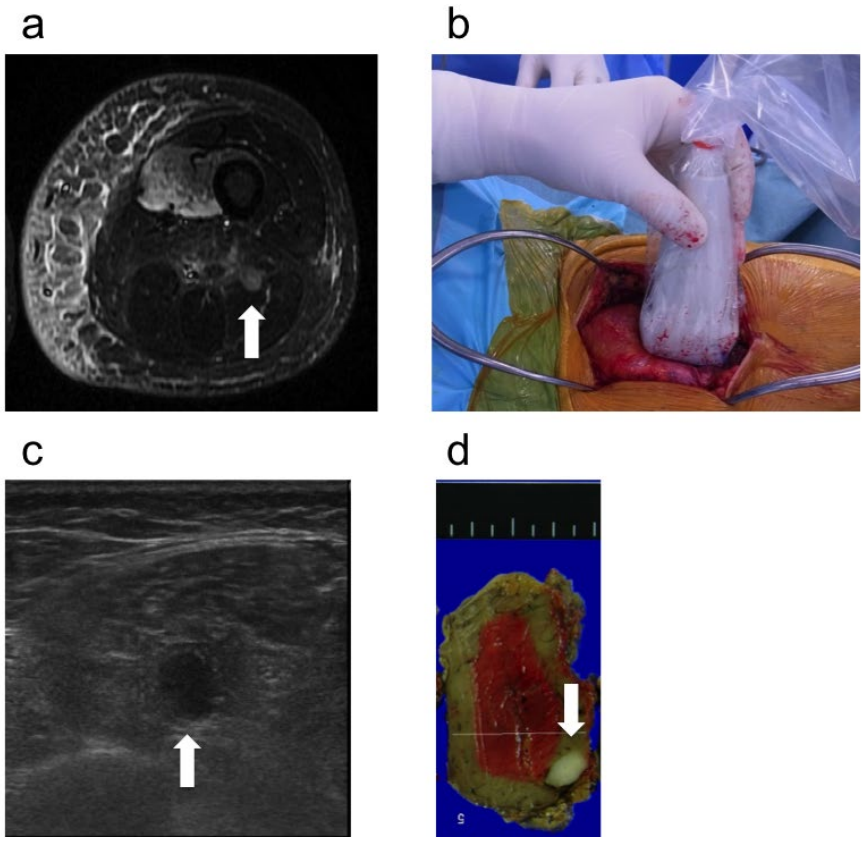

Fig. 2. 70-year old female. Recurrent leiomyosarcoma at the posterior thigh. a. MRI showed the small recurrent leiomyosarcoma (white arrow) in biceps femoris. b. After skin incision, the tumor was detected via biceps muscle by the US. c. US imaging detected the tumor (white arrow). d. A tumor (white arrow) was involved in the resected specimen.

Poster #323 3255858

IMMEDIATE, ALL INTERNAL DISTRACTION OSTEOGENESIS AND BONE TRANSPORT AFTER TUMOR RESECTION

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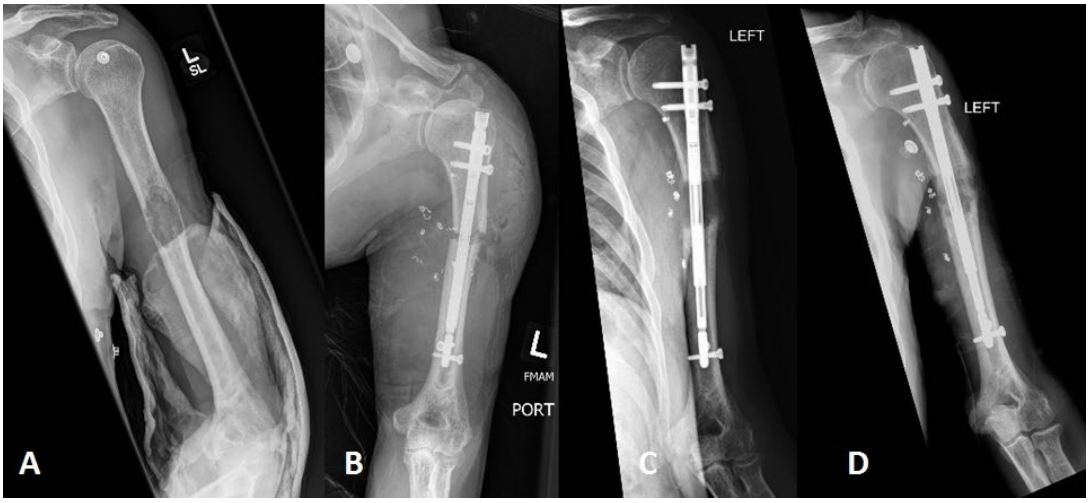
Objective: Reconstruction of large bony defects after tumor resection is challenging. The use of distraction osteogenesis and bone transport immediately after tumor resection allows for intercalary reconstruction utilizing the patient's own bone. All internal transport utilizing intramedullary nails is a newer technique for bone reconstruction. We present our initial experience utilizing these techniques.

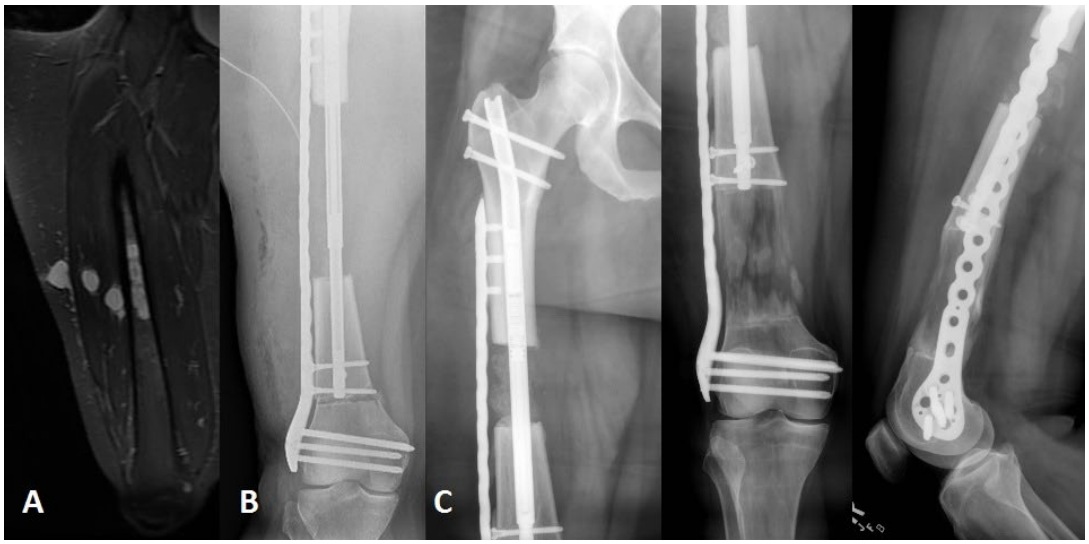
Methods: Six cases of all internal distraction osteogenesis and bone transport utilizing an electromagnetic intramedullary nail were reviewed. One patient was treated for metastatic myxoid liposarcoma, one for conventional high-grade osteosarcoma, three for for isolated metastatic renal cell carcinoma, and one for isolated neuroendocrine carcinoma. Three cases of plate assisted bone segment transport were performed, one case of acute shortening followed by immediate lengthening, and two cases utilizing a bone transport nail.

Results: A joint-preserving intercalary resection with negative margins was performed in all cases. Average follow-up was 10.9 months (5-18). The average defect was 9.7 cm (4-17). The 4 cm defect was treated with acute shortening followed by lengthening starting two weeks after surgery (Figure 1). The defects requiring bone transport averaged 11.3 cm (8-17) (Figures 2 and 3). All patients underwent successful transport of the bone with good regenerate noted. No complication including hardware failure or local recurrence was identified on latest follow-up.

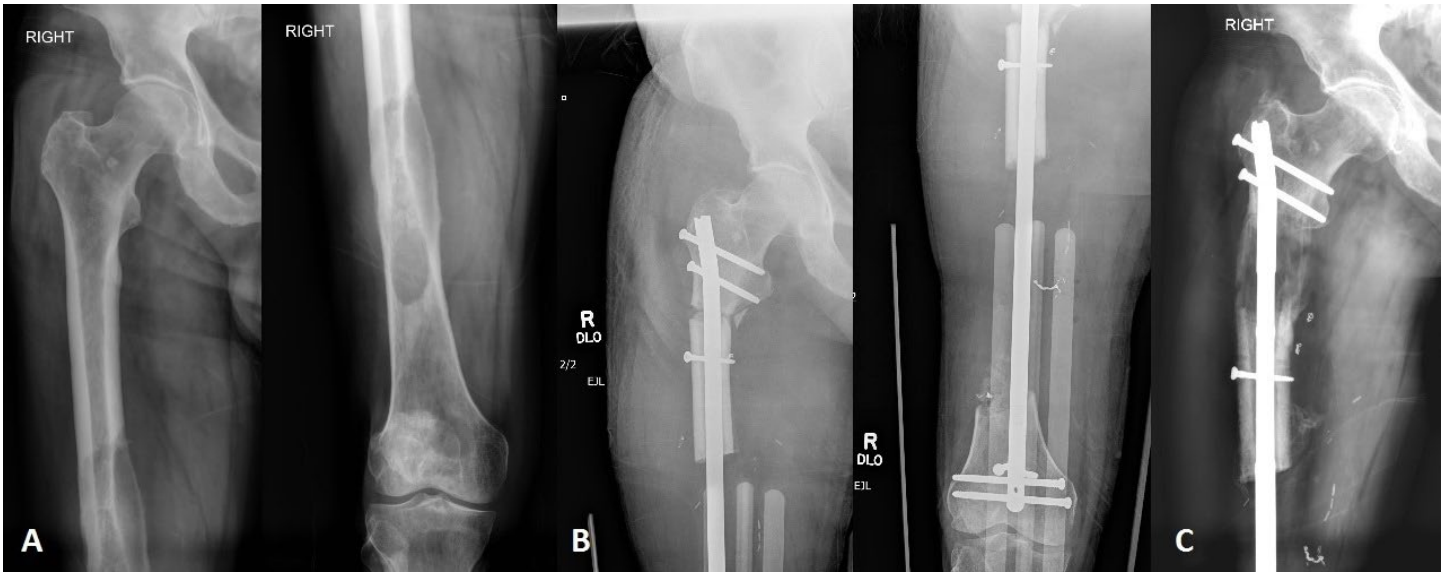
Conclusion: Immediate distraction osteogenesis and bone transport utilizing an electromagnetic nail after tumor resection was successful in all cases. The initial experience with this technique is promising for providing a viable method for reconstructing intercalary defects.



A) X-ray of the humerus demonstrating a destructive lytic lesion consistent with metastatic renal cell carcinoma. B) Immediately post-operatively after undergoing resection with acute shortening of 4 cm. C) After completion of the distraction osteogenesis. D) Good regenerate is noted at the most recent follow-up.



A) MRI of the femur demonstrating metastatic myxoid liposarcoma with contamination of the biopsy tract. B) X-ray of the femur immediately after surgery demonstrating the surgical resection site and distal osteotomy in preparation for plate assisted bone transport. C) Most recent follow-up with good regenerate noted distally and some incorporation of the bone graft at the remaining resection site.



A) X-rays of the femur demonstrating a destructive tumor consistent with metastatic renal cell carcinoma. B) Immediately post-operatively with placement of a bone transport nail and a 17 cm defect. C) Interval transport of the proximal segment with good regenerate noted.

Poster #324 3255974

MID- TO LONG-TERM CLINICAL OUTCOMES OF HEMICORTICAL RESECTION AND RECONSTRUCTION USING FROZEN AUTOGRAFTS IN OSTEOSARCOMA PATIENTS

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Objective: Osteosarcoma is the most common malignant bone tumor with a peak onset in teenage years. Together with the development of multidisciplinary therapy, its clinical outcome has improved. Wide excision and reconstruction using tumor megaprostheses is commonly performed as a standard surgery. However, in some clinical cases, considering long-term life expectancy after the treatment, joint preservation surgery using a biological reconstruction technique is attempted to aim for better limb function. In recent years, reports of reconstruction using liquid nitrogen-treated tumor-bearing bone after tumor resection have increased, but to the best of our knowledge, there are no reports of mid- to long-term clinical outcomes of hemicortical resection and reconstruction using liquid nitrogen-treated tumor-bearing bone in osteosarcoma. In this study, we investigated the mid- to long-term clinical outcomes of patients with osteosarcoma who underwent hemicortical resection and reconstruction using liquid nitrogen-treated tumor-bearing bone.

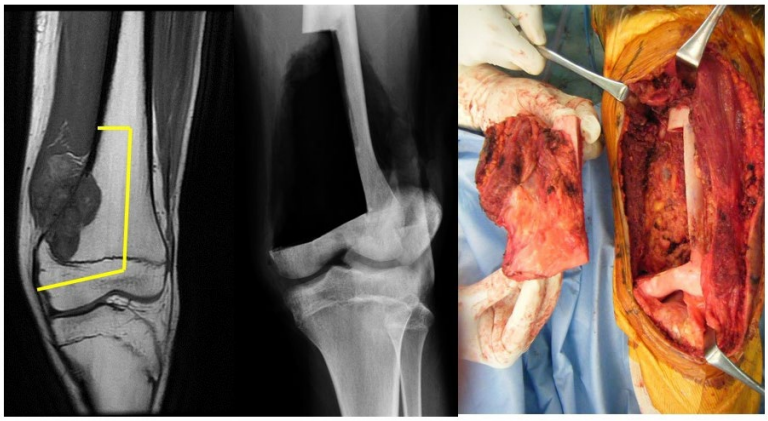
Methods: In this study, we investigated the treatment outcomes of patients with osteosarcoma who were capable of being observed for more than 5 years after hemicortical resection and reconstruction using liquid nitrogen-treated tumor-bearing bone. They underwent this surgical procedure because neoadjuvant chemotherapy was judged as effective. In all cases, tumor-bearing bone was treated using the free freezing method, and the treated bone was returned to the original site and rigidly fixed with locking plates and screws. After the surgery, bone fusion was evaluated by Xp and CT. Local recurrence and distant metastasis were evaluated using MRI and Tl scan. Limb function was evaluated based on the International Society Of Limb Salvage (ISOLS) score.

Results: The mean age was 14 years old (11–17) at the time of surgery, and the mean follow-up period after surgery was 80.7 months (68.7–112.0). The surgical sites were the distal part of the femur in two cases and proximal part of the tibia in two cases. In all cases, there were no local recurrence and distant metastasis, and all cases showed continuous disease-free survival. Bone fusion was achieved in all cases; complications such as absorption of the treated bone, fracture, and plate breakage were not observed. The treated bone was preserved in all cases. Surface infection occurred in one case of tibia, but the infection was managed well with additional treatment. Limb function was excellent in all cases, and the mean ISOLS score was 96.7% (94–100) at the time of the last follow-up. Favorable limb function was maintained even mid- to long-term after the surgery.

Conclusion: The grafted liquid nitrogen-treated bone was preserved even mid- to long-term after the surgery. All patients maintained excellent limb function. We consider that hemicortical resection and reconstruction using liquid nitrogen-treated tumor-bearing bone is a safe and beneficial surgical treatment method in carefully selected patients with osteosarcoma.

Operative views

Hemicortical resection



Poster #325 3256384

HYPERTHERMIC ISOLATED LIMB PERFUSION (HILP) IN EXTREMITY SOFT-TISSUE SARCOMA (ESTS): SHIFTING FROM PALLIATION TO THE NEO-ADJUVANT SETTING – BUT NOW OUTDATED? A MONOCENTRIC 18 YEAR EXPERIENCE

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Objective: HILP was primarily indicated in unresectable ESTS in order to avoid mutilating surgery by amputation. Reports demonstrated limb preservation in 80% of cases. Initial cases addressed palliative situations or recurrent STS. More recently, HILP has shown to obtain favorable results also in the neo-adjuvant setting. However, in this situation, alternative approaches exist. At Institut Bergonié, the indication of HILP in ESTS has remained very restrictive over time. However, despite the rarity of HILP procedures in our center, the rate of amputations in primary ESTS is #1%. We wondered whether in the long term HILP kept its promises as an alternative to amputation, or whether it had become obsolete.

Methods: Review of all HILP procedures performed at Institut Bergonié for ESTS through 2001-2018. Demographic data, tumor characteristics and outcome were extracted from Conticabase, a shared european sarcoma database constituted after patient consent and completed by HILP data extracted from patient charts. We distinguished 4 patient groups according indication of HILP, namely palliation (Pall), local recurrence after prior irradiation (XRT-LR), local recurrence without prior irradiation (noXRT-LR), and primary ESTS treated by neoadjuvant HILP (Prim). Endpoints were the final rate of amputation, local tumor control and death.

Results: HILP was performed in 68 patients, 39 men and 29 women, aged median 60 years. ESTS were located in the lower limbs (45 cases) and upper limbs (23 cases), comprising various histotypes most being undifferentiated sarcoma. The median TNF dose was 1mg. Characteristics and outcomes of 6 Pall, 15 XRT/LR, 21 noXRT/LR and 26 Prim patients are illustrated in the table. No patient in the palliative group had to be amputated, but all died. In the LR groups, amputation could be contained to 29% in the noXRT/LR group, but final local control was poor in both. Prim patients had to be amputated in 27% and nearly half them have died.

Conclusion: In this series of patients with various indications of HILP, late treatment results are globally poor. In the primary setting, HILP does not prevent patients to be amputated in ¼ of them, nor to die in ½ of them. Alternative, tumor tailored approaches differentiating local from general risks should be considered in these patients.

Table. Patient characteristics and Outcome in 68 patients with extremity soft-tissue sarcoma (ESTS) treated according four indications of HILP.

HILP Indication	N	Age (median)	Surgery after HILP (%)	F-up (median, m)	Amputation (%)	Local control (%)	Death (%)
Pall	6	69	1 (17)	14	0 (0)	3 (50)	6 (100)
XRT/LR	15	60	6 (40)	51	6 (40)	8 (53)	5 (33)
noXRT/LR	21	65	14 (67)	61	6 (29)	9 (43)	6 (29)
Prim	26	54	15 (58)	53	7 (27)	19 (73)	12 (46)

Pall.: palliative (metastatic) ESTS XRT/LR: local recurrence after prior radiotherapy noXRT/LR: local recurrence without prior radiotherapy Prim: primary, no metastatic ESTS

Poster #326 3256704

DOUBLE LEVEL BONE TRANSPORT FOR SARCOMA RECONSTRUCTION

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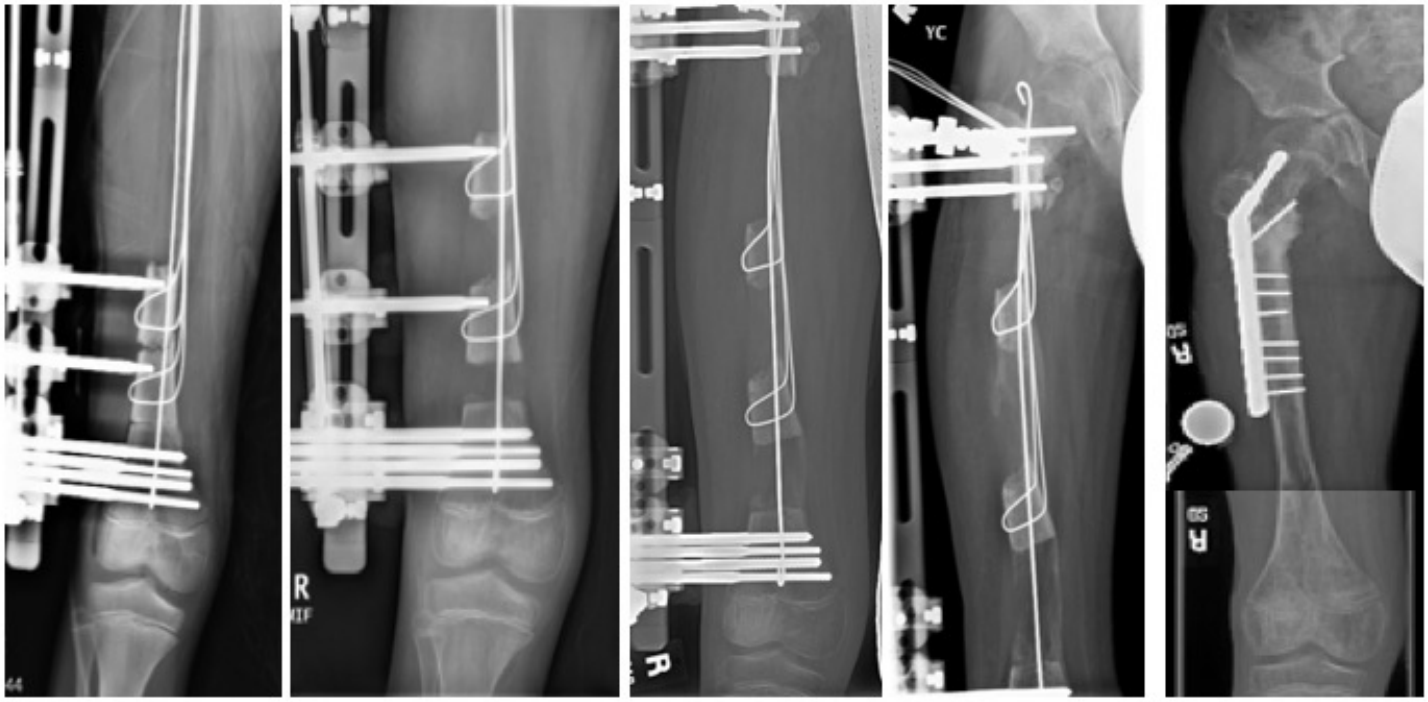
Objective: The objective is to review the efficacy and complications of double level transport performed wtih cables versus standard half pin configuration, comparing functional scores and range of motion of the affected extremity. Our hypothesis is that double level cable transport is as safe, effective and efficient as standard Ilizarov double level transport with half pins to reconstruct large bone defects after resection of sarcomas.

Methods: We evaluated 22 cancer patients who underwent unidirectional, parallel double level bone transport of the lower extremity at our institution since 2014. Data were collected regarding demographics, oncologic characteristics, treatment details, and postoperative complications. Functional outcomes were assessed using the physician-reported Musculoskeletal Tumor Society (MSTS) scores. We reviewed radiographs, clinical notes, and physical therapy evaluations.

Results: The mean age at time of surgery was 19 years (range 6 - 62) and minimum follow up is 12 months with a mean of 30 months (range 12 - 53 months). The most common diagnosis was osteosarcoma (52%), followed by chondrosarcoma and Ewings sarcoma each with 3 patients (13%). All patients are alive at most recent follow up, though 4 patients (17.4%) are alive with disease, the remainder have no evidence of disease. Three patients underwent tibio-talar joint fusion. No patients had positive margins at resection, all patients completed the bone transport reconstruction, and the rate of limb survival in our study is 100%. The mean defect size was 15.5cm (range 9 - 25cm) and the mean external fixation index was 0.8 months/cm. The mean MSTS score at follow up was 26.9 (range 14 - 30). The most common complication was infection requiring surgical debridement in 53% of our patients.

Conclusion: Despite high rates of infection, double level cable transport is an effective method for biological reconstruction of large bony defects with an acceptable external fixation index and high, durable functional scores. The infection rate is likely caused by the prolonged use of external fixators during concomitant chemotherapy in majority of patients (69.6%). We found no enhanced risk of local recurrence in our series. We postulate that the use of double level cable transport is safe and tolerable for reconstruction after resection of malignant bone neoplasms.



Representative example of double level cable transport of the femur converted to internal fixation at the end of transport.

Poster #327 3229449

DID THE PROPORTION OF SOFT TISSUE SARCOMAS PRESENTING AS UNPLANNED EXCISIONS INCREASE DURING THE GREAT RECESSION?

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Objective: The Great Recession lasted from December 2007 to June 2009 and is considered to be the period of worst economic decline since the Great Depression. Studies have since showed a profound negative impact across healthcare. These include declines of self-rated health status as well as increases in morbidity, mortality, and suicide. The growth of healthcare spending in the United States also slowed dramatically, and deferral of elective procedures were well-documented.

Unplanned excision of soft tissue sarcomas (STSs) are a common problem in musculoskeletal oncology. It results from attempted resection of a presumably benign growth by a surgeon without adherence to oncologic principles. They carry increased risk of positive margins at re-resection, morbidity, and the need for eventual amputation.

However, referral to a musculoskeletal oncologist at a tertiary care center can be costly and time-consuming, and financial constraints on both patients and surgeons could lead to attempted management in the community. To this end we sought to answer whether the proportion of unplanned excisions for soft tissue sarcoma changed during the Great Recession.

Purpose: We hypothesized that the proportion of unplanned partial excisions of STS would be increased during the Great Recession when compared to later years after its end. We further aimed to identify whether urban/rural status or distance from the authors' facility mattered.

Methods: All STS patients referred to our institution between 2008 and 2016 were reviewed. Demographic and location information of patients was collected. Rural/urban designations were determined by 10 mile proximity from a city of at least 40,000 people. Operative reports were reviewed to identify patients who had an unplanned excision at a referring facility. The proportion of STSs that presented as unplanned excisions were evaluated by χ^2 test partitioned by year. This was done first as a 2x9 test including all years available (2008-2016). The proportions during the recession (2008-2009) were then compared to later years (2015-2016).

Results: A total of 380 STS resections were identified, of which 112 (30%) had undergone an unplanned excision at an outside facility. The percentage by year ranged from 24% in 2015 to 39% in 2013. The percentage of unplanned excisions during the recession (2008-2009) was 29% compared to 27% for 2015-2016. This difference was not statistically significant (χ^2, $p = 0.94$). There was further no significant variation when all years were compared (χ^2, $p = 0.80$).

Urban-residing patients made up 275 (72%) of the total patients. Unplanned excisions made up 34.2% of rural patients and 27.8% of urban patients (χ^2, $p = 0.20$). Subgroup analysis also found no difference in the rate of unplanned excisions during the recession when confined to either urban or rural patients.

A post-hoc power analysis based on a χ^2 test showed that for a significance of 0.05 and 80% power, the same size would allow detection of a moderate effect size (ω=0.217) when comparing the years 2008-2009 and 2015-2016.

Conclusion: Contrary to the hypothesis, the data was not able to discern a difference between unplanned excision rates during the great recession, although the limited sample size limited the power of the χ^2 test.

More study is warranted on the temporal, geographic, and socioeconomic patterns of unplanned STS excision. Due to the rarity of STSs in general, future work in this area may benefit from larger, possibly national databases.

One strength of the study is that the authors' institution is the primary sarcoma center in its geographic catchment area, which encompasses the entire state and beyond. This lends high confidence in the estimate of a 30% unplanned excision rate, which as concerning, as presumably almost all such patients will be referred there rather than a competing center.

Poster #328 3244000

HARLEQUIN SYNDROME FOLLOWING MICROWAVE ABLATION THERAPY IN A 20-MONTH-OLD WITH PARASPINAL MASS

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Objective: Our goal is to describe a case of Harlequin Syndrome associated with microwave ablation in the treatment of a symptomatic paraspinal mass in a child. To our knowledge, no case of Harlequin Syndrome associated with minimally invasive procedures has been reported. Harlequin Syndrome is an irreversible, rare neurological condition characterized by unilateral sweating and flushing of the face, neck and upper chest. Though the specific mechanism is unclear, the majority of cases are believed to occur as a result of contralateral lesions along the bilaterally symmetric sympathetic chain, in close proximity to the stellate ganglion and the superior cervical ganglion (T2-T3). Since a lesion in the nerves of the sympathetic trunk is purported to be the cause of both Harlequin Syndrome and Horner Syndrome, it is easy to confuse the two neurological conditions. However, Horner Syndrome can be distinguished from Harlequin Syndrome as symptoms of Horner Syndrome are ipsilateral in relation to the site of lesion and is characterized by miosis, partial ptosis, anhyrosis, and enopthalamos. Though Harlequin Syndrome does not affect long-term survival, the quality of a patient's life may be negatively impacted by the irreversible neurological condition. Children and parents of children with Harlequin Syndrome frequently suffer from psychological stresses associated with embarrassment that arises due to unilateral facial flushing and sweating.

Methods: We conducted a literature search on Pubmed and Google Scholar using the keywords and phrases, "harlequin syndrome" "paraspinal mass" "pediatric."

Results: In current literature, there are four reported cases of pediatric patients with Harelquin syndrome associated with iatrogenic treatment of a paraspinal mass. (SurgNeurol 2007 Oct; 68(4): 461-3; PedAnesthesia June 2007; 17(6):597-598; BJA Dec 2005;95(6), 822-824; AAPrac April 2018; 10(8): 215-217) In all four of these cases, the patients were treated with radical excision.

We describe a 20-month-old patient with stage I histologically favorable neuroblastoma who presented at 16 months of age with bilateral LE weakness, generalized irritability, and pain. Imaging showed a dumbbell-shaped tumor at the T6-T7 site. After four cycles of chemotherapy, there was an increase in the size of the mass with encroachment of the cervical spinal cord. Metaiodobenzylguanidine (MIGB) scan showed had increased uptake at the site of mass (measure of tumor activity). However, a biopsy showed that the neuroblastoma had differentiated into a benign ganglionueroblastoma. At our multidisciplinary tumor board, discussion with neurosurgery and pediatric surgery concluded that a resection so close to the T6-T7 sympathetic region would be very risky and morbid. Instead, microwave ablation therapy was offered after informed consent. CT guided microwave ablation at the left T3-T6 region was performed and well tolerated. Following ablation therapy, symptoms characteristic of Harlequin Syndrome was contralaterally manifested in the patient, namely unilateral (right side) flushing and redness of the face (Figure 1). However, the latest imaging of the patient at five years of age showed a significant decrease in mass size, decompression of the spinal cord, and necrosis of the mass (Figure 2).

Conclusion: We hope that this case may increase awareness of the risk of iatrogenic Harlequin Syndrome when considering minimally invasive procedures as well as surgical excision treatment for children who present with a paraspinal mass.

Figure 1: A postoperative photo of contralateral hemifacial flushing and sweating (with parental consent)

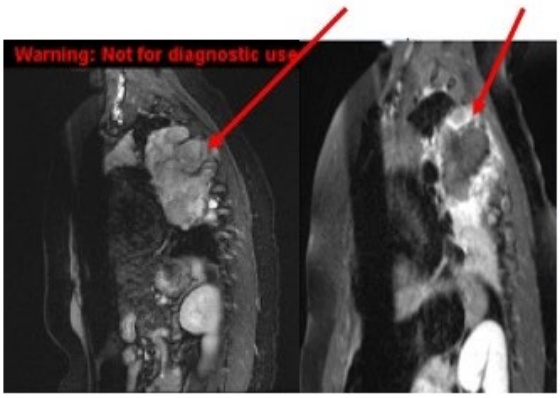

Figure 2: Before and after 3 months of microwave ablation therapy

Poster #329 3253130

OUTCOME OF SURGICALLY TREATED BONE METASTASES OF EXTREMITIES FROM RENAL CELL CARCINOMA

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Objective: Bone metastasis from renal cell carcinoma (RCC) often requires surgical treatment. Bone metastasis of extremities need surgical treatment to prevent pathological fracture due to the osteolytic lesion. Basically, radical surgery has been recommended for the isolated bone metastasis in RCC positively. However, in late years the management of metastatic RCC has changed due to the advent of several molecular targeted drugs, so the change of surgical intervention for bone metastasis in RCC is probably required. The aim of this study is to identify outcome following surgical treatment for bone metastasis in RCC.

Methods: We retrospectively monitored 19 patients with 29 bone metastases in RCC who underwent surgical treatment for extremities and pelvis between 2008 and 2018. The patients with vertebral involvement were excluded from this study. There were 16 male and 3 female patients with an average age of 66 years (range, 43–83 years). We divided the surgical procedures into internal fixation only (9 lesions), intralesional curettage (12 lesions), and metastasectomy (8 lesions). We evaluated Memorial Sloan Kettering Cancer Center (MSKCC) score, number of metastasis, history of chemotherapy and radiotherapy, and administration period of molecular targeted agents or immune checkpoint inhibitor. Overall survival was calculated with Kaplan-Meier analysis. The log-rank test was used to evaluate the effect of different variables on overall survival.

Results: The overall survival (OS) for the patients after surgery was 63% at 5 years and with the median survival of 72 months. The progression free survival (PFS) was 8 months. The OS and PFS related to the MSKCC score which had evaluated before the bone metastatic surgery. The previous chemotherapy, postoperative chemotherapy period, pathological fracture and tumor progression of surgical site were prognostic factors in log-rank analysis. The tumor progression of surgical site had no relevant to surgical procedures. Patients without previous chemotherapy or patients with postoperative chemotherapy for more than 18 months after bone metastasis surgery had a significantly better survival (Fig.1, 2).

Conclusion: The mainstream treatment for a solitary bone metastasis of RCC has been metastasectomy. The prognosis of metastatic RCC have improved due to new chemotherapy other than cytokine therapy, so we should change surgical intervention of bone metastasis of RCC. The MSKCC scoring system is useful to predict the postoperative prognosis of patient with bone metastasis of RCC. In this study, it was revealed that chemotherapy was a relevant prognostic factor of the bone metastasis of RCC. We need to perform surgical treatment that prevent SREs and do not disturb chemotherapy. The future study is needed to achieve a larger sample size and investigate the prognostic factor of surgically treated bone metastasis in RCC.

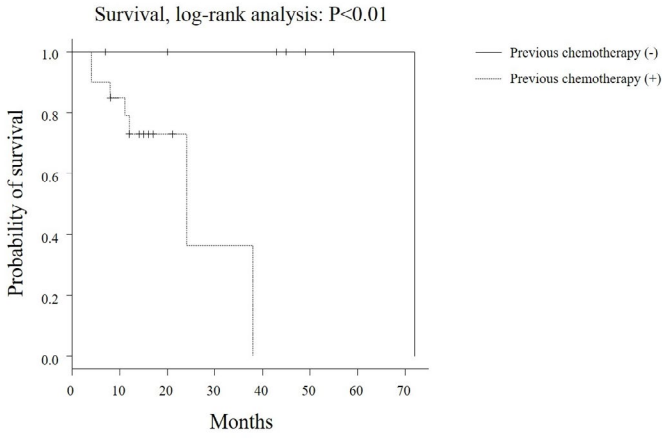

Fig.1

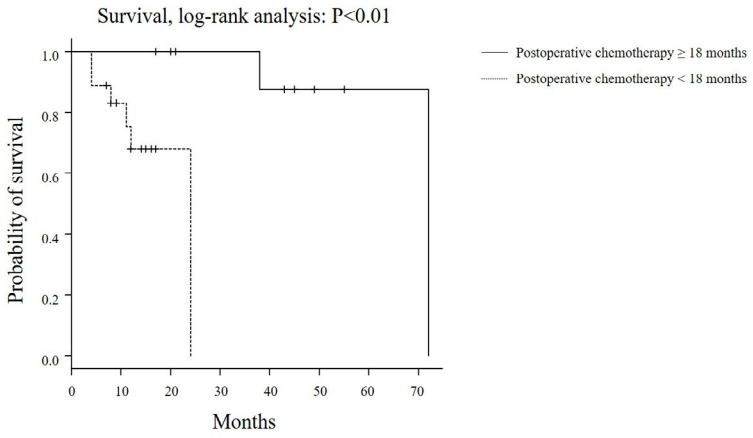

Fig.2

Poster #330 3253972

IS NEOADJUVANT CHEMOTHERAPY BENEFICIAL IN CARDIAC SARCOMA

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Objective: To determine if neoadjuvant chemotherapy is beneficial in cardiac sarcoma.

Methods: Literature scan of the Pubmed database using "neoadjuvant chemotherapy" , Chemotherapy and "cardiac tumour/tumor" disclosed 66 articles.

Results: The number of papers that discussed cardiac sarcoma, neo-adjuvant chemoherapy, margins and outcome were sparse. The largest study discussed less than 50 patients while most discussed less than thirty and usually less thn 15 patients. The presence of microscopically negative margins (R-0) was overwhelmingly the most important determinant of survival, not the administration of neo-adjuvant chemotherapy, which may have led to more R-0 resections. However, it was unclear whether the neo-adjuvent:R-0 effect was chemotherapy effect or time effect, with the more recent series having had more R-0 resections.

Conclusion: Reports of Neo-adjuvant chemotherapy for cardiac sarcoma are sparse. They mostly come from highly specialized centres. From the literature, it is unclear if neo-adjuvant chemotherapy prolongs survival or truely leads to more R-0 resections. The effect of neo-adjuvent chemotherapy may actually lie in the identification of those patients who do not respond and thus never undergo surgery. This has not been discussed in the literature. an international database would answer this and other questions.

Poster #331 3255327

REAMED VERSUS UNREAMED INTRAMEDULLARY NAILING FOR THE TREATMENT OF IMPENDING AND PATHOLOGICAL HUMERAL SHAFT FRACTURES: A RETROSPECTIVE COMPARATIVE STUDY

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Objective: There remains a compelling biological rationale for both reamed and unreamed intramedullary nailing for the treatment of long bone fractures. This particular question has never been addressed for impending and pathological fractures of the humeral shaft.

The purpose of the study was to compare uncemented reamed (R) versus unreamed (UR) intramedullary (IM) nailing for the treatment of Impending and Pathological fractures of the humeral shaft in terms of: (A) 24-h Post-operative pain; (B) Blood transfusion requirements; (C) Surgical time; (D) Surgical Complications; (E) Medical complications and length of stay; and (F) Consolidation rates (pathological fractures).

Methods: A retrospective comparative study of adult patients with an impending or pathological humerus shaft fracture between January 2013 and December 2018 was conducted. Humerus fractures treated non-operatively or with plating with or without cementation were excluded. Perioperative care was standardized, and the surgical indication was surgeon's preference. Demographic characteristics between both groups were similar. The primary outcome was pain during the first 24 hours postoperatively measured by visual analogue score (VAS) and total daily dose of opioid (in morphine milligram equivalents (MME) per day. Secondary outcomes were: Blood requirements (Estimated blood loss; Need for blood transfusion and 24-h change in HB), surgical time, surgical complications (Intra-operative fracture, radial nerve palsy, early and late infection, and need for revision surgery), medical complications (cardiovascular events), length of stay, and fracture consolidation. Student t-test, Mann-Whitney-U and Chi-square tests were used to detect significant differences between the variables within the two study groups. Multiple linear regression was done to adjust for possible confounders of the primary outcome.

Results: A total of 53 patients (33 R vs 20 UR) underwent humeral nailing. Fifteen (28%) were impending fractures (7 R vs 8 UR). The average age was 65.17+/- 11.9. Females were 52.83% (28/53). Multiple myeloma (49%) followed by metastatic carcinoma (39.6%) were the most common etiologies. Other associated fractures were observed in 26.42% (14/53) of patients (6 R vs 8 UR; p=0.081). Impending fractures constituted 28% of whole sample (15 fractures). Radiotherapy was performed in 73.58% (39/53) of patients. Average follow up was 6.75 months (range: 1-48 months). Pain score (5.13+/-0.68 R vs 6.78+/-0.62 UR; p=0.082) and total dose of opioids (33.125+/-27.6 R vs 33.3+/-22.28 UR; p=0.462) during the first 24 hours after surgery didn't show statistical significant difference. Blood transfusion was more common within the reamed nails group (12 R vs 4 UR; p=0.021) with a tendency of higher blood loss (238.39+/- 215.18 R vs 129.25+/-119.63 UR; p=0.061). There was not statistical significant difference in terms of surgical time, surgical and medical complications, and length of stay. There was a consolidation rate of 71.05% (27/38) with no statistical difference between both groups (73.08% (19/26) R vs 66.67% (8/12) UR; p=0.685).

Conclusion: Unreamed IM nailing of impending or pathological humeral shaft fractures is a safe, rapid and effective procedure. This study demonstrates a possible benefit in terms of less need for blood transfusions, and a tendency of less blood loss with no difference in consolidation rates within the pathological fracture group.

Poster #332 3255777

OUTCOME AFTER BIOLOGICAL RECONSTRUCTION FOLLOWING INTERCALARY RESECTION OF MALIGNANT BONE TUMORS

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Objective: Intercalary resection offers salvage of native joint & better long term function. Several reconstruction modalities after intercalary resections are reported but there are no optimal methods which can provide a long-term reconstruction with fewest complication. We present the outcome of reconstruction after intercalary resections using biological methods (recycled autograft/ vascularized/ non vascularized fibula/ or combined reconstruct).

Methods: We conducted retrospective review of 10 patients (9 males, 1 female); median age of 12.8yrs undergoing reconstruction using a recycled autograft (ECRT, n=4; ECRT + vascularized fibula, n = 2; vascularized fibula only, n=3 and non-vascularized fibula, n=1). Femur was involved in 4 cases, tibia in 3 cases, and humerus in 3 cases. Histological diagnosis was osteosarcoma in 5 cases, Ewings sarcoma in 3 cases, chondrosarcoma in 1 case and metastatic renal cell carcinoma in 1 case.

Results: Mean resection length was 16.1 cm (5-24cm). all patients were alive till last follow up. Mean follow up was 16.6 months (11 months - 26months). Mean period to union at metaphyseal osteotomy site was 14.3 weeks and diaphyseal osteotomy site was 22.8 weeks. No patient suffered infection, implant failure, or fracture of graft. All patients with femur resections developed decreased knee ROM. One patient with ECRT + vascularized fibula reconstruction developed bilateral foot drop. A patient with L/E tibia resection developed marginal flap necrosis which required a free flap. The mean MSTS score was 23.6 (17-29) at last follow-up.

Conclusion: Biological methods offers advantage over prosthesis in terms of reduced cost and reduced risk of infection. Combining vascularized fibula with recycled autograft in femur along with rigid fixation with a locking plate may offer superior outcome than only allografts/ recycled bone.

Poster #333 3256553

POST-RADIATION PATHOLOGIC FEMUR FRACTURES FOLLOWING RESECTION OF SOFT TISSUE SARCOMAS: IS ENDOPROSTHETIC RECONSTRUCTION A GOOD OPTION?

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Objective: To assess the outcomes and complications of patients who underwent tumor prosthesis replacement as a treatment for femoral radiation-associated fractures (RAF).

Methods: A retrospective study with a prospective database. We included 20 patients who had a tumor prosthesis as a management of their post radiation femur fracture using either proximal femur, distal femur or intercalary prosthesis. We had 14 patients who had proximal femur, 5 patients who had an intercalary replacement, and 1 who had distal femur replacement. The TESS and MSTS scores measured pre-op and the latest measure during follow-up are used to assess their functional outcome and complications such as infection, and reoperation.

Results: We had 20 patients included in our study. The mean age at tumor prosthesis surgery was 67 years (range 47-84). 7 patients received a tumor prosthesis as initial RAF treatment, 13 patients received a tumor prosthesis after failure of femur open reduction internal fixation. Mean follow-up from STS resection to fracture: 88 months (range 6-228). Mean follow-up after tumor prosthesis: 62 months (range 2-192). 4 (20%) developed surgical complications, 3 had surgical site infection, which required irrigation, debridement and liner exchange with retaining the remaining prosthesis. 1 developed a Prei prosthetic fracture, an intercalary that was converted to proximal femoral prosthesis. The PreOp and last follow up TESS score was 65.24 and 63.85 respectively. The PreOp and last follow up MSTS87 score was 24.50 and 25.33 respectively. The PreOp and last follow up MSTS93 score was 66.41 and 69.69 respectively. The patients latest functional scores were similar to their pre-fracture score level on average.

Conclusion: Risk Factors for RAF (Female gender, High dose of radiation (60-66 Gy), and periosteal stripping. The most important point is trying to avoid RAF form the start. Using endoprosthesis for the treatment of RAF rather than IM nail fixation due to the very high rate of nonunion, especially in elderly patients is a good option. Patients with endoprosthetic reconstruction returned to their pre-fracture functional level. Not to forget that we are dealing with a very complex group of patients who have many co-morbidities. We think that for younger patients, reconstruction of the femur with a vascularized fibula remains a reasonable option.

Poster #334 3256555

LONG TERM OUTCOMES OF VASCULAR RECONSTRUCTIONS IN SARCOMA SURGERY. WHAT TO EXPECT FROM VEIN RECONSTRUCTION?

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Objective: Limb salvage surgery with vascular reconstruction is currently considered as the standard treatment for extremity soft tissue and bone sarcoma (STS/BS), with equivalent patient survivals compared with amputation. Few publications assessed this specific type of reconstruction and their vascular outcomes, especially when vein is reconstructed. In this situation, surgeon still debate on whether vein has to be reconstructed.

In this study, surgical and functional outcomes after arterial and/or venous reconstruction in limb salvage surgery for STS were analysed with a focus on complications and outcomes of patient who underwent vein reconstruction.

Methods: Our prospective database was reviewed and all patients who underwent vascular management as part of limb salvage surgery for extremity STS or BS from 1996 to 2016 were included in this study. Incidence of surgical complication, graft patency, and patients' vascular and functional outcome were reviewed.

Results: During the study period, 52 STS patients (29 men, 23 women; mean age: 56 years) were included. Mean follow-up was 61 months. 33 patients had an artery + vein reconstruction, 11 patients had a vein ligation with arterial reconstruction, 5 had their vein alone reconstructed and 3 patients had a vein ligation only. All conduit in both arterial and venous reconstructions were autologous vein grafts (great saphenous or deep femoral) except for 2 synthetic grafts. Over the follow-up, 5% of patients recurred and 25 patients died (50%). 6 patients (11.5%) needed an amputation of the initially salvaged limb (3 because of reconstruction failure (thrombose or leakage) and 3 for infection control). There were 6 post-operative DVT, 8 superficial infections, and 6 flap failures with deep infection. 3 successful vascular revisions (1 arterial for acute occlusion, 2 venous: one graft leakage and one pseudoaneurysm) were performed besides the amputation cases.

At the last follow-up, 77 % of available patients; the vein reconstruction in arteriovenous reconstructions were patent on US. Vein graft patency was 100% in venous or arterial only reconstructions. Total, 86% of vein grafts were patent. One-year and 5-year post-op mean MSTS score were of 77 and 86, and TESS scores 75 and 85, respectively. Seventy percent had oedema and 40% used compression stocking. 50% had significant "vascular" symptoms (cramps, tightness or heaviness).

Conclusion: Limb salvage surgery of soft tissue tumour combined with vascular reconstruction showed favourable long terms surgical and functional outcomes with good local control (5% local recurrence rate). As reported in literature, oncological outcomes were comparable to classical survival rates of STS, advocating for limb salvage even when vessels are involved.

Even though amputation and complications rates were high (mostly because of selection bias studying more severe case and more complex surgeries), limb salvage should be considered (89% limb survival rate) with low impact of vascular symptoms on functional outcomes. Patients had indeed similar outcomes compared with those usually reported in STS resection where vessels weren't involved and even though some of them had significant vascular symptoms, this didn't seem to impact their overall function and their daily activities.

Vein reconstructions showed very good patency results. Besides pre-operative assessment, reconstruction decision was often intra-operatively taken by the vascular surgeons (mostly due to number of remaining patent axes and flow-back after tumour resection). Though comparison wasn't statistically feasible because of sample size and heterogeneity of cases, there was a tendency of a better function in patients with vein reconstruction (1 year-MSTS: 85) compared with no reconstruction (1-year MSTS: 77). In selected cases, venous reconstruction has to be considered as a safe procedure, which might provide better functional results.

Poster #335 3214469

SANDWICH ISOLATION SURGERY PREVENTS LOCAL RECURRENCE IN PROGRESSIVE DESMOID TUMORS: A PILOT OBSERVATIONAL STUDY

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Objective: Desmoid tumors are highly recurrent especially when involving nerves and blood vessels. Isolating desmoid tumors from normal tissues with artificial barriers may deprive desmoid tumors of nutrients. The aim of this observational study was to prospectively assess the efficacy of a new surgery technique, named as sandwich isolation surgery, on preventing the local recurrence of progressive desmoid tumors.

Methods: Patients with progressive desmoid tumor involving adjacent nerves and blood vessels and received sandwich isolation surgery were eligible for enrolment. Sandwich isolation surgery refers to using a biomaterial un-absorbable patch to envelop involved neurovascular bundles after marginal or intralesional excision of desmoid tumors, isolating residual tumor or tumor bed from normal tissue, and forming a "normal tissue- biomaterial patch -tumor/tumor bed- neurovascular sheath" sandwich structure.

Results: Nine patients were included in the study. Among them, six had recurrent tumors and received at least once resection surgery before sandwich isolation surgery. These patients were followed up for 16.7-56.7 months (median: 31.6 months). After the sandwich isolation surgeries, no local recurrence was observed in eight of them. As for the rest one with local recurrence 11.5 month after excision, magnetic resonance images demonstrated that recurrent tumor was located only in the region where neurovascular bundles were not isolated. No adverse event associated with the enclosed neurovascular bundles was observed in all patients.

Conclusion: Sandwich isolation surgery was a new and low-cost technique to prevent the local recurrence of desmoid tumors, even if residual tumors remain around neurovascular bundles, which avoided functional impairment caused by repeated operations.

Clinical characteristics and outcomes of the 9 patients.

Case	Age (years)	Sex	Disease stage	Number of previous surgeries	Time duration of previous recurrence (months)	Tumor site	Involved nerves and vessels and relationship with tumor	Radiotherapy or chemotherapy before surgery	Radiotherapy or chemotherapy after surgery	Follow up (months)	Local recurrence after surgery
1	10	Female	Recurrent	2	29, 6	Right thigh	Sciatic nerve, surrounded	None	None	56.7	No
2	23	Female	Recurrent	1	5	Left thigh	Sciatic nerve, surrounded	None	None	55.5	Yes
3	9	Male	Recurrent	3	6, 12, 29	Left upper arm	Axillary vessels and nerves, partly involved	Seven times chemotherapy	four times chemotherapy	47.4	No
4	17	Male	Recurrent	1	66	Left gluteal region	Sciatic nerve, partly involved	None	None	44.7	No
5	27	Male	Recurrent	1	9	Right forearm	Interosseous vessels and nerves, ulnar vessels and nerves, partly involved	None	Radiotherapy	31.6	No
6	51	Male	Primary	0	None	Right shoulder	Axillary vessels and nerves, partly involved	None	None	31.3	No
7	22	Female	Primary	0	None	Right shoulder	Axillary vessels and nerves, partly involved	None	Radiotherapy	30.5	No
8	39	Female	Recurrent	1	24	Right gluteal region	Sciatic nerve, surrounded	None	None	21.6	No
9	55	Male	Primary	0	None	Right gluteal region	Sciatic nerve, partly involved	None	None	16.7	No

Poster #336 3255865

WHEN SHOULD LIMB SALVAGE SURGERY BE CONSIDERED DURING A MEDICAL MISSION?

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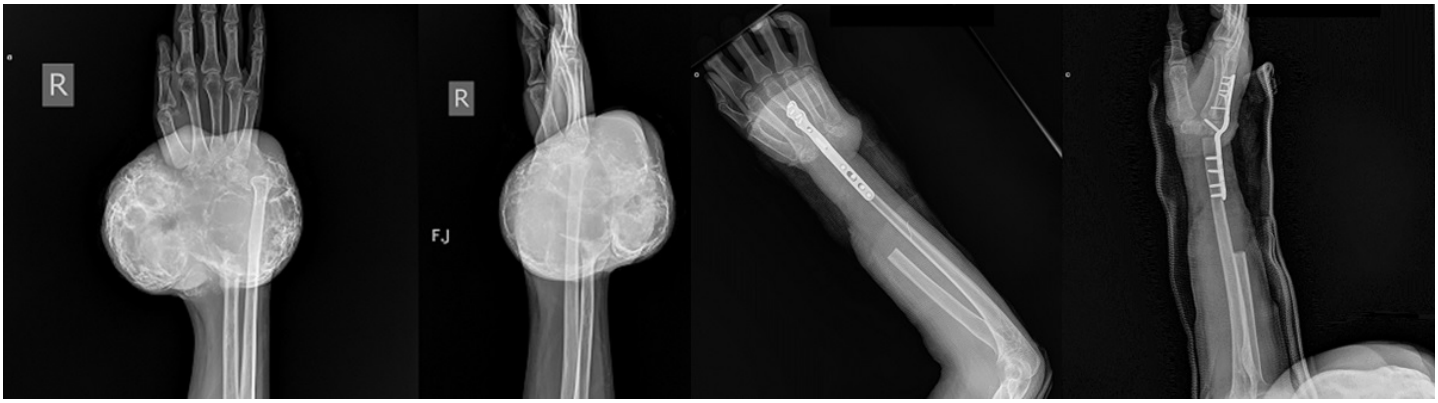
Objective: Medical missions can provide needed care to underserved populations. More recently, some training programs in the United States are providing an international elective in underserved countries. Although there is literature discussing the treatment of acute and chronic trauma, no literature or guidelines for treatment of musculoskeletal tumors exist. This series discusses case examples with considerations and pitfalls of performing limb salvage surgery in an underserved location.

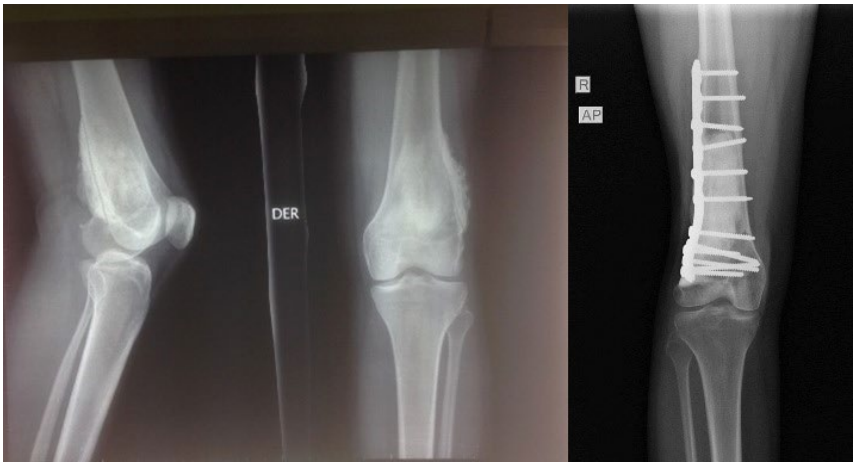
Methods: Cases of limb salvage surgery performed by the same Orthopaedic Oncologist in Haiti and the Dominican Republic are reviewed. Cases discussed include a recurrent giant cell tumor of the distal radius, recurrent parosteal osteosarcoma of the distal femur, recurrent giant cell tumor of the proximal tibia that had undergone malignant transformation, and recurrent infantile lipofibromatosis.

Results: All patients successfully underwent limb salvage surgery. The patient with a giant cell tumor of her distal radius underwent en bloc resection and fusion of the ulna to the carpus (Figure 1). The patient with the parosteal osteosarcoma underwent resection and fixation with a plate and cement (Figure 2). The patient with the malignant giant cell tumor of the proximal tibia underwent resection with a donated proximal tibial replacement (Figure 3). The decision to perform limb salvage surgery was based on multiple factors including tumor type and location. Patients with metastatic disease, likelihood of significant blood loss, and poor health were not candidates for limb salvage surgery. Continuity of care was provided by an American physician on a long-term medical mission and local surgeons being trained by these physicians. A discussion with the long-term surgeon was made regarding treatment of possible complications as well as follow-up. A local vascular and general surgeon were available for certain cases. All patients are disease free at most recent follow-up and have had no complications.

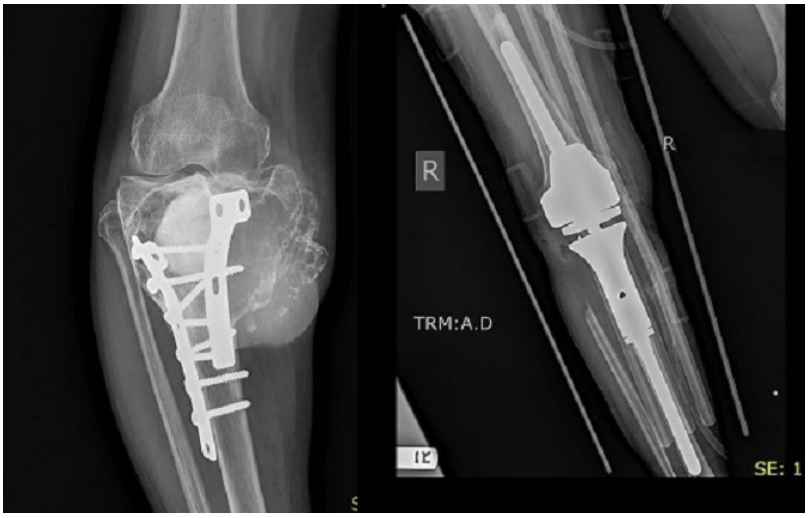
Conclusion: Medical missions and the development of partnerships with training programs in the United States makes limb salvage a greater possibility. A tour and understanding of the facility, anesthesia support, and instrumentation available is vital. There should be the understanding that advanced imaging, blood products, and allograft are likely unavailable or difficulty to obtain. Established continuity of care that can address complications is necessary, and training of the local surgeon should be provided. Surgery should only be considered if it is safe, provides more of a benefit to the patient than an amputation, and with informed consent.



Pre- and post-operative x-rays of a recurrent giant cell tumor of bone involving the distal radius that underwent resection with fusion of the ulna to the carpus.



Pre- and post-operative x-rays of a recurrent parosteal osteosarcoma that underwent resection and fixation with hardware and cement.



Pre- and post-operative x-rays of a recurrent giant cell tumor of bone that underwent sarcomatous degeneration. A wide resection was performed with reconstruction with a proximal tibial replacement.

Poster #337 3256401

CLINICAL STUDY TO EVALUATE SAFETY AND ACTIVITY OF AUTOLOGOUS T CELLS WITH ENHANCED NY-ESO-1-SPECIFIC T-CELL RECEPTOR (GSK3377794) IN HLA-A*02+ PREVIOUSLY-TREATED AND PREVIOUSLY UNTREATED PATIENTS WITH ADVANCED METASTATIC OR UNRESECTABLE SYNOVIAL SARCOMA AS PART OF A MASTER PROTOCOL DESIGN

Sandra P. D'Angelo, MD[1]*; Jean-Yves Blay*[2]*; Warren Chow*[3]*; George D. Demetri*[4]*; Fiona Thistlethwaite*[5]*; Michael J. Wagner*[6]*; David Loeb*[7]*; Steven Attia*[8]*; Albiruni Razak*[12]*; John Haanen*[9]*; Aisha N. Hasan*[13]*; Julia Billiard*[13]*; Laura Pearce*[13]*; Yuehui Wu*[13]*; Ran Ji*[13]*; Laura A. Johnson*[13]*; Chandra Srianth*[13]*; Aiman Shalabi*[13]*; Sandra J. Strauss*[10]*; Katherine Thornton*[4]*; Crystal Mackall*[14]*; William D. Tap*[1]*; Brian A. Van Tine*[11]

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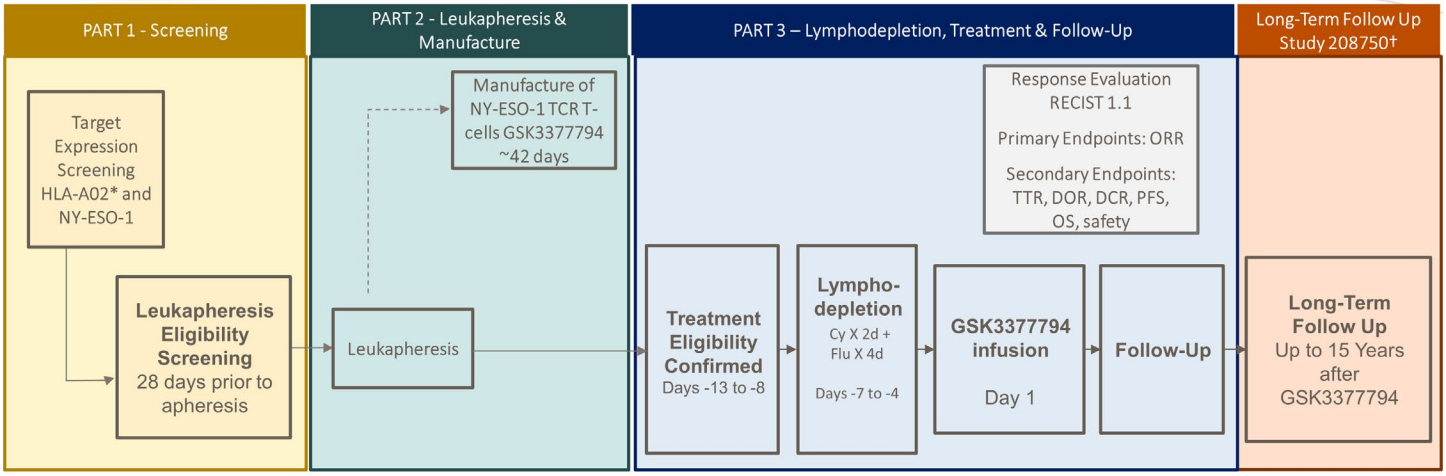
Objective: Synovial sarcoma accounts for ~5–10% of all soft tissue sarcomas.[1] Anthracycline-based chemotherapy is standard first-line treatment in advanced metastatic/unresectable disease, but response rates are low (<30%) and often not durable.[2] Clinical studies have demonstrated that T cells modified to target the NY-ESO-1 tumor-specific antigen have shown encouraging activity in HLA-A*02 patients with NY-ESO-1-positive synovial sarcoma, with response rates up to 60%.[3,4] While CAR-T therapies primarily target cell surface antigens and have demonstrated activity in hematological malignancies, engineered T-cell receptor T cells (TCR T) target intracellular antigens and have a broader range of potential targets. NY-ESO-1 is a cancer testis antigen that is uniquely expressed across multiple tumor types, but not in normal tissue outside of testicular germ cells,[5] and is highly expressed in synovial sarcoma. NY-ESO-1 TCR T (GSK3377794) are autologous polyclonal T cells transduced by a self-inactivating lentiviral vector to express an affinity-enhanced TCR capable of recognizing NY-ESO-1 antigen in complex with HLA-A*02. Ongoing Phase 1 and 2 trials are evaluating GSK3377794 in multiple solid tumors and in multiple myeloma.

Methods: We are now initiating a clinical trial utilizing a Master Protocol design that allows investigation of GSK3377794 in multiple tumor types under the same protocol (NCT03967223), in separate substudies. The first two substudies under the Master protocol are in metastatic synovial sarcoma – previously untreated (1st line, substudy 1) and previously treated (2nd line +, substudy 2) patients as single-arm trials. Substudy 2 will investigate GSK3377794 in HLA-A*02^{+} patients with NY-ESO-1^{+} advanced metastatic or unresectable synovial sarcoma who have progressed following treatment with anthracycline-based chemotherapy. Patients must be ≥10 years old, have adequate organ function, ECOG performance status 0-1, measurable disease, and evidence of progression from prior therapy. Patients must not have central nervous system metastases or any clinically significant systemic illness. Patients must not have received prior gene therapy with an integrating vector or NY-ESO-1-specific T cells, vaccine or targeting antibody, or previous allogeneic hematopoietic stem cell transplant. Patients will undergo eligibility screening; leukapheresis and manufacture of GSK3377794; lymphodepletion and infusion of GSK3377794 followed by safety follow-up and disease assessments; and long-term follow-up of 15 years conducted under a separate protocol (**Figure 1**). A total of 55 patients are planned to be enrolled in substudy 2.

Results: Substudy 1 or 2 do not yet have results to report. The primary objective of substudy 2 is to evaluate the efficacy of GSK3377794 by assessment of overall response rate per RECIST v1.1 by central independent review. Secondary objectives include time to response, duration of response, disease control rate, progression free survival, overall survival, and potential immune response to GSK3377794, in addition to safety and tolerability. Exploratory objectives include assessment of the correlation of T cell persistence with safety, clinical responses, and with the phenotype of infused T cells. Evaluation of quality of life and daily functioning of patients will also be assessed.

Conclusion: Following the encouraging activity demonstrated with GSK3377794 in earlier studies, a larger clinical trial will be initiated to further characterize the efficacy and safety in this biomarker-selected subset of synovial sarcoma patients. Furthermore, an innovative study design in the form of a Master Protocol will enable evaluation of other HLA-A*02^{+} and NY-ESO-1^{+} patients in separate substudies, including previously untreated advanced metastatic synovial sarcoma patients and other tumor types.

Figure 1


PART 1 - Screening
PART 2 - Leukapheresis & Manufacture
PART 3 – Lymphodepletion, Treatment & Follow-Up
Long-Term Follow Up Study 208750†
Target Expression Screening HLA-A02* and NY-ESO-1
Leukapheresis Eligibility Screening 28 days prior to apheresis
Manufacture of NY-ESO-1 TCR T-cells GSK3377794 ~42 days
Leukapheresis
Response Evaluation RECIST 1.1
Primary Endpoints: ORR
Secondary Endpoints: TTR, DOR, DCR, PFS, OS, safety
Treatment Eligibility Confirmed Days -13 to -8
Lympho-depletion Cy X 2d + Flu X 4d Days -7 to -4
GSK3377794 infusion Day 1
Follow-Up
Long-Term Follow Up Up to 15 Years after GSK3377794

Poster #338 3256432

EPIDEMIOLOGICAL STUDY IN A REFERENCE CENTER IN MEXICO FOR THE TREATMENT OF SARCOMA

Jorge L. Martínez Tlahuel, MsC[1]*; Jorge Alegria*[2]*; Alejandro Mohar*[2]*; Jaime de la Garza*[2]
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[2]*Research direction, Instituto Nacional de Cancerología, Mexico, Mexico*

Objective: To determine the clinical and pathological characteristics and treatment of patients with Sarcoma in a Reference Center in Mexico.

Methods: It is an observational, retrospective study. The clinical and pathological characteristics of the patients during the 2010-2017 period with Sarcoma in a Reference Center in Mexico were evaluated, all the patients were over 18 years of age and the type of treatment was studied (chemotherapy, radiotherapy and surgery). For its analysis, descriptive statistics were performed.

Results: During the period from 2010 to 2017, a total of 418 cases of sarcomas were identified, 232 (56%) in men and 186 (44%) in women. The median age was 38 years with a minimum of 14 and a maximum of 85 years. The most affected anatomical location were the limbs in 241 (58%) cases, followed by trunk with 83 (20%) cases, and retroperitoneum with 44 (10%) patients. Other regions were head and neck, pelvis and abdomen with less than 10% of cases.

The most frequent tumor was osteosarcoma with 94 cases, representing 23% of the series, followed by monophasic synovial sarcoma with 64 (15%) cases, highlighting the high frequency of this histological variant. At the time of diagnosis, more than 55% of these patients were in advanced stages of the disease. Where 51% presented, at diagnosis, tumoral lesions of more than 10 cm on its major axis, 282 (67%) of the cases were classified as high grade, and 365 (87%) of deep localization.

91%, 380 patients underwent surgical treatment; neo-adjuvant or adjuvant chemotherapy was proposed, but due to economic limitations of these patients only 120 (29%) received this type of consolidation treatment. Given the progress of the disease, palliative chemotherapy was used in 259 patients, either in the 1st to the 3rd line. In 190 (45%) cases, adjuvant radiotherapy was used. However, at 48 months of follow-up after the diagnosis, 50% of this group of patients was identified as abandoning treatment.

Conclusion: The delay in the early diagnosis observed in this series makes it necessary to review and improve the referral system to INCan and other Oncological Centers of the 1st and 2nd level of medical attention.

Poster #339 3224571

THE CLINICAL FEATURES OF GANGLIONEUROBLASTOMA IN ADULTS

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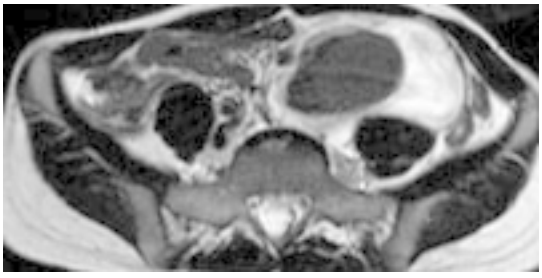
Objective: Ganglioneuroblastoma (GB), which occurs in the retroperitoneal sympathetic nervous system and adrenal glands, is a rare malignancy mainly found in children, and only about 50 cases have been reported in adults. GB in children present with variable prognoses, however, the clinical features of GB in adults is still unclear. To clarify the clinical features, we reviewed 12 cases including our case.

Methods: We searched English articles on PubMed database using the key words of ganglioneuroblastoma and adult. Four articles (published after 2014), which were two case reports and two papers of retrospective case series, were found and further analysis performed with twelve GB cases including our case.

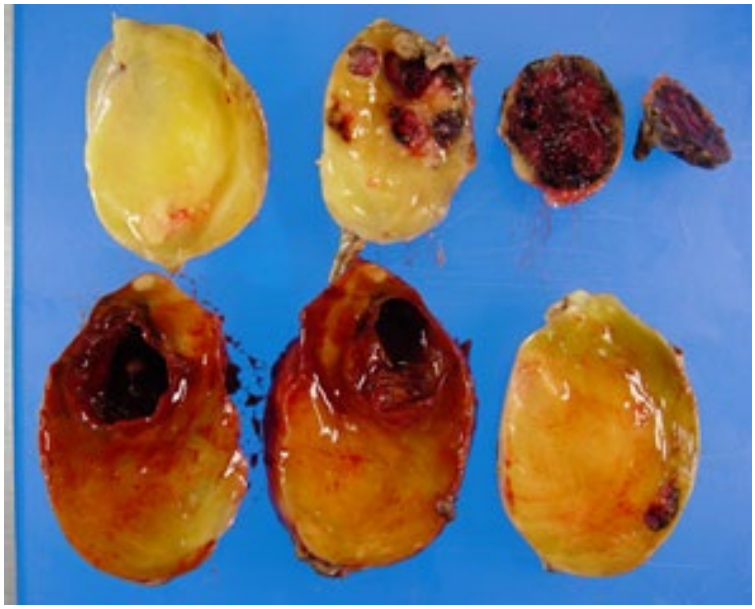
Results: Their age ranged from 19 to 38 years (mean: 25). The primary tumor site was located in retroperitoneal sympathetic ganglia in tow, in the adrenal in 3, in abdominal, thorax and pelvis in two each and spine in one patient. Metastasis was recognized only in one case. Surgical resection was performed in 11 cases (R0 or 1: 6 cases, R2: 5 cases). Chemotherapy was performed in three cases. The overall survival was 78% at five years, 67% at ten years and 33% at 13 years (final follow).

Our case report: A 27-year-old woman visited a local hospital with persistent low-back pain and computed tomography (CT) revealed a huge soft tissue tumor in the retroperitoneal space. A neurogenic tumor or liposarcoma was suspected and the patient was referred to the department of abdominal surgery in our hospital. On CT, a huge mass displaced the left common iliac artery and partially invaded the left psoas and L5 nerve foramina. Pathological diagnosis was submitted to consultation after excisional surgery (R2 resection) by abdominal surgeons. Final diagnosis was GB (nodular subtype). A part of the tumor in the psoas muscle remained and she was referred to our department for additional treatment after surgery. Although additional resection was suggested, the patient's consent was not obtained. We introduced another institute with experience in treating GB for further treatment including chemotherapy (Chemo) and radiation therapy (RT). As a result, Chemo or RT was not finally accepted, and follow-up was to be continued at our hospital. Although HVA and VMA were normal and PET scan showed slight accumulation of FDG in the remaining tumor. I-123MIBG scintigraphy showed no abnormal accumulation. The patient was followed up with MRI and PET scan, and the residual tumor showed a gradual increase, and multiple bone metastases were noted 8 years after surgery. Denosumab was started, and multiple bone metastases showed osteosclerosis in the course. Eleven years after the operation, spinal canal infiltration with metastases was confirmed with MRI, and RT was applied to the metastases. Afterwards, multiple metastases in brain and pleura were revealed and she was died of the disease twelve years after surgery due to anemia and thrombocytopenia caused by bone marrow dysfunction.

Conclusion: In literatures, several cases which survived for a long time even after they showed residual tumor or relapse as shown in our case, however eventually the outcome was a poor prognosis. Appropriate treatment including R0 resection is considered mandatory for better prognosis.



T2 weighted image at presentation



Cut sections of the resected specimen

Poster #340 3241689

APPLICATIONS OF CARBON FIBER INTRAMEDULLARY NAILS IN ORTHOPAEDIC ONCOLOGY

Caleb Yeung, MD; *Nelson Merchan; Erik Newman; Joseph Schwab; Kevin Raskin; Santiago Lozano-Calderon*
Department of Orthopedic Surgery, Massachusetts General Hospital, Boston, MA, USA

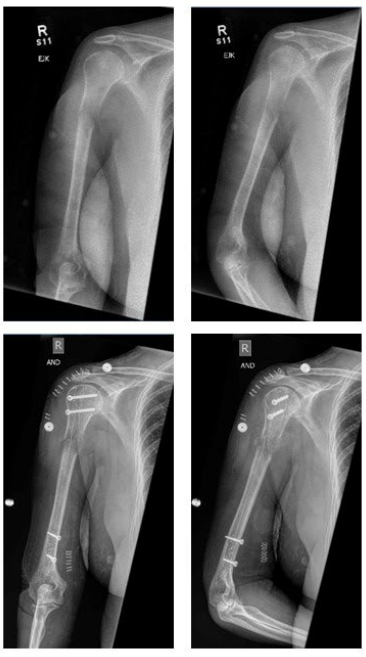
Objective: Carbon fiber intramedullary nails are being increasingly used as surgical options for treatment of pathologic fractures in orthopaedic oncology as they allow for quick recovery and resumption of weight bearing, relatively low complication rates, and enhanced ability for post-operative imaging surveillance of recurrence or disease progression. Carbon fiber has many advantages to traditional metal implants, including a significantly lower weight to strength ratio as well as a tensile strength over 2000 times stronger than that of cobalt chrome, with an elastic modulus of close to that of bone, decreasing stress concentration at implant-bone interfaces and boundaries. Importantly, carbon fiber implants are radiolucent on radiographic imaging and have decreased scatter and artifact on MRI imaging, providing an advantage over traditional metallic intramedullary nailing when considering post-operative surveillance of tumor recurrence, disease progression, visualization of bony fusion, or planning for radiation therapy. We evaluated the surgical characteristics and short-term outcomes of patients who underwent either prophylactic or therapeutic fracture fixation with a carbon fiber implant at our institution from 2017-2019.

Methods: This is a Institutional Review Board-approved retrospective case series of nineteen patients who underwent either prophylactic or therapeutic fixation for pathologic fracture with a carbon fiber intramedullary nail.

Results: Nineteen patients underwent either prophylactic (9 patients, 47%) or therapeutic fixation (10 patients, 53%) for pathologic fracture with a carbon fiber implant. 10 patients (52%) underwent femoral intramedullary nailing, 7 (37%) underwent humeral intramedullary nailing, and 2 (11%) underwent tibial intramedullary nailing. Median surgical time was 90 minutes (95% CI 72-180 minutes) and median fluoroscopy time was 144 seconds (95% CI 94-176 seconds). Median time of follow up of was 4 weeks. Median estimated blood loss was 150 cc (95% CI 121-419 cc). 2 patients (11%) suffered wound complications (one MRSA surgical site infection requiring irrigation and debridement and IV antibiotics, one with delayed wound healing that resolved with wound care). There was one intra-operative complication of a unicortical femur fracture during intramedullary rod insertion that did not require additional fixation. There were no complications of implant rejection, implant fatigue, fracture complications, or complications requiring implant exchange. 7 patients had post-operative radiation with one patient developing post-radiation skin changes.

Conclusion: Although not yet widely used, our early cohort demonstrates a favorable surgical profile supporting further consideration of carbon fiber implants in orthopaedic oncology. Given their enhanced accommodation of imaging modalities compared to traditional metal implants and high tolerance to fatigue stress, the benefits of carbon fiber implants warrant further investigation into their application and feasibility as implants for both pathologic fracture fixation as well as limb salvage and reconstruction.

Figure 1.



A: Anteroposterior and lateral radiographs of the right humerus with a pathologic fracture from a lung cancer metastatic lesion.

B. Anteroposterior and lateral radiographs of the right humerus after intramedullary nail fixation with carbon fiber radiolucent implant, demonstrating its ability to allow for ongoing visualization of metastatic lesion size and humeral involvement in clinical follow up.

PO #01 3253423

A CASE OF HUGE, ABC-LIKE RIB TUMOR DIAGNOSED AS GCT OF BONE BY H3.3 G34W-IMMUNOSTAINING

Masayuki Morishita[2]*; Toshiko Sakuma*[1]*; Ikuo Fujita*[2]*; Takuya Fujimoto*[2]*; Takanori Hirose*[1]
[1]*Diagnostic Pathology, Hyogo Cancer Center, Akashi, Japan;* [2]*Orthopaedic Surgery, Hyogo Cancer Center, Akashi, Japan*

Objective: Giant cell tumor of the bone (GCTB) is a benign but locally aggressive primary bone neoplasm characterized by giant cell-rich morphology, which overlaps with other giant cell-containing lesions of the bone, such as aneurysmal bone cyst (ABC), chondroblastoma, and giant cell-rich osteosarcoma. We report a case of huge rib tumor mimicking ABC, the diagnosis of which was revised by immunohistochemical staining of H3.3 G34W, a specific marker of GCTB.

Methods: Case report.

Results: A 14-year-old girl was referred to our hospital, because a right rib bone tumor was pointed out by follow-up imaging examination for idiopathic scoliosis. A plain radiograph and a CT scan showed an expanding lesion of 15 cm in size in the right sixth rib with thinning of the bone cortex. In MR images, the tumor was multicystic and fluid-fluid level formation was observed. Needle biopsy revealed mixed proliferation of mononuclear cells and osteoclast-type giant cells associated with osteoid formation, and ABC was clinicopathologically suspected. Denosumab was administered 5 times every month, and the size of the tumor was reduced by about 19%. We performed En Bloc resection of the right sixth and seventh ribs. The resected tumor, 15 cm in diameter, was a hard, multicystic mass like volcanic foam. Microscopically, cyst walls were surrounded by dense osteoid, and mononuclear cells and giant cells were indiscernible. Then the biopsy specimen was reexamined with H3.3 G34W immunostaining, which clearly demonstrated positive staining in the nuclei of mononuclear cells, but not in those of giant cells (Fig. 1). Therefore, the diagnosis was revised as GCTB. There is no evidence of recurrence at the last follow up one year after surgery.

Conclusion: Recently, recurrent mutations in histone H3.3 gene, most of which were H3F3A G34W, were found in GCTB. A monoclonal antibody specific to mutated protein were developed soon and became a powerful tool for the diagnosis of GCTB. Although the present case was at first suspected to be ABC because of relatively young age of the patient, images showing multiple cysts with fluid-fluid level and limited pathologic materials, the reexamination with H3.3 G34W immunostaining revised the diagnosis from ABC to GCTB. The present case indicated the crucial role of H3.3 G34W immunostaining for the diagnosis of giant cell-rich bone lesions.

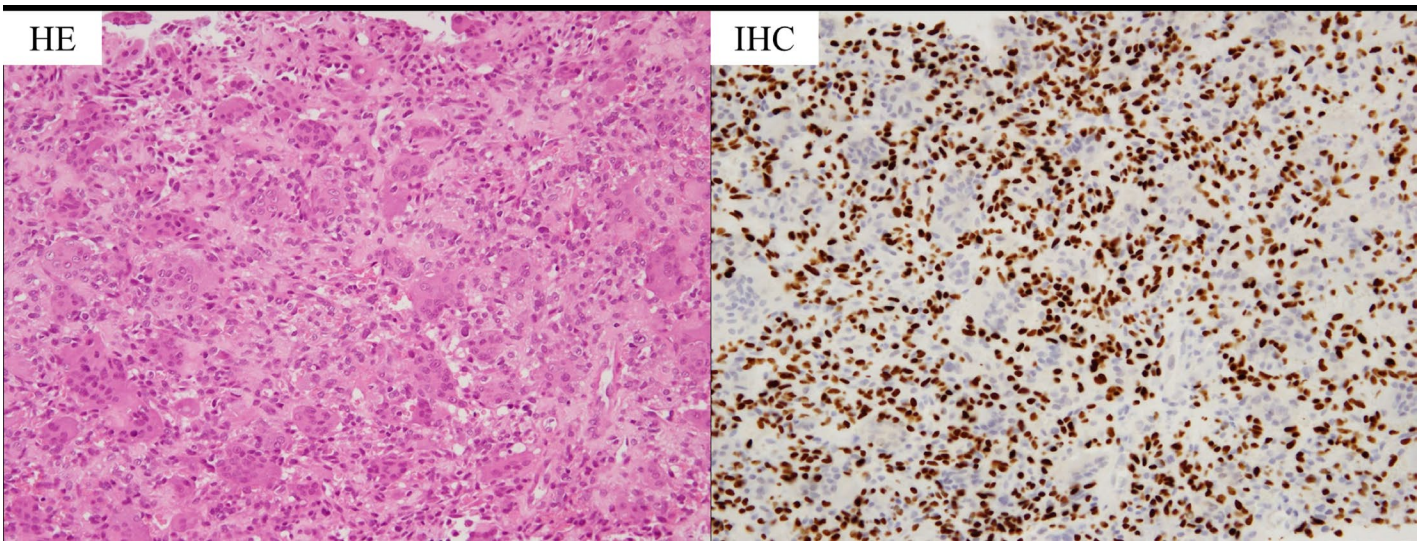


Fig.1 Mononuclear stromal cells show nuclear expression of H3.3 G34W, whereas osteoclast-like giant cells are negative.

PO #02 3255755

COMPLETE PATHOLOGIC RESPONSE WITH DOXORUBICIN AND DACARBAZINE IN METASTATIC UNDIFFERENTIATED PLEOMORPHIC SARCOMA (UPS) TO THE LIVER IN AN ELDERLY PATIENT

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Objective: Doxorubicin remains a standard of care for the treatment of metastatic sarcoma as a single agent or as part of a doublet. In combination with Adriamycin, there remains significant toxicities - particularly in patients older than 70. As such, we have utilized Doxorubicin and Dacarbazine as a useful alternative in doublet therapy for older patients. We present a case of a 75-year-old patient who developed a complete pathologic response to a hepatic metastasis from a lower extremity undifferentiated pleomorphic sarcoma treated by Doxorubicin and Dacarbazine therapy.

Methods: A 75-year-old female presented with a 10cm Undifferentiated Pleomorphic Sarcoma (UPS) of the right thigh 3 years prior (Fig 1).

At the time of initial presentation, patient was deemed too frail to undergo neoadjuvant chemotherapy. Instead, she had preoperative radiation to the tumor for a total of 5200cGy. Patient underwent an R0 radical resection of the tumor and vastus lateralis as seen in figure 1. Two years later, she developed a solitary hypervascular lesion in Segment 4 of the liver ~5cm in size (Fig 2). Biopsy confirmed metastatic UPS. Patient underwent chemotherapy followed by surgery. She tolerated 5 of 6 cycles of Doxirubicin (75mg/mm2 bolus) plus Dacarbazine (750mg/mm2 Infusion over 1 hr).

Results: Per RECIST criteria, patient had a partial response with a 50% reduction in the size of her metastasis (Fig 3). She was then taken to the operating room for a left hepatectomy. Pathologic evaluation of the liver metastasis demonstrated no viable tumor. Patient now remains disease free 1 year after her metastasectomy and 3 years after primary resection.

Conclusion: Given the patient's advanced age, AIM regimen was contraindicated. Doublet chemotherapy (Doxorubicin and Dacarbazine) was utilized over single agent Doxorubicin - as the intent of treatment was curative. Patient had significant toxicities after the 5th cycle so the last cycle was held. A post chemotherapy CT scan demonstrated significant size reduction. Thus, the patient was taken to the operating room for extirpation of the tumor. Patient now remains NED and off treatment for 1 year since the metastasectomy. As the toxicity for Dacarbazine is significantly less than Ifosfamide, we have successfully substituted this agent when treating patients >70 years old. Doublet therapy should still be considered in older patients when treating them for oligometastatic disease.

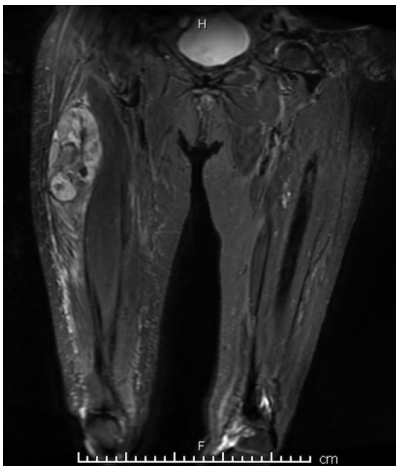

Figure 1. Undifferentiated Pleomorphic Sarcoma in the Vastus Lateralis.

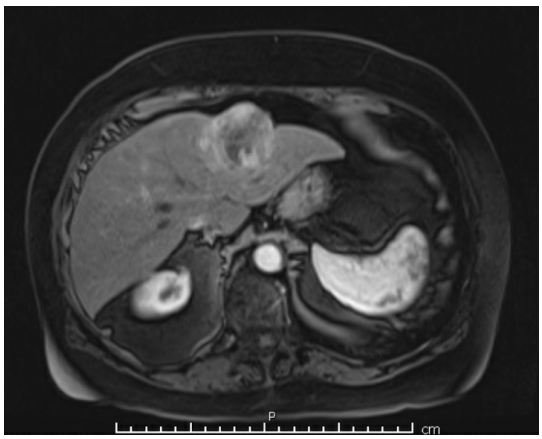

Figure 2. Segment IV Hepatic Metastasis

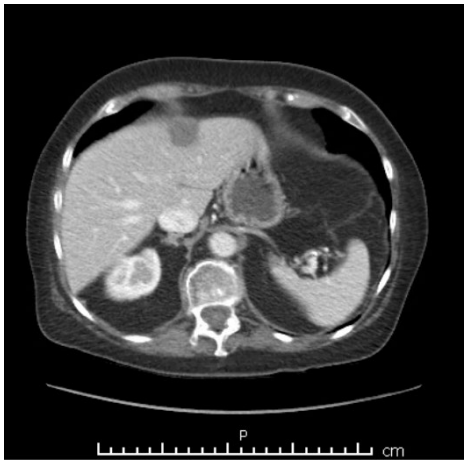

Fig 3. Treated Segment IV Hepatic Metastasis

PO #03 3255245

EFFICACY OF PAZOPANIB AS SECOND-LINE TREATMENT IN ASIAN PATIENTS WITH METASTATIC SOFT TISSUE SARCOMA: A REAL-WORLD RETROSPECTIVE STUDY

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Objective: Pazopanib received approval for the treatment of certain soft tissue sarcoma (STS) subtypes based on phase III trial, which showed significantly improved PFS compared to placebo. We conducted a retrospective analysis to assess the role of pazopanib in the real world of Asian STS patients.

Methods: We reviewed STS patients treated with pazopanib after one or more cytotoxic regimens, from 2014 to 2019. Pazopanib 800mg was given daily. The primary end-points were progression free survival (PFS) and disease control rate (DCR).

Results: Thirteen patients were enrolled. Median age was 53.0 (range, 35-75) and male was dominant (61.5%). In relation to ECOG performance status, 4 patients (31%) were in 1 and 9 (69%) were in 2 or 3. Tumor subtype was as follows: leiomysarcoma, 4 (30.7%); angiosarcoma, 3 (23.1%); rhabdomysoarcoma, 2 (15.4%); others STS types, 4 (30.7%). Sites of primary were trunk/retroperitoeum (8, 62%), extremity (3, 23%), and Head and Neck (2, 15%). The median treatment duration was 27.2 months. The median PFS was 4.0 months (95% CI, 0.0-10.43) and OS was 6.0 months (95% CI, 1.8-10.2). Of the 13 patients, 10 patients were evaluable for tumor response as follows: PR 2 (20%), SD 5 (50%), PD 3 (30%). So, DCR was 70%. Treatment duration was 5.5 months (range, 0.2-22.3). Causes of treatment off were progression (10), toxicity (1), and other reasons (2).

Conclusion: Pazopanib is a feasible treatment options with acceptable antitumor activity in Asian advanced STS patients of real-world setting including poor performance. Our study also showed that pazopanib is well tolerated by Asian STS patients, considering the very low rates of toxicity as cause of treatment discontinuation.

PO #04 3253590

A CASE OF RESOLVED VINCRISTINE INDUCED CONSTIPATION FOLLOWING OSTEOPATHIC MEDICINE IN A PATIENT WITH INFANTILE FIBROSARCOMA

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Objective: Chemotherapy-induced constipation (CIC) is a well-reported side effect in pediatric oncology patients. Since the advent of osteopathic medicine in the 1890's, this adjunctive therapy has been implemented successfully in both adult and pediatric populations for a myriad of illnesses that do not include oncologic illnesses. To date, there has been no literature on the use of osteopathic manipulative treatments (OMT) in pediatric patients with soft tissue sarcomas. We report a case of an infant with histologic diagnosis of infantile fibrosarcoma who developed significant constipation with ongoing vincristine administration.

Methods: Case report performed by retrospective chart review.

Results: Case Presentation: A Caucasian girl presented at birth with a large right sided facial mass. Tumor pathology was consistent with an infantile fibrosarcoma, and treatment was initiated at 6-weeks of age. Chemotherapy consisted of vincristine (0.05mg/kg), dactinomycin (0.025mg/kg) and cyclophosphamide (25mg/kg) (VAC). Throughout the first cycle, bowel regimen consisted of lactulose following vincristine for 24 hours. She had multiple soft stools daily. Seven days following cycle 2, she was admitted for fever, abdominal distension, and imaging consistent with diffuse pneumatosis of the colon. She was treated with antibiotics, total parenteral nutrition, medical observation, and discharged home after 9 days. Chemotherapy was resumed with slow dose escalation of vincristine. Lactulose was scheduled for 48 hours following doses of vincristine. By cycle 6, she had difficulty stooling without lactulose. OMT was introduced at 7 months of age. The patient underwent 4 weekly OMT sessions (session length 10 minutes). During each session, myofascial-release treatment was applied to the abdominal and thoracic regions. Following week 1 of OMT treatment, our patient required six doses of lactulose between week 1 and week 2 vincristine administrations (Figure 1). She averaged 3-4 soft, formed stools daily without straining. Week 2 osteopathic physical exam showed improvement in occipital compression, improved restriction in the thoracic and lumbar areas, as well as resolved left innominate restriction. She had continued stool in the descending colon with sustained abdominal facial restriction. Between weeks 2 and 3, she required no doses of bowel medications at home and continued with 3-4 soft, formed stools daily without straining. Week 4 and 5 of her osteopathic exam demonstrated continued improvement of her occipital compression, resolved restriction of thoracic and lumbar areas, and no palpable stool in her abdomen. She continued to demonstrate minimal but improved abdominal fascial restriction. Throughout her 4 weeks, family reported consistent twice daily use of mesenteric release and colonic milking with no missed treatments. OMT was consistently well tolerated without adverse effects. Her chemotherapy regimen and diet were not modified during this time. She remained off of all home bowel medications with continued soft stools for the remainder duration of treatment.

Conclusion: We present the first pediatric patient with fibrosarcoma suffering from severe CIC successfully treated with OMT. Standard medical therapy for CIC in pediatrics have limited efficacy and potential side effects especially in infants. In contrast, OMT could represent a long-term effective, noninvasive, and well-tolerated therapy. To our knowledge, this is the first reported case that demonstrates the benefit of OMT for CIC as an effective and simple supportive care option without added adverse events. Larger prospective studies investigating efficacy are being planned to demonstrate the impact of OMT in the pediatric sarcoma field.

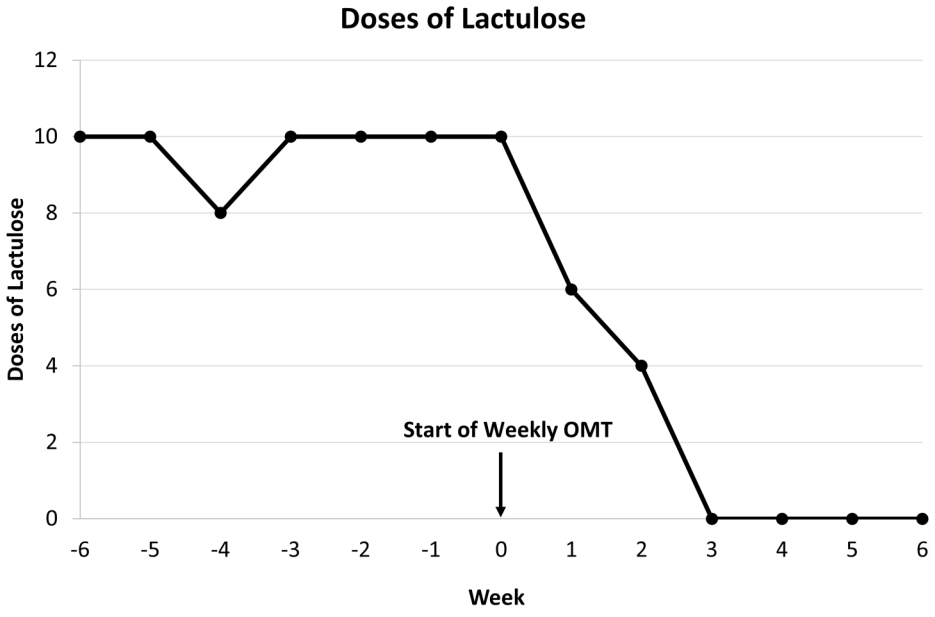

Figure 1: Osteopathic manipulative treatment effects on lactulose administration during vincristine therapy.

PO #05 3257776

ERIBULIN DOES NOT HAVE RELEVANT ANTI-TUMOR EFFICACY IN PATIENT-DERIVED XENOGRAFT (PDX) MODELS OF GASTRO-INTESTINAL STROMAL TUMORS (GIST)

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Objective: Most GIST are driven by mutated receptor tyrosine kinases KIT or platelet derived growth factor receptor α (PDGFRα). Due to this, advanced GIST are commonly treated with tyrosine kinase inhibitors (TKI) (e.g. imatinib). Regardless of their initial response, the vast majority of GIST patients develop TKI-resistance, mainly because of secondary mutations in *KIT/PDGFRA*. One strategy to overcome this TKI resistance may be to use drugs with other mechanisms of action, such as cytotoxic compounds. In the pre-imatinib era, clinical data suggested that advanced GIST are resistant to established cytotoxic agents. More recent data, however, indicate that some chemotherapeutic agents, such as mithramycin A, mitoxantrone and plocabulin, may have activity against GIST. Eribulin is a cytotoxic agent with activity in non-GIST soft tissue sarcoma. Here we evaluated whether eribulin has anti-tumor effects in GIST PDX models when used as single agent and whether it can overcome resistance to imatinib when coadministered with the TKI.

Methods: Two GIST PDX models were used to assess the *in vivo* efficacy of eribulin mesylate: UZLX-GIST9F^{res} (*KIT*: p.P577del;p.W557LfsX5;p.D820G, imatinib resistant) and UZLX-GIST4^{sens} (*KIT*: p.K558_G565delinsR, imatinib sensitive). Fourty-five mice were implanted bilaterally. Xenografted animals were randomized into four treatment groups per model: (1) vehicle (20% dimethyl sulfoxide) intravenously once every four days, (2) imatinib 50 mg/kg orally twice daily (UZLX-GIST9F^{res}) or 25mg/kg orally twice daily (UZLX-GIST4^{sens}), (3) eribulin mesylate 1.0 mg/kg intravenously once every four days or (4) imatinib combined with eribulin (same doses and schedules as the monotherapies). Treatment lasted 13 days and antitumor activity was assessed by tumor volume analysis, histopathology and Western blotting. Tumors with volumes smaller than 100mm^3 at start of experiment were excluded from the tumor volume analysis. All tumors in which a sufficient number of evaluable high-power fields could be obtained were included in the histopathological assessment. Kruskal-Wallis test with Dunn's multiple comparisons test as *post hoc* non-parametric test was used for statistical analysis with $p < 0.05$ considered as significant.

Results: Neither eribulin monotherapy, nor the combination of eribulin with imatinib resulted in a significant reduction of tumor volume or improved histologic response when compared to vehicle or imatinib monotherapy, respectively. Additionally, no antiproliferative, proapoptotic or antiangiogenic/antivascular effects were seen with the cytotoxic compound.

Conclusion: Eribulin monotherapy does not have anti-tumor effects in PDX models of GIST with different sensitivity to imatinib. Furthermore, it is unlikely that eribulin can overcome imatinib resistance in imatinib resistant GIST. Our results do not warrant further testing of eribulin in other preclinical models of KIT-driven GIST.

PO #06 3256514

METASTATIC EWING SARCOMA IN A 76M WITH DEMENTIA AND EXCELLENT RESPONSE TO CHEMOTHERAPY: CASE REPORT AND REVIEW OF THE LITERATURE

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Objective: A 76 year old retired physician presented with L iliac mass 25 cm in size and hypermetabolic lung nodules. Biopsy revealed small round blue cells positive for EWSR gene rearrangement. Although he had significant impairments due to dementia, he was still active, gardening, and otherwise without major comorbidity. After comprehensive geriatric assessment and discussion with him and his wife, he did wish to pursue reasonable treatment options, particularly if it would relieve symptoms and prolong life. Ewing sarcoma is usually a pediatric disease, and clinical trials generally exclude patients over age 50. Given the differences in goals of care and tolerance to chemotherapy in the elderly population compared with children and young adults we reviewed the literature for similar cases of Ewings sarcoma in adults over age 65.

Methods: Pubmed was searched for "ewing" and "elderly".

Results: There were 55 hits; 9 were specific to Ewings sarcoma in elderly patients. 7 were case reports of Ewings in patients over age 65; two were in adults ages 50-65, and one was an epidemiological review of Ewings in patients over age 40. Of the 7 case reports in patients over 65, 5 were referred for chemotherapy or received chemotherapy; one received surgery and radiation, one received only pazopanib due to poor performance status and rapidly passed away. A 67M with localized disease was treated adjuvantly with vincristine (1.4 mg/m2), doxorubicin (75 mg/m2) and cyclophosphamide (1.2 g/m2), alternating with ifosfamide (1.2 g/m2; along with MESNA) and etoposide (100 mg/m2), given every three weeks for a total of 17 cycles [1]. 2 more 68 year old patients were treated with named agents though dose and schedule were not reported [2-3]. 2 patients, ages 68-80, were referred for chemotherapy, though agents and actual receipt and tolerance were not reported.[4-5]

Conclusion: Case report: Our patient underwent geriatric assessment, who found him fit but with mild-to-moderate cognitive impairment. MOCA: 22/30. He was independent with ADLS but needed assistance with IADLs. He was able to participate and comprehend discussions but unable to recall his cancer diagnosis and treatment discussions shortly after. Physically, despite the left hip mass, his strength and mobility were intact. Based on the reviewed case reports and extrapolating from mini-CHOP regimen in lymphoma, we recommended vincristine/doxorubicin/cyclophosphamide (VDC) q3 weeks with 25% dose reduction; vincristine 1.4 mg/m2 D1, cyclophosphamide 900mg/m2 D1, and doxorubicin 28mg/m2 D1, D2 with mesna, dexrazoxane, and growth factor support. Given lack of data for benefit, particularly overall survival benefit, of ifosfamide/etoposide (IE) in the metastatic setting, and patient's underlying cognitive impairment, we did not recommend alternating with IE. Patient tolerated VDC remarkably well, "wouldn't even know I was sick", and was able to continue his usual activities. His LDH dropped from an initial value of 1,229 u/L to 636 1 week after cycle 1 and 269 prior to cycle 2, and he experienced relief of pain and required minimal opiates subsequently. Follow up PET scan after 3 months/4 cycles revealed resolution of prior hypermetabolic lung nodules and over 50% decrease in primary tumor size. He then received radiation to the primary with outpatient VC 900mg/m2 with 240mg/m2 q3 weeks. Given resolution of lung nodules and some difficulty with radiation tolerance (itching and excoriation to primary) decision was made to forgo whole lung radiation. He has received 6 total doses of VDC and 2 doses VC while on radiation, and is now on maintenance VC with plan for up to 14 cycles, and break if continuing to do well.

To our knowledge this is the first reported case of chemotherapy in an elderly patient with metastatic Ewing sarcoma. We report excellent tolerance and response to dose reduced VDC and radiation to the primary 5 months into treatment.

Citations: Reported cases of Ewings in patients over age 65

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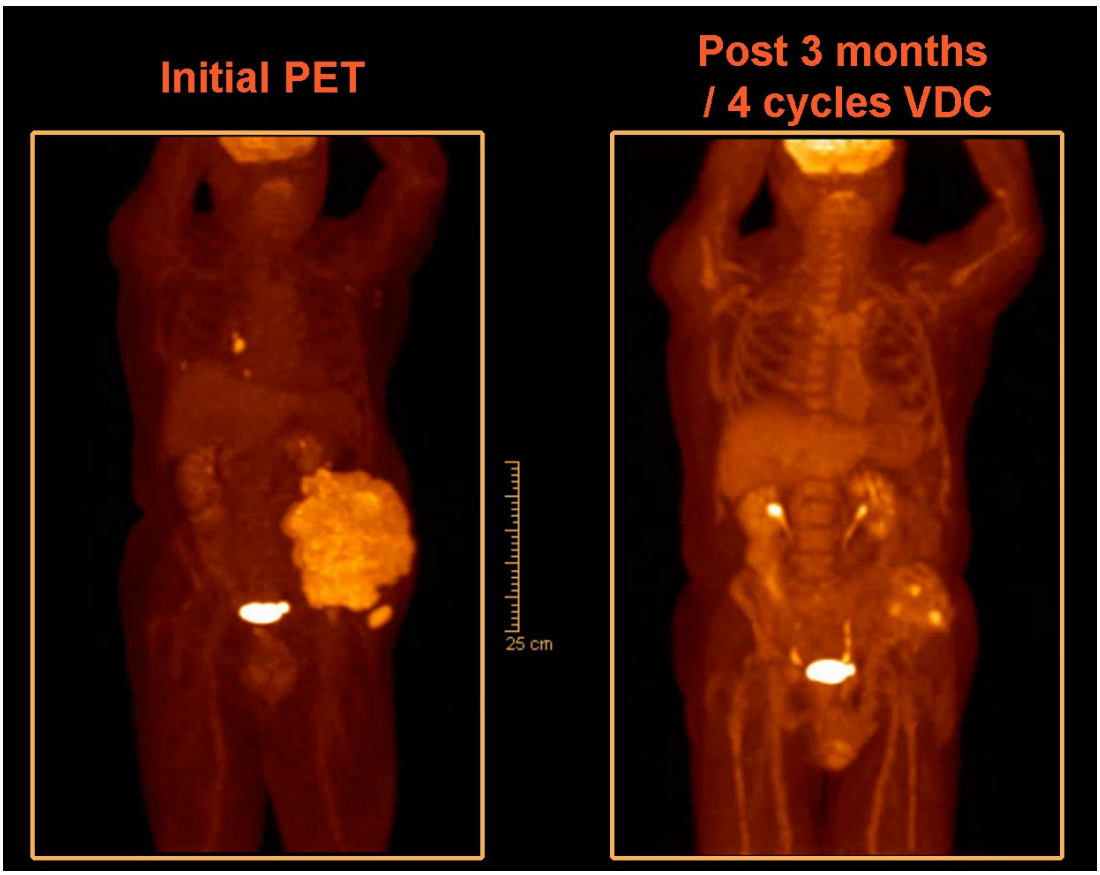

Changes in PET activity after 12 weeks / 4 cycles vincristine/doxorubicin/cyclophosphamide with 25% dose reduction, given every 3 weeks, in 76 year old patient with Ewings and dementia.

PO #07 3254381

REPLACEMENT OF EXOGENOUS L-THYROXINE [L-T4] WITH L-TRIIODOTYRONINE [L-T3] IN HYPOTHYROID WOMEN WITH METASTATIC HIGH GRADE UTERINE SARCOMA IS ASSOCIATED WITH TUMOR RESPONSE AND IMPROVED SURVIVAL

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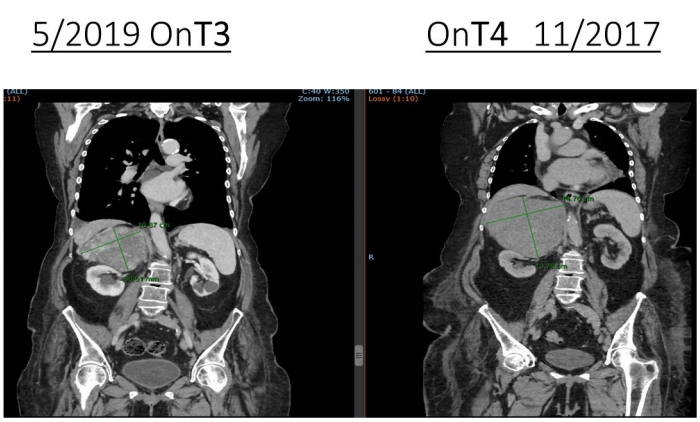
Objective: Preclinical studies suggest that in physiological concentrations, thyroxine [L-T4] may have an increased pro-oncogenic effect in solid tumors compared with physiological triiodothyronine [L-T3]. Clinical observations in patients with terminal cancers have reported that lowering serum free-T4 (FT4) [hypothyroxinemia] in patients metabolically supported by L-T3 is associated with extended survival. The objective of this study was to substitute the less pro-oncogenic L-T3 for exogenous L-T4 in hypothyroid metastatic uterine sarcoma patients (pts) and monitor outcomes.

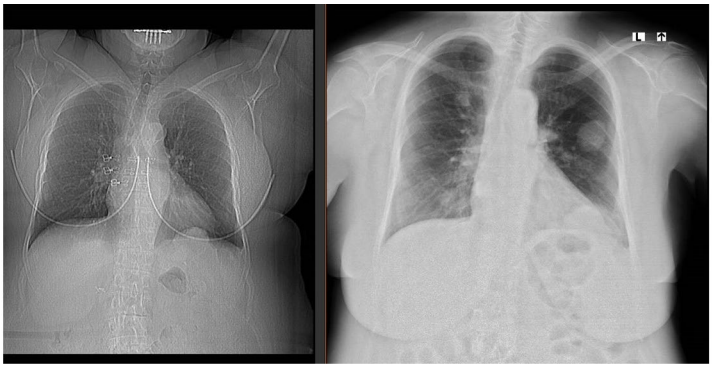
Methods: All patients in this study had advanced (metastatic/unresectable) high grade uterine sarcoma deemed incurable by conventional therapies. Patients were converted abruptly from L-T4 (50-200 mcg daily) to L-T3 (12.5-50 mcg daily), After 'washout' period of 1 week, and were initiated with exogenous L-T3, 12.5-50 mcg/day in one or two daily divided doses. The objective was to reduce the FT4 below the normal range, preferably to a non-measurable level. exogenous L-T3 was initiated prior to, during, or after the oncological treatments. Serum F-T4, F-T3 and TSH were regularly monitored to enable adjustments according to hormone levels (maintaining FT3 in the normal range regardless the TSH level). Survival was calculated from date of advanced disease diagnosis.

Results: Nine patients with advanced uterine sarcoma (leiomyosarcoma 7 pts, unclassified pleomorphic sarcoma of uterus 2 pts) were included with a median age 64 [range 60-74]. In all pts, F-T4 levels declined below the reference range to a nadir by 4 weeks. All pts received one or more oncologic treatments (cytotoxic chemotherapy, pazopanib, anti estrogen hormonal therapy, metastectomy), Except for one patient who was on artificial respiration for 1 year due to chronic obstructive pulmonary disease and on L-T4 after thyroidectomy due to thyroid cancer who did not receive any oncological treatment. Median follow up since L-T3 initiation is 16 months [4-53+ months]. We did not observe any toxic effects from conversion of L-T4 to L-T3. During treatment with L-T3, one patient had a complete pathological response (CR), four patients experienced partial responses (PR), one patient had stable disease, and three had progressive disease, for a combined overall response rate (CR+PR) of 55%. Notably, one patient experienced a partial tumor regression without active oncologic treatment (L-T3 switch only) and reports improved quality of life for more than 18 months since stage IV diagnosis. One patient with leiomyosarcoma and low level of estrogen receptors has PR for more than a year while on Letrozole and L-T3 treatment only. Median overall survival for patients in this study was 19 months (range 9-90+ months).

Conclusion: Exogenous L-T3 replacement of L-T4 supplementation in hypothyroid patients with metastatic uterine sarcoma is safe, and no observed complications or impact on quality of life were reported. The exceptional longevity observed in some patients, and spontaneous tumor regression (following termination of L -T4 only) suggests that induced hypothyroxinemia supported by exogenous L-T3 may have an added therapeutic effect in incurable uterine sarcoma patients. Prospective studies of induced hypothyroxinemia with exogenous L-T3 in hypo- and euthyroid patients may be reasonably investigated.



T4 termination only with no other oncological treatment



High grade Uterine Leiomyosarcoma on Letrozole+T3 and T4 termination.
Left on treatment and Right before

PO #08 3225063

USE OF A TRK-INHIBITOR AS NEOADJUVANT THERAPY FOR PEDIATRIC NTRK-MUTATED SARCOMAS: A CASE REPORT

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Objective: Neurotrophic tropomyosin receptor kinases (NTRKs) are tyrosine receptor kinases in the nerve growth factor family. NTRK mutations have been implicated in a number of neoplasms including soft-tissue sarcoma, papillary thyroid cancer and neuroblastoma, among others. In particular, infantile fibrosarcoma has been linked to NTRK3-ETV6 fusion mutations. There is an increasing body of literature to support successful use of TRK inhibitors in the setting of metastatic or locally advanced NTRK driven tumors. However the majority of reported cases have been previously treated with alternative therapies and moreover, most are treated for a number of months prior to undergoing any attempt at definitive surgery. In this report, we describe the use of neoadjuvant Larotrectinib in two therapy-naiive cases, with the intention of subsequent definitive surgical resection. Rationale for medical management included minimizing surgical morbidity and maximizing the likelihood of an R0 resection, with the added benefit of being able to assess tumor responsiveness in the event of eventual relapse.

Methods: Patient#1: A 2-month-old otherwise healthy male presented with a 5 x 5 cm enlarging mass on the left forearm. Initially thought to represent a hemangioma, it was briefly managed with propranolol. Rapid enlargement prompted an urgent open biopsy, which demonstrated a spindle cell neoplasm positive for an NTRK3-ETV6 fusion mutation consistent with infantile fibrosarcoma. The findings were discussed in a multidisciplinary tumor board and recommendations were to start Larotrectinib immediately, with the aim of permitting a limb-salvage surgery and to minimize surgical morbidity.

Patient #2: A 12-year-old otherwise healthy male presented with a 3.5 x 3 cm mass within the distal aspect flexor carpi ulnaris of his right forearm. An open biopsy was performed, demonstrating a TRK-rearranged mesenchymal neoplasm marked by a uniform proliferation of spindle cells infiltrating the surrounding tissues. The findings were discussed in a multidisciplinary tumor board and recommendations were to start Larotrectinib as a means of minimizing surgical morbidity and preserving as much upper extremity function as possible in his dominant hand.

Results: Patient #1 was treated with 34 mg orally twice a day, demonstrating excellent tolerance with no reported adverse events to date. Response was noted clinically in under 5 days time from the initiation of therapy. At 6 weeks, tumor size decreased by approximately 50% and he is currently awaiting a follow up MRI in anticipation of surgical management.

Patient #2 was treated with 100 mg orally twice a day. Response was noted clinically in approximately 1 week with continued response at 2 week follow up. Increased liver enzymes prompted discontinuation of the treatment and thereafter, he underwent successful R0 resection. The flexor carpi ulnaris muscle was only partially resected, which would not have been possible prior to neoadjuvant therapy. He healed his surgical wound without incident and has normal upper extremity function at early follow-up. No additional therapy is planned and he will undergo clinical and radiographic surveillance.

Conclusion: In this report, we describe two therapy-naive pediatric mesenchymal tumors with NTRK-positive mutations which were treated with neoadjuvant Larotrectinib. The goal of therapy in both cases was to minimize surgical morbidity and effectively permit RO definitive surgery. While there is increasing excitement and experience in treating NTRK-driven tumors with targeted therapy, very few have evaluated its use in this manner and for these reasons. While these results are too early to draw definitive conclusions, initial experience is very positive. Response appears to be clinically notable much earlier than reported in the literature and surgical benefits appear to be promising. Longitudinal follow up and additional clinical experience will help define ideal application of this exciting and well tolerated therapy.

PO #09 3256410

PLOCABULIN, A NOVEL TUBULIN INHIBITOR, HAS ANTITUMOR ACTIVITY IN A PATIENT-DERIVED XENOGRAFT (PDX) MODEL OF DEDIFFERENTIATED LIPOSARCOMA

Yannick Wang[1]*; Agnieszka Wozniak*[1]*; María José Guillén*[2]*; Pablo M. Avilés*[2]*; Maria Debiec-Rychter*[3]*; Raf Sciot*[4]*; Patrick Schöffski*[5]

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Objective: Adipocytic sarcomas are a relatively common histological subfamily of soft tissue sarcoma (STS). Dedifferentiated liposarcoma (DDLPS) represents around one-quarter of all liposarcomas and arises often in the retroperitoneum. Doxorubicin (DOXO), sometimes combined with ifosfamide, remains the first line treatment for patients with advanced soft tissue sarcoma for more than 40 years. However, response rates for single-agent DOXO are only about 15%. There is a clear need for more effective and novel therapeutic compounds for treating liposarcoma. The aim of our study was to test plocabulin (PLO; PM060184, PharmaMar), a potent cytotoxic tubulin-dynamics modifier, in a PDX model of dedifferentiated liposarcoma.

Methods: Female NMRI *nu/nu* mice (n=20) were transplanted bilaterally with human xenografts of DDLPS (UZLX-STS124p.11). The tumor originates from a patient with DDLPS prior to systemic treatment with doxorubicin and did not respond to the chemotherapy. Xenografted animals were randomly assigned to three treatment groups: 1) vehicle (20% hydroxypropyl β-cyclodextrin) 6.4ml/kg once weekly (QW) intravenously (i.v.), 2) DOXO 3.0mg/kg QW i.v., or 3) PLO 16mg/kg QW i.v. Treatment lasted 22 days and antitumor activity was assessed by tumor volume analysis, histopathology and Western blotting. Tumors with volumes smaller than 100mm^3 at start of experiment were excluded from the volumetric analysis. However, all tumors in which a sufficient number of high-power fields could be evaluated were included in the histopathological assessment. Kruskal-Wallis test with Dunn's multiple comparisons test as *post hoc*, non-parametric test was used for statistical analysis with $p < 0.05$ considered as significant.

Results: PLO treatment resulted in tumor volume stabilization in this PDX model and showed better activity than DOXO in terms of tumor volume control (140% *vs.* 295%, p=0.02). Focal or partial necrosis was observed in 70% of PLO treated tumors (*vs.* 8% of vehicle treated tumors and 0% of DOXO treated tumors). An increased mitotic count was observed in PLO treated tumors as assessed by hematoxylin and eosin staining, while no effect was seen on apoptosis or angiogenesis. The experimental drug was well tolerated throughout the experiment at the dose administered.

Conclusion: PLO is a novel anti-tubulin agent showing antitumor activity in a PDX model of dedifferentiated liposarcoma. Our results demonstrate that this novel compound suppressed tumour growth in a DOXO-resistant model. This study provides strong arguments to study PLO further in additional histological subtypes of STS and to explore the compound in clinical trial.

PO #10 3256541

RADIATION THERAPY COMBINED WITH CHECKPOINT INHIBITOR IN PATIENTS WITH UNDIFFERENTIATED PLEOMORPHIC SARCOMA: A PROMISING TREATMENT APPROACH

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Objective: The role of immunotherapy in treating patients with advanced soft tissue sarcomas is unclear. This is partly related to the heterogeneity of soft tissue sarcomas and their different biologic behaviors and responses to different treatments. The expanded cohort of SARC 028, a phase II trial showed 23% ORR of Pembrolizumab in patients with Undifferentiated Pleomorphic Sarcoma (UPS) while having lower to minimal activity in other STS subtypes. We present here two patients with metastatic UPS who were treated with radiation in combination with Pembrolizumab with success at controlling their disease.

Methods: We present here two patients with metastatic UPS who were treated with radiation in combination with Pembrolizumab with success at controlling their disease.

Results: Patient 1 is a 38 year-old man, who is a Jehovah's witness, and was diagnosed with UPS of the left thigh in November 2015. Tumor was PDL-1 negative. He underwent 2 cycles of neoadjuvant chemotherapy with MAI (Mesna, Adriamycin, and Ifosfamide). The second cycle was complicated by neutropenic fever and severe anemia (hgb 5.9 g/dl) for which he refused blood transfusion due to his religious beliefs. His mass increased in size after these 2 cycles of chemotherapy and underwent neoadjuvant radiation followed by surgical resection and adjuvant chemotherapy was waived due to his intolerance. On surveillance scans 5 months after resection he was found to have metastatic disease in his lungs and was started on Pembrolizumab (200 mg every 3 weeks) through compassionate use. His disease was stable for 7 months at which time one of his lung nodules, in his left lower lobe, increased is size with the remaining lesions stable. He underwent SBRT for that lung nodule and continued on Pembrolizumab for 3 months at which time it was held for severe fatigue. He was restarted on Pembrolizumab every 6 weeks on which he remains with stable disease for 2 years.

Patient 2 presented with a left arm mass that was biopsied, revealing a UPS. PDL-1 from the original tumor was negative. His staging scans revealed multiple bilateral small lung nodules, the largest of which was 2 mm in size. He underwent neoadjuvant radiation after which restaging scans revealed increase in the size of the lung nodules, the largest of which, in the RLL, was biopsies confirming metastatic disease. He was started on systemic chemotherapy with MAI (Mesna, Adriamycin, and Ifosfamide), but progressed after 2 cycles. He was then switched to Gemcitabine and Docetaxel with control of his disease for 1 year. Upon progression, he was started on Pembrolizumab at 200 mg every 3 weeks then changed to every 6 weeks as the patient developed fatigue and falls. 18 months after starting the Pembrolizumab (January 2019), the patient's RLL metastatic mass was increasing in size with the remaining of his disease being stable . He underwent SBRT for this mass and resumed Pembrolizumab with stable disease so far.

Conclusion: Combining radiation with immune checkpoint inhibition is a valid strategy in treating metastatic UPS after failing multiple lines of chemotherapy or in patients with contraindication or intolerance to chemotherapy.

PO #11 3257996

RECONSTRUCTIVE MANAGEMENT OF PATIENTS WITH SARCOMA OF THE FOOT

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Objective: sarcomas are rare and aggressive tumors which require extensive surgery to get satisfactory control locally. It remains challenging for the surgeon to find a safe balance between the oncologic requirement and the functional preservation of the region. The aim of this study was to evaluate the surgical management of patients with soft tissue sarcoma of the foot and the outcomes.

Methods: All patients treated for soft tissue sarcoma of the foot between 2017 and 2019 in rennes's university hospital and bergonié institute were included. Characteristics of the patients, characteristics of the tumor, reconstructive management and clinical outcomes were analyzed.

Results: A total of 8 patients were included. In 6 patients the tumor was on the dorsal side of the foot and in 2 patients the tumor was on the plantar side. Two patients had preoperative radiations and four patients had adjuvant radiations. We report the therapeutic sequence chosen for each patient and discuss the reconstructive strategy. Local reconstruction was possible in three cases, skin graft was used in two cases and faciocitaneous free flaps were used in three cases. Amputation occurred in one patient with recurrence of sarcoma.

Conclusion: This study evaluates the functional and cosmetic outcomes regarding limb preservation and offers discussion of existing technics for foot coverage.

PO #12 3255332

A PROSPECTIVE CORRELATIVE TRIAL OF PERSONALIZED PATIENT-DERIVED XENOGRAFT (PDX) AS AVATARS FOR DRUG THERAPY IN PATIENTS (PTS) WITH METASTATIC OR RECURRENT SOFT TISSUE SARCOMAS (STS)

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Objective: The overall benefit from systemic treatments in advanced STS remains modest despite advances in cancer therapies. PDX models may help as avatars in guiding individualized drug use decisions.

Methods: In this prospective single center trial, fresh tumors from pts with suspected or recently diagnosed STS were engrafted into immunodeficient mice avatars (TumorGraft; Champions Oncology) and tested against a number of standard or non-licensed agents. PDX drug sensitivity profiles were then compared with real-life treatment outcomes.

Results: Of 18 patients enrolled, 3 patients were excluded (consent withdrawal/non-sarcomas). Patient baseline characteristics are summarized in Table A. Rate of engraftment was 40% (6/15 pts), while the median time from biopsy to availability of drug sensitivity profile was 379 days (186 – 421). In patients with available drug sensitivity profile (9 different drugs involving 6 pts), the mouse avatar correctly predicted the drug efficacy or lack thereof of drugs in 7 of 9 drug selection time-points (78%) and in 5 of 6 patients (83%).

Conclusion: PDX avatars can accurately predict drug responses in STS pts. The rate of engraftment and time taken to produce drug sensitivity profiles are limitations for using this platform in guiding treatment for individual patients in real time. Nonetheless, the high degree of clinical predictability of this PDX platform may offer therapeutic value for personalized oncology approaches.

Table A. Patient baseline characteristics

Item	Eligible patients (n=15)	Engrafted patients (n=6)
Median age (range)	57 (23-76)	57 (45-69)
Gender (M:F)	8:7	3:3
Subtype: - Liposarcoma - Leiomyosarcoma - UPS - Others	- 5 3 1 6	- 2 2 1 1

PO #13 3255808

EPITHELIOID AND SYNOVIAL SARCOMA MIMICKING A PERIPHERAL NERVE SHEATH TUMOR

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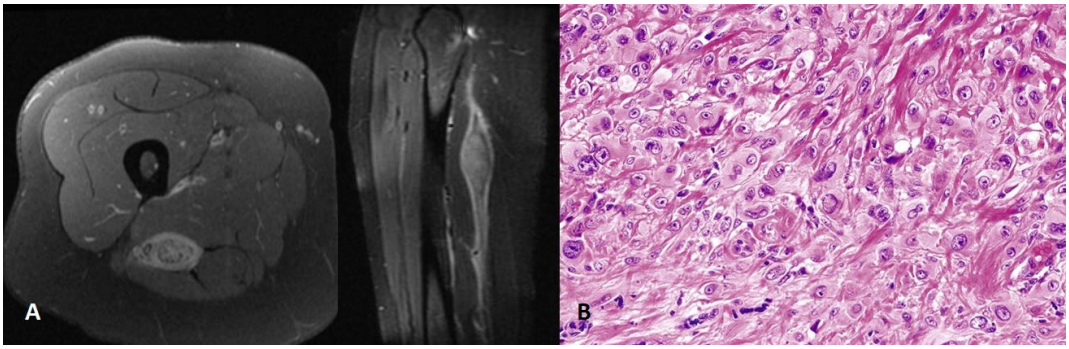
Objective: Intraneural involvement by epithelioid and synovial sarcoma is rare. Although benign peripheral nerve sheath tumors are much more common, there should be always be consideration for malignancy. We describe the cases of two patients found to have sarcomas mimicking a benign peripheral nerve sheath tumor.

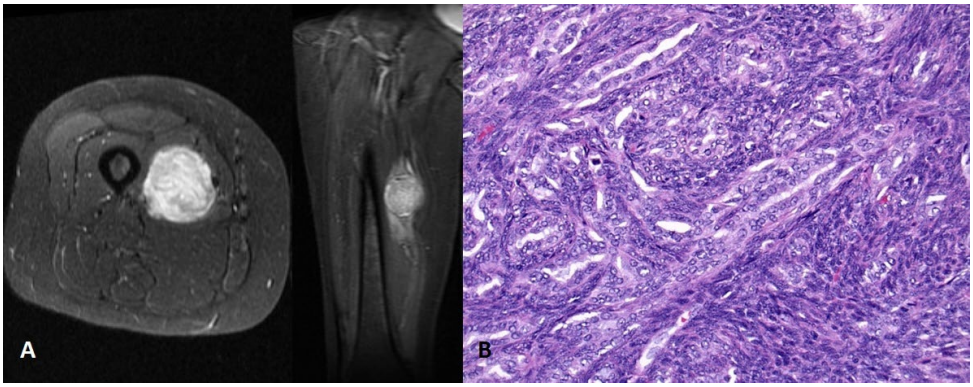
Methods: A 21-year-old male and a 30-year-old female presented to with a history of progressive pain, numbness, and tingling with the presence of a mass. Both patients noted a history of worsening pain and loss of sensation. The male patient had symptoms in the sciatic nerve distribution over 6 months with no motor symptoms. The female patient had progressive pain in the anterior thigh and quadriceps weakness for 1 year. Both patients had tenderness over the mass and a positive Tinel's. Although both patients noted a mass, they did not feel that the mass had progressed in size. Neither patient had a history or clinical symptoms of neurofibromatosis.

Results: Both patients underwent staging with an x-ray followed by an MRI. No abnormality was found on x-ray. The male patient was found to have a fusiform mass that was continuous with the sciatic nerve (Figure 1A). A biopsy demonstrated mixed spindle and epithelioid tumor that was positive for cytokeratin and vimentin, negative for S100 and INI1 deficient, most consistent with an epithelioid sarcoma (Figure 1B). The female patient had a fusiform tumor that involved a portion of the femoral nerve (Figure 2A). A biopsy demonstrated a biphasic synovial cell sarcoma confirmed with a t(X;18) translocation and SS18-SSX2 fusion protein. Both tumors were found to be within the nerve sheath with invasion of the nerve. The male developed metastatic disease 6 months after resection and died one year after diagnosis. The female is free of disease and alive 8 years after diagnosis.

Conclusion: Although uncommon, a soft tissue sarcoma arising within a nerve sheath other than a malignant peripheral nerve sheath tumor can occur. The clinical and radiologic presentation significantly overlapped that of a benign peripheral nerve sheath tumor. These cases demonstrate the need for a high index of suspicion for malignancy when evaluating a peripheral nerve sheath tumor.



A) Axial and sagittal MRI of a 21-year-old male with a fusiform tumor involving the sciatic nerve. B) The pathology demonstrated an epithelioid sarcoma.



A) Axial and coronal MRI of a 30-year-old female with a tumor involving the femoral nerve. B) The pathology confirmed a biphasic synovial cell sarcoma.

PO #14 3255908

THE CT AXIAL IMAGING CAN DETECT FEMORAL METASTATIC BONE TUMORS AT EARLY STAGE

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Objective: Metastatic lesions of the proximal femur occur frequently and require surgical treatment. Medical oncologists usually perform computed tomography (CT) and positron emission tomography/computed tomography (PET/CT) to evaluate local recurrence and distant metastasis. This study aimed to evaluate the usefulness of CT axial imaging for the early diagnosis of femoral metastatic bone tumors. We retrospectively analyzed patients who underwent surgery for metastatic bone tumors of the femur. We reviewed CT, magnetic resonance imaging (MRI), bone scans, and PET/CT scans. We also investigated the feasibility of CT axial imaging for the early diagnosis of femoral metastatic bone tumors.

Methods: From March 2008 to June 2018, thirty-seven (37) patients with bone metastases of the femur were recruited for this study. We defined the medulla sign as a higher-attenuation area of bone medulla than the intramedullary fat tissue on CT axial imaging. We defined the "date D" as the date of diagnosing the patient with a femoral metastatic bone tumor and "date M" as the date of diagnosing positive medulla sign. The duration between these two dates was also evaluated.

Results: The mean age of the 37 patients was 63.2 (range 33–85) years. In 28 cases (75.7%), the tumor was located in the proximal femur (femoral head, femoral neck, trochanteric, and sub trochanteric), and in the femoral shaft in 9 cases (24.3%). The medulla sign was identified earlier than date D in 9 patients (24.3%). Of the patients with proximal femoral tumors, 8 patients(28.6%) were diagnosed with positive medulla sign earlier than date D. Two medulla sign-positive patients were found fractured perfectly before operation. Date M was at an average 207.7 (22–861) days earlier than date D.

CT was frequently used for follow-up of patients with tumors. The femur was only partially visible on CT or PET/CT of the pelvis. In this study, we diagnosed metastatic bone tumors earlier by only using CT axial imaging. We suggest that if radiologists, medical oncologists, and orthopedic surgeons consider that the proximal femur is a preferred site for metastatic bone tumors, a diagnosis can be established earlier by follow- up CT axial imaging. Furthermore, we believe that early diagnosis provides patients with more adequate therapy.

Conclusion: Metastatic bone tumors demonstrate the findings of medulla sign on CT axial imaging. These findings are useful for the early radiological diagnosis of femoral metastatic bone tumors.

PO #15 3255058

SURGICAL MANAGEMENT OF BREAST DERMATOFIBROSARCOMA PROTUBERANS: A FIVE CASES SERIES

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Objective: Dermatofibrosarcoma Protuberans (DFSP) is the most frequent soft-tissue sarcoma with essentially local malignancy. The most frequent locations are trunk, extrimities, head and neck. Occurrence in the breast is rare. Until a few years ago, the treatment was wide resection with 3 to 5 cm margins and excision of the underlying fascia. Three-dimensional histology using the modified "Slow Mohs" technique is now the gold standard in France allowing significant skin savings. When located to the breast, the goal of the resection is not only carcinologic but also cosmetic. We report the cases of 5 fives patients who had breast DFSP resection and try to elaborate a surgical strategy towards these tumors.

Methods: 5 patients presenting with a breast DFSP were operated by 2 surgeons in 2 institutions. Preoperative workup, surgical procedure, and postoperative outcomes were evaluated.

Results: All the patients were women, average age was 39. A cutaneous biospie was realized to confirm the diagnostic in all patients before surgery. A chest CT-scan was also realized prior to surgery to check the absence of pulmonary metastases. A Slow Mohs surgery was performed for all patients. The defect was closed primarily in 3 cases (2 DFSP located in the internal inferior quadrant and 1 at the junction of the uppers quadrants), with a rotation flap in 1 case (internal upper quadrant) and with a skin graft in 1 case (intermammary cleft). All the patients remain disease-free without any tumor recurrence at the last follow-up.

Conclusion: The local aggressivity of DFSP used to impose large resection with 3 to 5 cm margins. The Slow Mohs surgery allows to reduce theses margins and thus allows skin savings, which is very important for the esthetic result. In our serie, the defect was closed primarily with minimal detachment when possible. In one case, we realized a skin graft because of the median location of the DFSP with poor skin elasticity. Primarily closure or skin graft has little effect on the anatomic relation of the region which is important for surveillance and if a revision is needed for recurrence. We realized a breast rotation flap in one case for an important defect located in internal upper quadrant, using the laxity from the inferior quadrants of the breast and resulting in a rounded shaped breast. The type of closure to obtain a natural shaped breast depends on the location and size of the defect and the size of the breast. The pectoralis fascia was not removed in 2 cases because the DFSP was located in periareolar area. The cosmetic result was good for our 5 patients, with a natural shaped breast and no need for augmentation or contralateral reduction.

PO #16 3253292

ROLE OF SURGICAL RESCUE OF RETROPERITONEAL LIPOSARCOMA RECURRENCE

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[1]*Surgery, Hospital General Universitario Gregorio Marañón, Madrid, Spain;* [2]*Radiation Oncologist, Hospital General Universitario Gregorio Marañón, Madrid, Spain;* [3]*Oncology, Hospital General Universitario Gregorio Marañón, Madrid, Spain*

Objective: Our center was designated one of the five National Referral Center for the treatment of sarcomas three years ago. Since them many patients with retroperitoneal liposarcoma were referred to our hospital. The objective is to evaluate the results of surgical resection in patients with retroperitoneal liposarcoma relapses, treated in our centre.

Methods: Prospective database was retrospectively analysed. From january 2011 to december 2018 all 66 patients with retroperitoneal liposarcoma treated in our institution were included The number of patients that were treated for primary liposarcoma was 35 and 31 were treated for abdominal recurrence. Overall survival , local and sistemic recurrence and prognostic factors were evaluated.

Results: Of the 66 patients, 31 patients were operated for abdominal recurrence. Median of follow-up was 15 months.13 patients were treated for the first recurrence, 8 for the second, 6 for the third, 2 for the fifth and one patien was treated for the seventh relapse.The location of recurrence were retroperitonealin 16 patients, pelvic in 2, pelvic and retroperitoneal in 1 and abdominal in 11.Well differentiated liposarcoma was diagnosed in 7 patients, dedifferentiated in 17, myxoid in 3, pleomorfic in 2 and solitary fibrous tumour in 1. The grade od FNCLCC was1 in 4 patients, 2 in 14 and 3 in 10. The type of resection was as follow: in 7 patients compartimental resection was performed and citoreductive surgery in 24. Neoadjuvant treatment with radiotherapy was performed in 11 patients and chemotherapy in 9. Intraoperative radiation was applied in 19 patients. Median overall survival was 50 ± 9.04 months. Patients treated for second and third recurrence had a 3 years survival of 55.6% and 44% respectively. Histological grade was found as prognostic factor.

Conclusion: Recurrence of retroperitoneal liposarcoma is complex situation that shoul be treated in referral centers. Repeated resections provide the patients with significant survival benefit. Histological grade is one of the most important factor that influence survival in these patients.

PO #17 3254847

DO WE NEED ROUTINELY PLACE URETERAL CATHETERS PRIOR TO SURGRIES IN PATIENTS WITH PRIMARY RETROPERITONEAL LIPOSARCOMA?

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Objective: Prophylactic ureteral catheters placement (PUCP) was advocated for decreasing ureteral morbidities in colorectal surgeries. However, whether it should be routinely used prior to retroperitoneal liposarcoma(RPS) surgeries remains unknown. This study aimed to explore the frequency and risk factors of ureteral injury (UI) during and post retroperitoneal liposarcoma resection surgeries.

Methods: It was a retrospective study, conducted at a tertiary sarcoma center. Medical records of patients with primary retroperitoneal liposarcoma (PRPS) undergoing surgeries from January 2015 through December 2018 were reviewed. Primary endpoint was the rate of ureteral morbidities during and after retroperitoneal liposarcoma resection procedures. Risk factors associated with UI in patients were determined through uni- and multi-variate analysis.

Results: A total of 55 patients (male 29, mean age 55) of PRPS who underwent resection surgeries were included. UIs were identified in 16 patients (complete transection 3, ureteral damages 11, postoperative hydronephrosis 2). 14/55 (25.5%) patients underwent PUCP, with one ureteral injury (7.1%) identified. 41 patients with no prophylactic ureteral catheters, exhibited with 15(36.6%) UIs. Prophylactic ureteral catheter placements were found significantly associated with UIs ($p=0.045$). Resection surgeries combine with colectomy and relationship between tumor and ureter were two risk factors significantly associated to UIs ($p<0.05$). Age, BMI, tumor size, pathologic type and differentiation were not related to UIs through univariate and multivariate analysis.

Conclusion: Prophylactic ureteral catheters placement was not suggested as a routine process of preventing ureteral injuries in PRPS patients undergoing surgeries. Patients with lesions encased ureter or combine with colectomies had higher probability of developing to UIs.

Table 1.Univariateand multivariate analysis of ureteral injury in patients undergoing primary retroperitoneal liposarcoma resection

Variables	N	UI		Univariate	Multivariate	
		+	-	P	95% CI	P
Total	55	16	39			
Age (Mean)	29-77(55.2)			0.60		
Male gender	29	9	20	0.74		
BMI (Mean)	16-32(23.1)			0.047	0.89-1.69	0.21
History of Diabetes	3	2	1	0.20	0.02-2164.86	0.54
PUCP				0.045	0.006-1.27	0.07
Yes No	14 41	1 15	13 26			
Co-colectomy	12	7	5	0.012	1.01-74.23	0.048
Histologic subtype				0.67		
WDLPS Other	30 25	8 8	22 17			
Relationship of tumor and ureter				0.001	1.57-40.17	0.012
Adjacent Encased	32 23	4 12	28 11			
Operativetime(min)	100-490 (247)			0.06	0.99-1.01	0.97
Blood loss (ml)	100-5000 (1175)			0.15	0.99-1.00	0.56

PO #18 3255227

THE CLINICAL RESULTS OF TRABECTEDIN OR ERIBULIN CHEMOTHERAPY IN ADVENCED SOFT TISSUE SARCOMA

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Objective: We examined the clinical results of Trabectegin (TBT) and Eribulin (ERB), new options in chemotherapy for advanced soft tissue sarcoma.

Methods: The subjects were patients who underwent prior chemotherapy at our hospitals and then TBT or ERB chemotherapy. There was observed Pathological diagnosis, age at the start of each treatment, PS, number of metastatic organs, number of prior treatment regimens, number of prior regimens, first dose of TBT and ERI, number of treatments, adverse events, and outcome

Results: TBT group consisted of 8 males and 4 females, age 30-78 (median 53.5) years, PS 0 and 1, 8 total, PS 2 and 3 total 4, cases diagnosed with clear cell sarcoma, myxoid liposarcoma, UPS 2 each. At the start of treatment, the number of metastases in one organ is the largest in 7 cases, the number of preceding regimens is 1 to 4 (median 2), frequency of administration 1 to 11 (median 4). TBT initial dose was 75 to 100 (median 93) %, The number of administrationsis 1 to 10 (median 3), CTCAE G3 or more adverse events were observed 3 times of AST elevation, 5 times of ALT elevation, and 1 time of CK elevation. Eleven patients discontinued on PD, EFS was 22 to 234 days, and the outcome was OS 46 to 904 days and 6 cases were AWD and 6 DOD. On the other hand, in the ERB group, there were 9 males, 6 females, age 52 to 76 (median 61) years old, 3 cases were PSO, 10 PS 1, 2 PS 2, and diagnosis, 6 cases was leiomyosarcoma . At the start of treatment, the number of metastases in one organ is 9 cases, the number of preceding regimens is 3 in 5 cases, the number is the largest, the number of administrations is 2 to 17 (median 6 times) Adverse events were G3 leukopenia 18 times, neutropenia 29 times, G4 leukopenia 4 times, neutrophilic reduction 8 times (median 6). CR was observed in 1 case, EFS was 48 to 462 (180 days), and the outcome was OS 56 to 532 (median 298) days in 1 case of NED, 12 cases of AWD, 3 cases of DOD. Five patients have taken both treatments. EFS 50% was significantly different from TBT 44 days and ERB 226 days ($P < 0.05$), but OS 50% was not significantly different.

Conclusion: Although there is a difference in subjects, there is a significant difference in EFS with no significant difference in OS, and furthermore, Eribulin is considered to be a more easy-to-select drug in terms of less serious adverse events. We would like to proceed with the study by tissue type and grade of malignancy.

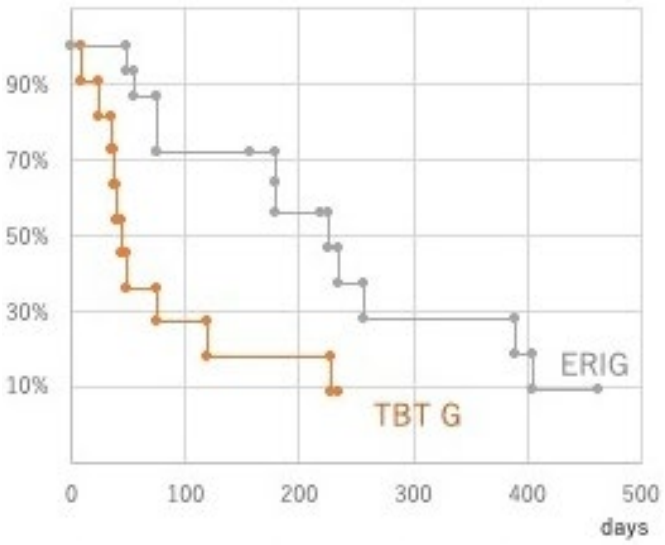

Fig.1-a Event Free Survival

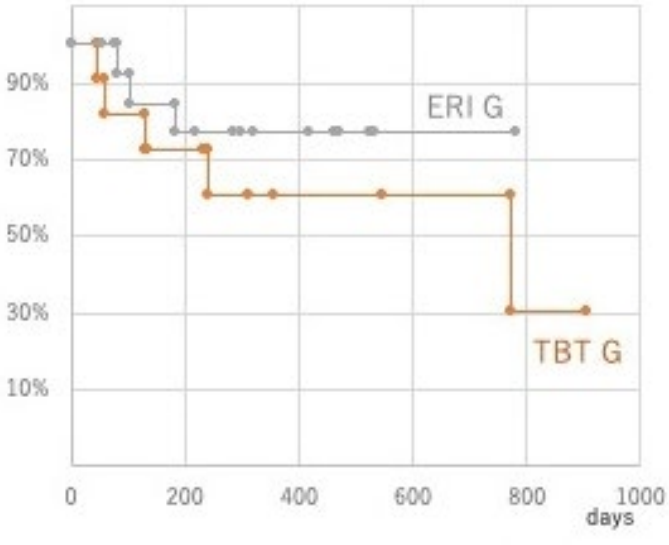

Fig.1-b Overall Survival

Characteristic

		TBT G	ERI G
sex	male	8	8
	female	4	6
age (years)	mean	53	61
	range (min-max)	30-78	52-76
ECOG perfomance score	0	1	3
	1	7	9
	2	2	2
	3	2	0
number of metastatic site	0	0	2
	1	7	8
	2	4	3
	3	1	1
diagnosis	leiomyosarcoma	0	6
	UPS	2	2
	liposarcoma myxoid	2	1
	liposarcoma didiff.	1	1
	clear cell sarcoma	2	0
	ESMCS	2	9
	phyllodes tumor	1	1
	others	2	2
number of prior regimen	1	4	6
	2	5	3
	3	1	5
	more	1	0

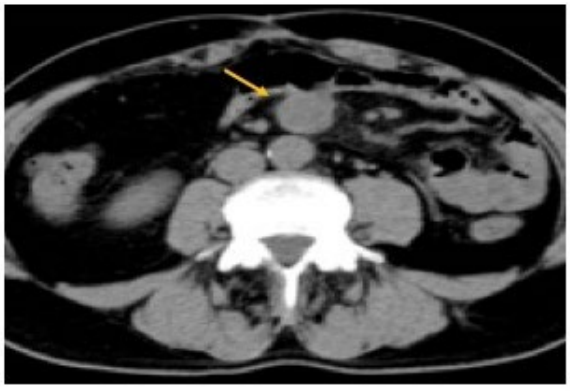

Fig.2-A

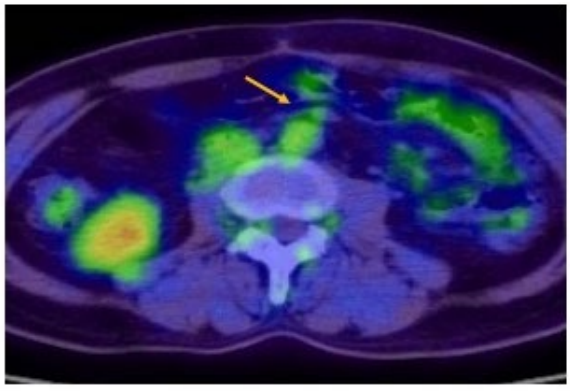

Fig.2-B

fig.2 CT / FDG-PET CT
52 y.o. male leiomyosarcoma of retroperitonea
fig2-A : pre-treatment fig2-B : FDG-PET CT after 6 course

PO #19 3255273

ANLOTINIB FOR ADVANCED PROGRESSIVE SARCOMA: A RETROSPECTIVE STUDY

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Objective: Patients with advanced progressive sarcoma (APS) who are failed in the standard treatment (relapse or drug resistance), usually have multiple metastases or unresectable lesions with continuous disease progression. Targeted therapy such as anlotinib could provide a new approach to improve the long-term survival of these patients. The goal of our study is to explore the disease control rate (DCR) and to evaluate the efficacy and safety of anlotinib in APS after 2-cycle treatment.

Methods: Between June and December of 2018, 17 patients were recruited in this study. 10 patients were soft tissue sarcoma (STS) and the others were primary bone sarcoma (PBS), including osteosarcoma (n=4), chondrosarcoma (n=3), undifferentiated polymorphous sarcoma (n=3), epithelioid sarcoma (n=2), leiomyosarcoma (n=2), alveolar soft part sarcoma (n=1), desmoplastic small round cell tumor (n=1), and fibrosarcoma (n=1). Patients received anlotinib 12mg once daily on a 2-week on/1-week off schedule. Patients with surgical indications should have cytoreductive surgery. Response rate was assessed using RECIST1.1. Toxicity was recorded using CTCAE version 4.03.

Surgical indications: a) hypofunction of spinal cord due to the compression of dural sac; b) the weight-bearing bone is or will be instable; c) several intractable pains; d) progressive growth of tumor leads to symptoms.

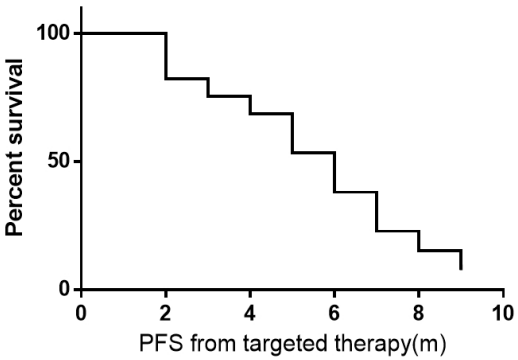
Results: Our study found that 2-months DCR and ORR（overall response rate）were 76.47% (13/17) and 11.76% (2/17), respectively. Median PFS was 5.3 months, and the 6-month PFS rate was 41%. There was no significant difference of PFS between STS and PBS (P=0.2803, HR=0.59, 95%CI: 0.14-1.58).

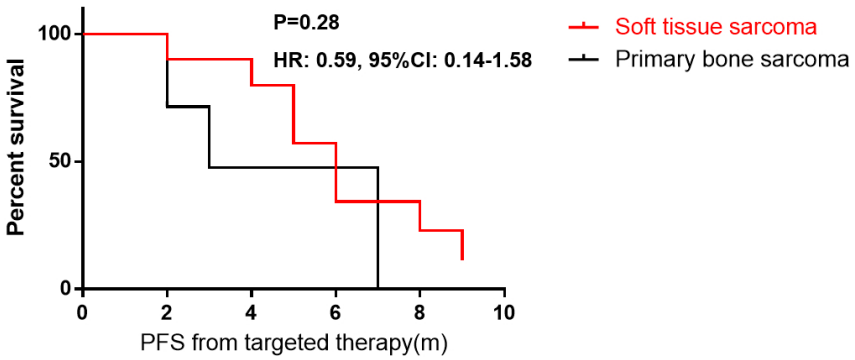
The adverse event (AE) had happened in all patients. The most common grade 1/2 AE were anorexia (35%), fatigue (24%), hypertension (12%). The most common grade 3/4 AE were hypertension (6%), hand-foot skin reaction (6%), pneumothorax (6%). Dose reductions and drug interventions occurred in 1 and 2 patients, respectively.

Interventions were recommended in some conditions:
a) new lesions: if total tumor burden hadn't increased, the patient would be revaluated after 2-cycle treatment. Otherwise, the patient would stop taking anlotinib or change to other TKIs（tyrosine kinase inhibitors）. Local radiation is available at the same time.

b) various reactions of lesions: if it wasn't progressive disease (PD), we recommend local treatment to PD lesions, such as argon-helium cryosurgery, cytoreduction, interventional embolization, and local radiation.

Conclusion: Anlotinib has antitumor activity in APS entities with a manageable tolerability. There is no significant difference of PFS between STS and PBS. We recommend that patients with surgical indications should have cytoreductive surgery before targeted therapy.





PO #20 3248434

MALIGNANT TUMOR WITH OVERLAPPING FEATURES OF MYOEPITHELIAL CARCINOMA AND EWING SARCOMA WITH EWSR1-ETV1 FUSION: A MOLECULAR CASE STUDY

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Objective: To report a rare malignant tumor with overlapping features of Myoepithelial Carcinoma and Ewing Sarcoma with an *EWSR1-ETV1* fusion in the forearm of a child with bone metastases.

Methods: The medical record, imaging studies, and histopathology were reviewed. Molecular studies including fluorescent *in situ* hybridization (FISH) and RNA sequencing (Illumina TruSeq) were performed and analyzed to characterize the tumor.

Results: An 8-year-old Japanese boy presented with a 3-month history of a palpable mass on the volar aspect of the right forearm and a 2-month history of progressive low back pain. Diagnostic imaging studies revealed a 3.8 cm-sized intramuscular tumor in the right forearm with widespread bony metastases to the cranium, vertebrae, pelvis, and bilateral proximal humeri and femurs; there was no pulmonary metastasis. Histological evaluation of the primary tumor tissue revealed an infiltrative tumor composed of solid sheets and nodules of round, ovoid, to short spindle-shaped tumor cells with frequent nuclear atypia and numerous mitotic figures. Immunohistochemistry showed multifocal positivity for CD99, TLE1, CD56 and GFAP; focal positivity for synaptophysin, S100 and desmin; moderate to weakly positive for CD117 and myogenin; and negative for MyoD1, Sox10, chromogranin A, BCOR, NUT, SMA, CD45, TdT, CD34, ERG, CK, pan-keratin, CAM5.2, EMA, and p63. Staining for H3K27me3 and INI-1 were positive, *i.e.* normal/retained. Staining for WT1 was positive in cytoplasm. FISH of *EWSR1*, *FUS*, *FLI1*, *SS18*, *CIC*, *NCOA2*, and *ETV6* showed no evidence of gene rearrangement. RNA sequencing revealed a cryptic *EWSR1-ETV1* fusion. The consensus diagnosis of the tumor was a malignant round to spindle cell neoplasm, most consistent with a high-grade malignancy with overlapping features of myoepithelial carcinoma and Ewing Sarcoma. Under the initial working diagnosis of a stage IV round cell sarcoma-like malignancy with thoracolumbar spinal cord compression, emergent focal radiotherapy to the T11-L4 vertebral tumor at 3,600 centigray/12 fractions with TomoTherapy was performed with concurrent systemic chemotherapy with Ifosfamide (1,800 mg/m^2/day for 5 days) and Etoposide (100 mg/m^2/day for 5 days) (IE) for 2 cycles with excellent clinical and radiographic response. A metal brace was also used during sitting and upright positions to support the lower back and to prevent compression fractures. Two further cycles of chemotherapy were given in the induction period using IE followed by Vincristine (1.5 mg/m^2), Doxorubicin (75 mg/m^2/48 hours), and Cyclophosphamide (2,200 mg/m^2) (VDC), with granulocyte colony-stimulating factor support through nadir periods. The patient tolerated the chemotherapy well, although grade 4 cytopenias and grade 2 vomiting were noted. The mean interval between chemotherapy cycles was 16.3 days. Very Good Partial Response of the non-irradiated bony lesions was observed after the 4 cycles of induction chemotherapy. The primary tumor was resected with an R1 resection with radiotherapy to the primary site planned.

Conclusion: A rare case of a high-grade malignancy with overlapping features of Myoepithelial Carcinoma and Ewing Sarcoma with *EWSR1-ETV1* was diagnosed by histopathology showing a heterogeneous tumor cell population with round to spindle cell morphology. The malignancy responded rapidly to interval-compressed induction chemotherapy with VDC/IE.

PO #21 3255829

SECONDARY CHONDROSARCOMA ARISING FROM THE PROXIMAL FIBULA PRESENTING AS SCIATICA

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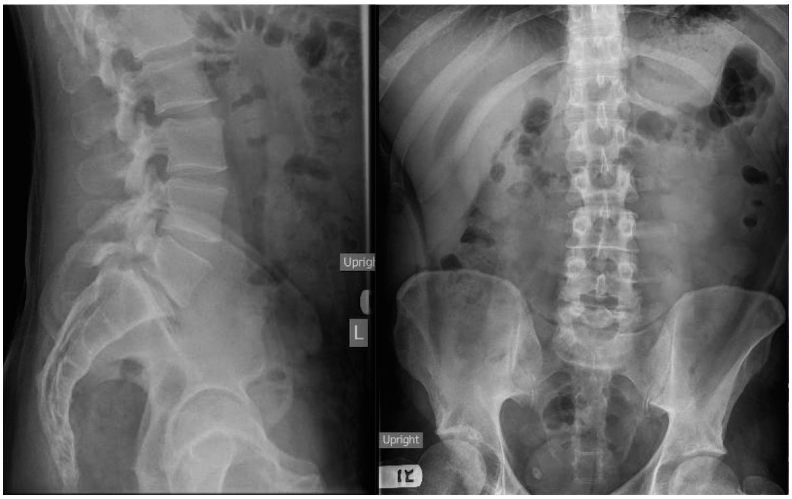
Objective: Secondary chondrosarcoma is a rare entity arising from a pre-existing cartilaginous lesion. Transformation of an osteochondroma to a chondrosarcoma occurs in less than 1% of cases. Sciatica is a common problem that can cause significant pain, weakness, and numbness. This case describes a secondary chondrosarcoma mistaken for a prolonged course of sciatica.

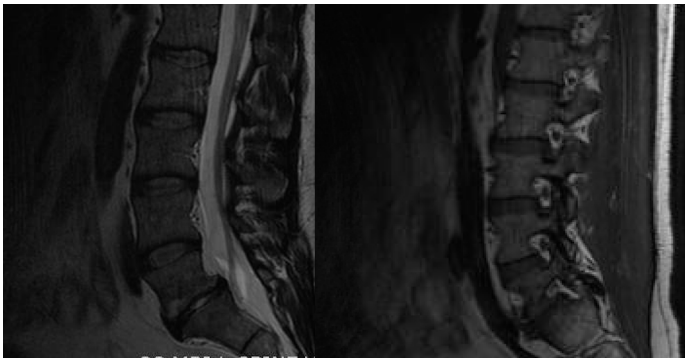
Methods: A 36-year-old male presented to the Orthopaedic Oncology service after being treated for sciatica for 3 years. The patient had significant pain along his sciatic distribution and a chronic foot drop. An x-ray (Figure 1) and MRI (Figure 2) of the lumbar spine demonstrated degenerative disc disease with mild inferior foraminal narrowing at L5-S1. He had undergone multiple epidural steroid injections without improvement in his symptoms. A firm, non-mobile mass was palpated at the proximal fibula.

Results: An x-ray of the knee demonstrated a tumor arising from the proximal fibula with soft tissue calcifications (Figure 3A). An MRI revealed the tumor encased the peroneal nerve and was likely arising from an underlying osteochondroma in the proximal fibula (Figure 3B). A biopsy confirmed a Grade II chondrosarcoma. Staging revealed no evidence of metastatic disease. The patient underwent resection of the tumor which included resection of the peroneal nerve. Negative margins were obtained. Five years after resection the patient is disease free and uses an ankle-foot orthosis for ambulation.

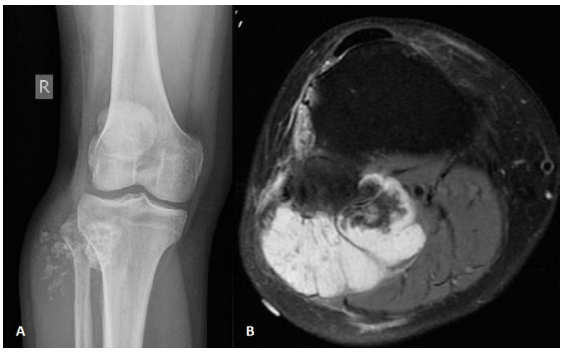
Conclusion: This case demonstrates the importance of evaluating a patient with peripheral nerve symptoms for a lesion within the involved extremity. While sciatica is extremely common, the importance of a physical examination and correlation of the imaging of the lumbar spine is essential to confirm the diagnosis.



AP and lateral x-rays of the lumbar spine demonstrating evidence of degenerative disc disease at L5-S1.



Sagittal MRI's of the lumbar spine demonstrating degenerative disc disease and mild inferior foraminal narrowing at L5-S1. No significant cord or nerve root compression is noted.



A) AP x-ray of the knee demonstrating a tumor arising from the proximal fibula with calcifications in the surrounding soft tissues. B) An axial MRI demonstrates an osteochondroma arising from the proximal fibula with a very large cartilaginous component.

PO #22 3256396

PARASPINAL MASS SUCCESSFULLY TREATED WITH MINIMALLY INVASIVE PROCEDURE IN 20-MONTH-OLD CHILD

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Objective: Our goal is to increase awareness regarding the possibility of using a minimally invasive procedure in select patients with a cervical paraspinal mass. The Children's Oncology Group (COG) protocol for the treatment of a paraspinal neuroblastoma maintains that a patient should undergo invasive surgical excision of the mass (i.e., laminectomy). However, a laminectomy in a child is often a morbid procedure that can inadvertently cause long term detrimental effects. We wish to report what we believe to be the first successful treatment of paraspinal ganglioneuroblastoma in a child using a minimally invasive procedure, namely microwave ablation therapy.

Methods: Microwave ablation therapy is a minimally invasive procedure that utilizes thermal electromagnetic waves to destroy tissue. This method is often used in interventional radiology to treat solid tumors. In most cases of patients who present with a paraspinal mass, an excision via laminectomy is the standard of treatment. A laminectomy is an extensive, open surgery in which portions of the vertebra bone (lamina) are removed. There are often detrimental long-term consequences that accompany a laminectomy such as spinal instability or deformity, persistent back and leg pain, and pulmonary complications. A laminectomy is often avoided unless it is absolutely necessary given the circumstances.

Results: We conducted a literature search on Pubmed with keywords and phrases: "paraspinal mass" "neuroblastoma" "pediatric" "ablation therapy"

Case Report:
We describe a 20-month-old patient who presented at 16 months of age with bilateral lower extremeity hypotonia, limping, generalized irritability, and back pain. Images showed a 4.2 x 2.2 x 6 cm dumbbell shaped tumor at the T6-T7 site. After four cycles of chemotherapy, there was an increase in the size of the mass (4.4 x 2.7 x 7 cm) with encroachment upon the cervical spinal cord. Metaiodobenzylguanidine (MIGB) scan showed increased uptake at the site of the mass (measure of tumor activity), suggesting probable progressive refractory cancer. A subsequent biopsy had shown that the neuroblastoma had differentiated into benign ganglionueroblastoma. At our multidisciplinary tumor board, discussion with neurosurgery and orthopedic spinal surgery concluded that a resection so close to the spinal cord would be risky and morbid (Figure 2). Microwave ablation therapy was offered after informed consent. CT guided microwave ablation at the left paraspinal tumor at T3-T6 was performed and well tolerated except for injury to the synaptic root causing contralateral facial flushing (Figure 1). The patient was home within 48 hours post-operation. Post-operative imaging has shown significant decrease in mass size and increased necrosis of the neuroblastoma (Figure 2).

Conclusion: In current literature, there are no reported cases of microwave ablation therapy used in the treatment of paraspinal masses in pediatric patients.

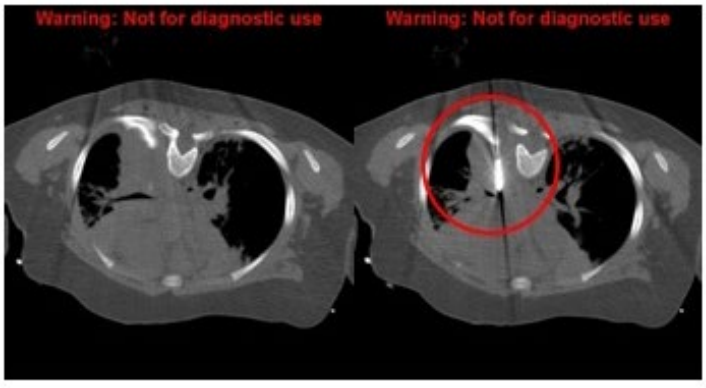

Figure 1: Before and during microwave ablation therapy (ablation is circled on right side)

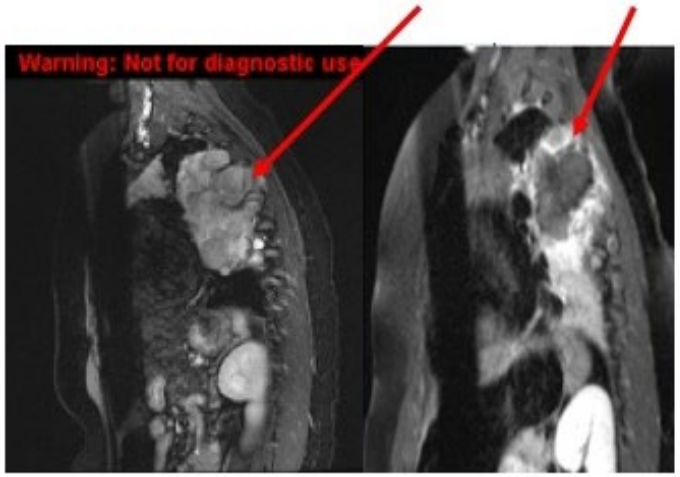

Figure 2: Before and after 3 months of microwave ablation therapy

PO #23 3255987

ADAMANTINOMA OF PELVIS: A RARE ENTITY AT AN UNUSUAL LOCATION

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Objective: Admantinoma is a low-grade malignant bone tumour, commonly affecting the mid-diaphyseal tibial region. It's a slow growing locally aggressive tumour which has metastatic potential in the range of 15-20%. Numerous cases related to admantinoma affecting the appendicular skeleton have been reported; those affecting the axial skeleton are a rarity. Admantinoma of pelvis is an extremely rare occurrence and only 3 previous cases have been reported in literature. We present here a case of admantinoma pelvis with supra-acetabular lysis, treated with bisphosphonates followed by type 1+2+3 internal hemipelvectomy.

Methods: We present the case of a 25 years old male with history of painful lesion in hemipelvis. He underwent multiple biopsies and one intra-lesional surgery outside our institute. A repeat biopsy along with review of previous slides established the diagnosis of Adamantinoma. Staging work-up showed no distant metastatis.He received 2 inections of zolendronic acid preoperatively at a gap of 3 weeks (in view of lysis in supra-acetabular region). He underwentinternal hemipelvilectomy (Type 1+Type 2 +part of Type 3) and reconstruction with mesh pseudoarthrosis. His post-operative period was uneventful.

Results: The final histopathological report confirmed the diagnosis of Admantinoma with negative resection margins. Patient is on a regular clinical and radiological follow-up. His MSTS score is 19/30.

Conclusion: High index of suspicion along with sound clinical, radiological and histological inputs are required for establishing the correct diagnosis of admantinoma at unusual sites before erroneously passing it off as a benign condition. The considerable chances of local recurrence and distant metastases (15-20%) in admantinoma warrant an early aggressive treatment with a long –term follow-up.

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